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# Intratympanic gentamicin treatment 'as needed' for Meniere's disease. Long-term analysis using the Kaplan–Meier method

**Silvia Quaglieri · Omar Gatti · Elisabetta Rebecchi · Marco Manfrin · Carmine Tinelli · Eugenio Mira · Marco Benazzo**

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**Abstract** In recent years, several titration or on-demand protocols using low-dose repeated intratympanic (IT) gentamicin injections have been adopted for the vertigo control in unilateral medical refractory Menière's disease (MD). Because of the frequent recurrence and the need to treat the patients several times, it is difficult to strictly follow the 1995 AAO-HNS criteria to classify the results. The Kaplan–Meier analysis provides an effective and simpler method to address these concerns. We report the results of a long-term study (7 years) on a large population of MD patients (174) treated with on-request low-dose delayed IT gentamicin injections analysed using the Kaplan–Meier survival method. Effective vertigo control was obtained with a single injection in 40.2 % of the patients (*excellent responders*) and with repeated injections (2–9) in 43.7 % of the patients (*moderate responders*). Only six patients (3.5 %) needed to be submitted to vestibular neurectomy because of the persistence of vertigo attacks (*non-responders*). A subgroup of 22 patients (12.6 %) reporting a late recurrence of vertigo attacks after an initial vertigo-free interval lasting more than 2 years (*short-term responders*) were successfully treated with a further cycle of injections. In no cases, we observed significant signs of cochlear or vestibular toxicity. Kaplan–Meier survival analysis provided an excellent method for reporting treatment success or failure in patients followed for variable length of time with our kind of protocol.

**Keywords** Menière's disease · Intratympanic gentamicin · 'As needed' treatment · Long term follow-up · Kaplan–Meier analysis

S. Quaglieri (✉) · O. Gatti · E. Rebecchi · M. Manfrin · E. Mira · M. Benazzo
Department of Otorhinolaryngology, University of Pavia and IRCCS Policlinico S Matteo Foundation, Piazzale C Golgi 2, 27100 Pavia, Italy
e-mail: silviaquaglieri@libero.it

C. Tinelli
Clinical Epidemiology and Biometric Unit, IRCCS Policlinico S Matteo Foundation, Pavia, Italy

## Introduction

Treatment of medically refractory unilateral Menière's disease (MD) with intratympanic (IT) aminoglycoside injections has now become a standard therapy [1–5]. Over the years this therapy, introduced by Schuknecht using streptomycin [6] and later by Lange using gentamicin [7, 8] and initially conceived as ablative or sub-ablative, has increasingly tended to conserve vestibular and cochlear function and aimed at the complete or substantial control of vertigo attacks avoiding serious vestibulotoxic or cochleotoxic effects. Therefore, there has been a trend towards using lower doses of gentamicin, fewer injections, and longer time intervals between the latter. We have switched from the 'heavy' protocol initially adopted as an alternative to labyrinthectomy or vestibular neurectomy [7–9] to a more flexible *titration method* [10, 11] to an *interval therapy* [8–12] to a *single-shot therapy* [8] to a *variable titration method* [13] and to an *on-demand method* [14, 15]. Using these protocols, complete or substantial control of vertigo attacks (class A and B in the 1995 AAO-HNS guidelines [16]) ranges between 80 and 90 %, with a minimal risk of significant hearing loss or persistent dizziness/imbalance and with a marked improvement in the patients' quality of life [13–15]. The increasing use of IT gentamicin in recent years, usually requiring repeated injections even at time intervals <2 years after the initial

one, make it difficult to strictly follow the 1995 AAO-HNS criteria to evaluate results in terms of effective control of vertigo for any given treatment [17].

The Kaplan–Meier survival analysis [18], widely used in cancer research, provides an efficient method to describe/determine the treatment's success or failure, when repeated IT gentamicin injections are given as needed to patients who are followed for variable lengths of time and is becoming a popular method to report long-term results of MD treatments [15, 17, 19, 20]. We report the results of a long-term, retrospective analysis of IT gentamicin treatment in MD outpatients, treated with low-dose delayed injections on-request. The main outcome measure was vertigo control, assessed using Kaplan–Meier analysis, over a 7-year period. Secondary outcomes were long-term modifications of cochlear and vestibular function, assessed with PTA threshold, VEMPs and caloric tests.

