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Original Article

Response Over Time of Vertigo Spells to Intratympanic Dexamethasone Treatment in Meniere's Disease Patients

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OBJECTIVE: To assess the effectiveness and response over time of intratympanic dexamethasone on the symptoms of Meniere's disease.

MATERIALS and METHODS: We performed a matched cohort study of 24 patients with Meniere's disease who were unresponsive to initial treatment and underwent 3 sessions of weekly intratympanic dexamethasone injections using a concentration of 16 mg/mL and 24 matched controls with the same characteristics with regard to vertigo spells.

RESULTS: Compared with control subjects, intratympanic dexamethasone injections resulted in a decrease in the frequency of vertigo spells in the first 6-month period. In the dexamethasone-treated group, a ≥60% decrease in vertigo spells was achieved by 70.8% of patients in the first 6 months. Total remission was achieved by 20.8% of patients in the first 8 months, but after this, the effect tapered. A slight improvement in Tinnitus loudness and no changes in hearing levels were found. The stage of Meniere's disease, years from disease onset, and mean number of vertigo spells per month did not have any effects on the percentage of decrease in vertigo spells.

CONCLUSION: Intratympanic dexamethasone temporarily reduces the frequency of vertigo spells during the initial months but does not remove the probability of having further spells in the future. This therapy provides a valuable tool to accomplish a rapid decrease in vertigo spells in subjects with Meniere's disease, and it is considered an alternative to chemical or surgical labyrinthectomy.

KEYWORDS: Intratympanic dexamethasone, Meniere's disease, vertigo, dexamethasone

INTRODUCTION

The initial treatment of Meniere's disease (MD) is based on dietary therapy, (restricting caffeine and salt) and pharmacological treatments such as systemic administration of diuretics and vasodilators, regardless of whether they are accompanied by corticosteroids. Despite initial treatment, there are patients who show no response or lack of improvement and continue to have disabling vertigo attacks. In these cases, intratympanic dexamethasone (ITD) or intratympanic gentamicin (ITG) injections or classic surgical treatments are widely used. ITD injection is a simple and non-destructive method that does not injure the anterior or posterior labyrinth.

Several authors have studied this method of using different protocols of ITD injections to control vertigo spells in patients with MD and have reported varied but encouraging results. In 2013, Martin-Sanz et al. [1] used 3 consecutive weekly injections of 4 mg/mL dexamethasone and achieved 44% of complete and 14% of partial vertigo control during a 2-year follow up period. In 2001, Sennaroglu et al. [2] instilled into the symptomatic ear of patients with MD 5 drops of dexamethasone (1 mg/mL: each instillation having 0.25 mg) through ventilation tubes every other day for 3 months. Complete control was achieved in 42% of the patients, and substantial control was achieved in 30% of patients. Overall, 72% of patients had satisfactory relief from vertigo, 16% showed an improved pure-tone audiometry (PTA) average, and 8% showed a decrease of 20 dB or more in the PTA average. In 2004, Barrs [3] conducted a study of 34 patients with intractable MD and used 5 injections of dexamethasone at 10 mg/mL intratympanically (0.3 to 0.5 mL). Within 1 month, 8 (24%) had complete control of vertigo for 2 years, 3 (9%) had control of vertigo for 12 months, and 4 (12%) had control of vertigo for 6 months. A total of 16 patients (47%) from the 34 patients studied had control of vertigo at some point. Garduno-Anaya [4], in 2005, conducted a double-blind, randomized trial treating patients with definite MD, who were unresponsive to medical therapy, with dexamethasone (4 mg/mL) inner ear perfusion for 1 hour daily for 5 days. Comparing the treatment group (dexamethasone) with the placebo group after 24 months demonstrated a statistically significant improvement in vertigo as defined by a respective improvement in the class (82% versus 57% of patients achieving class A - complete con-

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trol) and a mean vertigo subjective improvement (90% versus 57%). Boleas-Aguirre [5] published a study in 2008 of 129 patients with MD receiving intratympanic treatment with 12 mg/mL of dexamethasone. Satisfactory vertigo control (meaning no further treatments were needed or asked for) was achieved in 117 (91%) of 129 cases. Vertigo control required only 1 dexamethasone injection in 48 cases (37%), 2 injections in 26 cases (20%), 3 injections in 18 cases (14%), and 4 injections in 10 cases (8%). More than 4 injections were needed in 15 cases (21%). In Phillips et al. [6], in 2011, a trial of 22 patients with definite MD compared the effectiveness of ITD injections (5 consecutive daily administrations of 4 mg/mL of dexamethasone) on the frequency and severity of vertigo spells versus a placebo and found a clinically and statistically significant improvement in functional levels (90% vs. 42%) and class (82% vs. 57%) measured 24 months after ITD injections.

Regarding the effect of ITD on tinnitus and hearing loss in patients with MD, usually no improvements have been described. Silverstein et al. [7], in 1998, performed a prospective, randomized, double-blind, crossover study in patients with MD, comparing improvements in hearing loss and tinnitus secondary to ITD (3 consecutive daily administrations) versus a placebo. ITD showed no benefit over the placebo for the treatment of hearing loss and tinnitus. Arriaga and Goldman [8], in 1998, did not detect any hearing improvement in 21 patients with MD who had a single injection of ITD.

Unlike other publications regarding this subject, we have studied the effectiveness of ITD on the symptoms of MD over different periods and the frequency of vertigo spells on a monthly basis. In addition, we have evaluated the response to ITD treatment in regard to the stage of the disease, the years from disease onset, and the number of vertigo spells per month prior to ITD injections.

MATERIALS and METHODS

We performed a matched cohort study, conducted and developed in a tertiary hospital, with a sample of 24 patients with definite MD, according to the criteria of the AAO-HNS '95 [9], treated with ITD injections, and a control group of 24 MD patients, matched by the number of vertigo spells in the last 6 months.

The institutional ethics committee approved this study (approval code FPNT-07-05-EC-B). All patients included in the study had recurrent vertigo spells despite pharmacological treatment and dietary therapy, which was administered for a mean of 6 years in the ITD group and 3 years in the control group before inclusion in this study. All patients gave their informed consent to participate in this study. If vertigo spells were not controlled according to patient satisfaction, the subject was treated with ITD injections. The procedure was performed in an Otoneurology office, with a standard microscope, after topical anesthesia with 10% lidocaine (Xilonibsa; Inibsa, Barcelona, Spain) using a 25 gauge needle attached to a syringe filled with 1 ml or more of dexamethasone, specially prepared for this procedure with concentrations of 16 mg/mL.

The injection was placed in the uppermost portion of the anterior-inferior quadrant of the tympanic membrane, instilling between 0.5 to 1 mL of dexamethasone. Then, the patient had to remain in a supine