## Materials and methods

A total of 180 patients affected by definite unilateral MD according to 1995 AAO-HNS criteria were treated with at least one dose of IT gentamicin at our Institution between 1 January 2005 and 31 December 2011. By the time, the study was closed six patients (four females and two males, mean age 55.3 years, SD 14.5 years) had been lost to the follow-up (four address unknown, two deceased for unknown cause) such that the remaining 174 were included in the study. Inclusion criteria were: typical recurrent vertigo attacks during the previous 6 months, which did not respond to conventional medical treatment (salt restriction, diuretics, betahistine), no evidence of MD and serviceable hearing in the non-affected ear, informed consent, in particular for the risk of auditory loss and possible onset of persistent post-treatment dizziness/imbalance due to the cochlear or vestibular toxicity of gentamicin. Exclusion criteria were: presence of systemic or neurological comorbidities, which could hinder the process of vestibular compensation, previous middle ear surgery, and allergy to aminoglycosides.

### Preoperative assessment

After a thorough neuro-otological examination, including an evaluation of spontaneous, positional and positioning nystagmus, head thrust test, head shaking test, hyperventilation test, all were evaluated with a VOG recorder, dynamic visual acuity test, subjective visual vertical test, Romberg test, past-pointing test, and stepping test. An otomicroscopic examination was performed to evaluate the state of the tympanic membrane and to rule out any disorders of the middle ear. Hearing function was evaluated with tympanometry and pure tone audiometry and the PTA was calculated on air conduction thresholds at 500, 1,000, 2,000 and 4,000 cps. Vestibular semicircular canal excitability was evaluated using the caloric test and defined as unilateral weakness according to the conventional Jongkees formula or, in the absence of nystagmus, the ice-water test. Saccular function was evaluated by means of acoustic-click vestibular-evoked cervical myogenic potentials (c-VEMPs), considering normal a p13-n23 amplitude side difference $<30$ %.

### Injection protocol

One phial of gentamicin sulphate (80 mg/mL) was buffered (pH 6.4) with 1 mL of 8 % sodium bicarbonate solution and then, under otomicroscopic control, 1 mL of the solution, corresponding to 26.7 mg of gentamicin, was injected in the affected ear through the posterior–inferior quadrant of the tympanic membrane using a 22 g spinal needle after local anaesthesia with a 2.5 % lidocaine spray. The patient was instructed to avoid swallowing and to maintain a supine position with the head tilted toward the healthy side for at least 20 min. The injection was performed in an outpatient procedure.

### Treatment protocol

The patients were re-evaluated 1 month after the first gentamicin injection. During this period, close phone contact was maintained and the patient was instructed to inform staff of any significant symptoms, namely hearing loss, persistent dizziness/imbalance or other signs of severe vestibular hypofunction. In the absence of any further vertigo attacks, patients were re-evaluated a month later. The procedure was repeated with further re-evaluations after 3–6–12 months and then every year. At the follow-up visit, the patients underwent a complete, bed-side vestibular examination including audiometric tests, caloric tests and c-VEMPs. The patients were asked to fill in questionnaires recording the number and severity of vertigo attacks they had experienced since the previous visit. This number was used to calculate the monthly rate of vertigo. In some cases, the monthly rates were calculated on very few attacks, sometimes even one. The severity of the attacks was scored according to their duration (less than 1 h, 1–3 h, more than 3 h) and their intensity (mild: no vegetative symptoms, moderate: nausea only, severe: nausea and vomiting). Apart from the re-evaluation visits, scheduled for research purposes, during the entire 7-year follow-up period, patients were instructed to contact staff if they experienced any further occurrence of typical vertigo attacks, suggesting failure to control vertigo symptoms. In this case, patients were given several options: resumption

of conventional medical treatment plus vestibular suppressants, a repeated IT gentamicin injection or vestibular neurectomy. If the gentamicin option was chosen, IT treatment was performed only if the patient responded to caloric stimulation or if there was a p13-n23 VEMP response. The IT gentamicin protocol was discontinued if PTA worsened by more than 15 dB, if signs of vestibular-ototoxicity were present or if there was no response to caloric or VEMP tests.

According to this protocol, the minimum time interval between two consecutive injections was 1 month. Repeated injections were given when patients felt they were needed to control vertigo. All patients gave their written informed consent to take part in the research protocol.

### Data analysis

The Kaplan–Meier time-to-event method was used to analyse follow-up time after any IT gentamicin injection. This allowed us to evaluate the percentage of patients who responded to one IT injection and the follow-up time needed before another injection or surgical procedure was required. In accordance with Nguyen et al. [17], we used the term 'surgery', to define the percentage of all patients who were scheduled for vestibular neurectomy due to the increase in frequency and/or intensity of vertigo attacks (1995 AAO-HNS class E + F) after repeated IT gentamicin injections. In this case, all gentamicin injections performed during the study were considered. By 'failure' we mean a patient experiencing recurrent vertigo after an IT gentamicin injection and needing a subsequent injection. The term 'control' was used when complete or substantial control of vertigo attacks (1995 AAO-HNS class A + B) was achieved. Follow-up was administratively censored ending at a pre-specified date (31 December 2011). Time for evaluation was measured in units of months. The procedure was closed and the treatment considered successful, when complete or substantial control of vertigo attacks (1995 AAO-HNS class A or B) was achieved in the 6 months following the last gentamicin injection. During follow-up, patients were allowed to continue their conventional medical treatment for MD.

### Statistical analysis

For quantitative variables, descriptive statistics were computed as mean and Standard Deviation (SD) or median and Interquartile Range (IQR 25th to 75th percentiles), if they were not normally distributed, and as absolute frequency and percentage for qualitative variables. The Kaplan–Meier time-to-event method was used to analyse the follow-up time after any IT gentamicin injection and log-rank test was used to compare between groups. Univariate and multivariate Cox proportional hazards models were used to determine the factors associated with failure. Two-sided $p$ values $<0.05$ were considered statistically significant. Stata 10.0 (StataCorp, College Station, Texas) was used for all computation.

## Results

Follow-up lasted from 6 to 81 months (median 51.2 months, IQR 31.8–69.7). Final evaluation was performed on 174 patients, whose demographic characteristics are reported in Table 1. In the 6 months prior to treatment, the patients experienced a mean frequency of six vertigo attacks per month (range 1–15), five of whom (2.9 %) had Tumarkin attacks. The median PTA in the affected ear was 40 dB (IQR 30.5–43.5), median unilateral caloric weakness was 40 % (IQR 30–55) and median VEMP amplitude side difference was 45 % (IQR 35–60).

The number of gentamicin injections applied in all patients to achieve vertigo control is shown in Fig. 1. None of the patients had to interrupt treatment due to acute and significant signs of cochlear or vestibular toxicity. In six patients, treatment was stopped after 3–9 injections because of persistent or increasing frequency or intensity of vertigo attacks and the patients were scheduled for vestibular neurectomy. In the remaining 168 patients, control of vertigo attacks, assessed for a minimum of 6 months, was complete (class A) in 107 patients and substantial (class B) in 61 patients. Therefore, total effective control for class A + B was 96.5 % (168/174). In 168 responding patients, control of vertigo was obtained after a single injection in 79 cases (45.4 %) and after repeated injections (2–9) in 89 cases (51.1 %).

A subgroup of 146 patients with a 2 years complete or substantial control of vertigo attacks were followed for up to 7 years. Twenty two of them (12.6 %), after a symptom-

**Table 1** Demographic characteristics of the 174 patients

| Parameter | |
|---|---|
| Sex | |
| Female | 82 (47 %) |
| Male | 92 (53 %) |
| Age | |
| Mean SD, (years) | 53.8 (13.1) |
| Affected ear | |
| Left | 79 (45 %) |
| Right | 95 (55 %) |
| Duration of symptoms (months) | |
| Mean | 24 |
| Range | 6–90 |

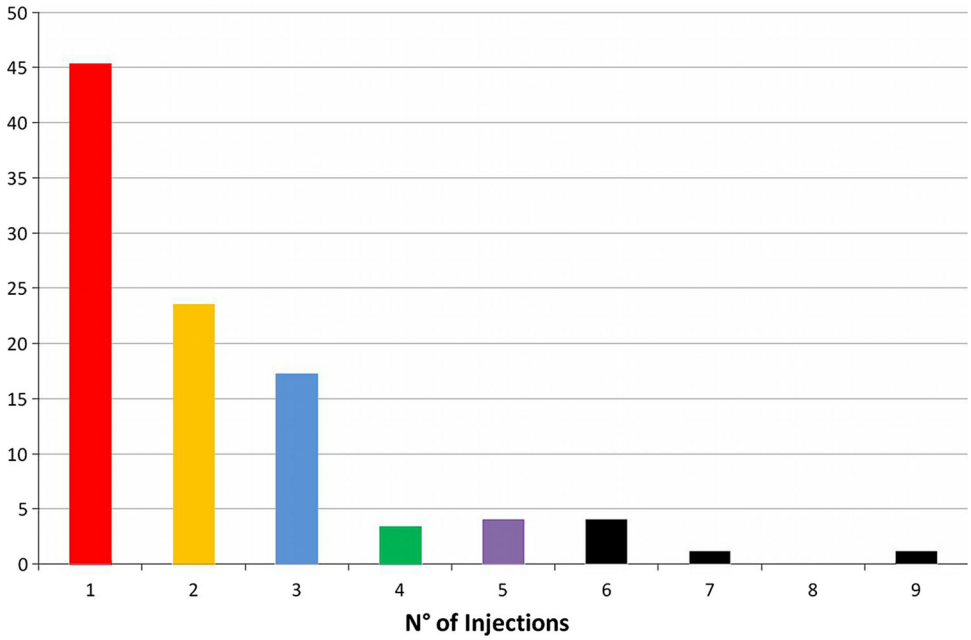


**Fig. 1** Number of gentamicin injections applied to achieve vertigo control

free period ranging 24–80 months (mean 33 months) presented a recurrence of vertigo attacks that did not respond to conventional medical treatment. On patients' request, a second cycle of IT gentamicin was performed, with a number of injections ranging 1–4 (mean 1.5 injections), administered over a time period ranging 1–18 months (mean 3.3 months). Twenty of them presented complete or substantial control of vertigo after a 6-month follow-up period. In these patients, who were re-treated after a long symptom-free interval, vertigo occurred at reduced rates in comparison to the initial pre-treatment rate or with less severe spells in comparison to the attacks at onset of the disorder.

In the responding patients after treatment, mean PTA in the affected ear was 53 dB (IQR 25–95), mean unilateral caloric weakness was 75 % (IQR 45–85) and mean VEMP amplitude side difference was 65 % (IQR 45–70). A significant difference between pre- and post-treatment values ($p < 0.01$) was observed only in caloric weakness.

The Kaplan–Meier survival plots after gentamicin treatment is reported in Fig. 2. The uppermost curve indicates survival for all patients and surgery refers to the need for vestibular neurectomy; the remaining curves indicate survival after a given gentamicin injection (1–5. Data for 6th to 9th injections are not reported) and failure refers to the need for a subsequent injection. Time to failure is measured in months.

None of the considered variables that could predict IT response to gentamicin treatment (age or sex, disease duration, number and severity of vertigo attacks, pre-treatment PTA, VEMPs amplitude and canal paresis, pre- to post-treatment difference in PTA, VEMPs amplitude and canal paresis) were significantly associated with survival curves.

Thirty-seven patients reported mild imbalance or dizziness occurring within 24 h or up to 1 week after the injections. However, the symptoms were mild and did not interfere with their daily activities or continuation of IT gentamicin treatment. The patients were counselled and advised to carry out any kind of physical activity as an elementary form of vestibular rehabilitation. Forty-three patients who reported moderate imbalance or dizziness lasting for a longer period of time were successfully submitted to a cycle of vestibular rehabilitation.

## Discussion

IT gentamicin injections administered several times and at different time intervals, according to several titration or on-demand protocols, are becoming increasingly common to ensure adequate vertigo control in MD patients. However, the unpredictable occurrence of vertigo attacks and their unpredictable recurrence after nonsurgical and nonablative treatments, with the corresponding need for repeated treatment, makes it difficult to strictly follow the AAO-HNS recommendations to classify results. We agree with the views of other authors [14, 16, 20, 21] about the present-day limits of the 1995 AAO-HNS guidelines for the evaluation of this kind of treatment of MD: their criteria limit the patients to be studied by requiring an arbitrary 24 month follow-up period, do not specify how to handle repeated treatments such as IT gentamicin injections, may bias clinicians against retreating patients who

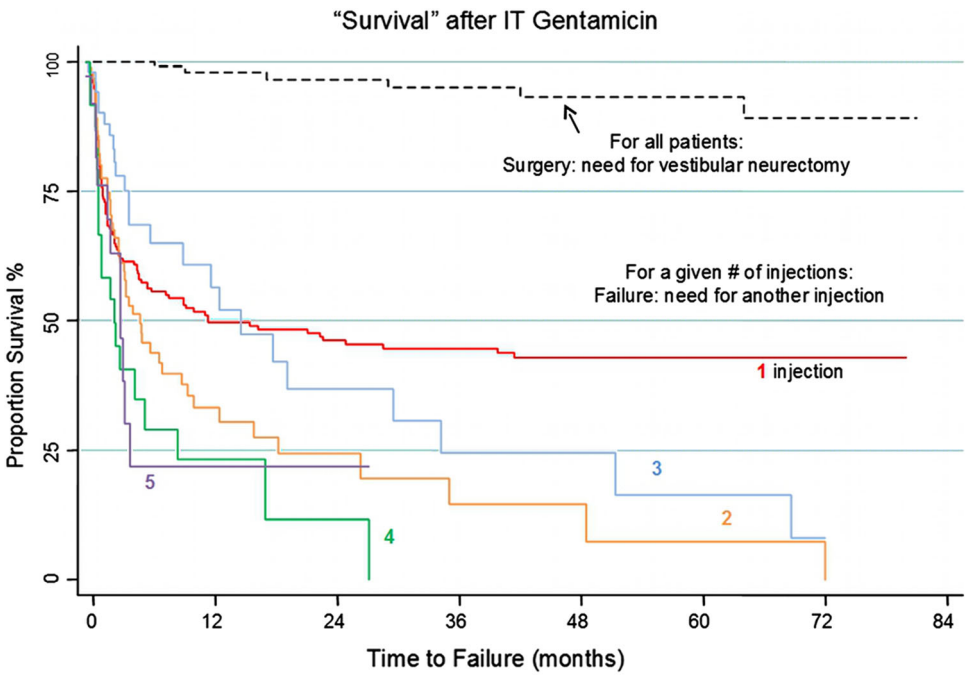


**Fig. 2** Kaplan–Meier survival plots after gentamicin treatment

have recurrent vertigo at time intervals <2 years after previous treatment. Our experience supports these authors' conclusions concerning the advantages of Kaplan–Meier survival analysis in monitoring patients who enter the study at different time points up to a given termination date and who thus have varying lengths of follow-up. Moreover, Kaplan–Meier analysis provides a clear and complete representation of the clinical course of patients submitted to treatment that must be repeated over time and enables the investigator to predict the probability of success at any given time after treatment.

Recent meta-analysis [1–5] proves that IT gentamicin treatments using either a titration protocol or a low-dose protocol with repeated injections, as needed, for recurrent vertigo ensures effective control of vertigo attacks in MD ranging 80–90 % with significant hearing loss and/or significant persistent disequilibrium ranging 1–3 %. Several differences between reported vertigo recurrence rates, especially when titration or lower dose protocols were used, might be related to the duration of follow-up. Studies in which patients were followed for an extended period of time prove that vertigo may recur more than 2 years after IT gentamicin treatment [8, 15, 17, 22, 23]. Our study shows that a treatment protocol based on low-dose on-request delayed IT gentamicin injections is safe and effective: in no case did we observe significant and persistent signs of cochlear or vestibular toxicity and vertigo control was achieved after a single injection in 45.4 % of cases and after repeated injections in 51.1 %. Total effective control of vertigo (class A + B) was obtained in 96.5 % of patients. The worsening of hearing (PTA) and vestibular canal (caloric) or saccular (VEMP) function is limited, partly attributable to the natural disease progression during our very long-term follow-up and even acceptable in light of the goals of the treatment.

The large case series (174 patients) and the prolonged follow-up period (up to 7 years) are the most valuable contribution of our study. On the basis of our experience, we can distinguish different subgroups of patients: *excellent responders* ($n$ 70 = 40.2 %), who had effective control of vertigo attacks lasting over 2 years after a single gentamicin injection, with a maximum follow-up duration of about 7 years; *moderate responders* ($n$ 76 = 43.7 %), who reported the same long-term results after several injections; *non-responders* ($n$ 6 = 3.5 %), in whom vertigo attacks persisted unchanged despite repeated injections and who were enrolled for ablative surgery; *short-term responders* ($n$ 22 = 12.6 %), who reported a late recurrence of vertigo attacks after an initially complete vertigo-free interval lasting at least 2 years and who needed a further cycle of gentamicin injections.

In the last subgroup, vertigo attacks occurred at reduced rates or with less severe spells compared to onset rates. Nonetheless, the patients chose repeated IT gentamicin injections for less frequent or less severe recurrent vertigo symptoms than originally experienced. We agree with the previous authors' opinion [15, 17, 21] that once patients are aware that office treatment might relieve vertigo, the level of vertigo tolerated may decrease with subsequent recurrences. The expectation of a treatment that can be easily repeated, when vertigo frequency and/or severity recur will inevitably lead to requests for such treatment shortly into

the course of worsening. Thus, recurrent vertigo treated with further IT gentamicin cycles does not necessarily reflect a return to the same vertigo burden suffered before IT gentamicin treatment.

In a long-term evaluation of vertigo control with an 'on-demand' protocol of IT gentamicin injections, we have to take into account the spontaneous rate of vertigo remission in MD [22]. It is well known that over time, MD patients eventually experience a reduction in rate and severity of vertigo attacks even without treatment. Therefore, long-term vertigo control observed in our patients may be considered as not being solely due to gentamicin treatment but in part to the natural course of the disease.

In terms of prediction, according to Manrique-Huarte et al. [15] MD duration was the only pre-treatment parameter that seemed to significantly correlate with vertigo control. A number of studies have been performed with the aim of identifying post-treatment parameters able to correlate a modification of one or several labyrinthine functions caused by IT gentamicin application with the control of vertigo or with the risk of significant cochlear or vestibular toxicity [21, 24–28]. In our study we did not find any correlation between vertigo control and any of the considered variables (age or sex, disease duration, number and severity of vertigo attacks, pre-treatment PTA, VEMPs amplitude and caloric or VOR gain unilateral weakness, pre- to post-treatment difference in PTA, VEMPs amplitude and unilateral weakness).

In our opinion, individual response to IT gentamicin treatment is largely unpredictable, and depends on several poorly understood parameters, such as permeability of the round window membrane, gentamicin diffusion in different inner ear fluids, gentamicin uptake by different hair cell types or by peri-ampullar and peri-macular dark cells, gentamicin sensitivity, in terms of activity and/or toxicity, of all these kind of inner ear cells [29–31]. We can only observe that analysis of our survival curves suggests that most cases of failure, referred as non-responder patients, occur in the early stages of treatment, as shown by the relative steepness of the curves toward the left of our graph. On the other hand, the late post-treatment recurrence of vertigo attacks observed in the subgroup of patients defined as short-term responders could be explained in terms of late recovery of canal or utricular function observed in individual cases [8, 24].

## Conclusion

Our study provides further support to the present-day opinion that in unilateral medically refractory MD outpatient-based IT gentamicin treatment with low-dose delayed injections as needed ensure effective vertigo control in over 90 % of cases, with a minimal risk of significant hearing loss and vestibular damage. Approximately 40 % of the patients required only a single injection and about 50 % needed multiple injections. Individual response to IT gentamicin treatment is, however, largely unpredictable and no correlation has been found at present with several considered parameters such as disease duration, number and severity of vertigo attacks, pre-treatment PTA, VEMPs amplitude and unilateral weakness values, pre-to post-treatment difference in PTA, VEMPs amplitude and unilateral weakness values. Thanks to our very long-term follow-up we observed that about 10 % of patients, defined as short-term responders, present a recurrence of vertigo attacks after a vertigo-free interval lasting up to 5 years after an initial successful IT gentamicin treatment. In this case, patients often choose to receive further IT gentamicin injections for less frequent or less severe recurrent vertigo attacks than originally experienced. Subjectively, given the simple and easy procedure of IT gentamicin injection and with the goal of preserving a good quality of life, the level of vertigo tolerated by MD patients may decrease with subsequent recurrences. Vestibular ablation is not requested to assure an effective control of vertigo attacks in medical intractable MD patients. However, even if the present protocol of IT gentamicin treatment is proven as safe and effective, further large scale randomized controlled trials are needed to confirm its long-term efficacy, to assess the probability of significant cochlear or vestibular damage and to define the possible predictive factors. Kaplan–Meier survival analysis is an excellent method to report the results of repeated IT gentamicin treatment given as needed over a 7-year period to patients with persistent or recurrent episodes of vertigo followed for variable lengths of time.

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**Conflict of interest** None.

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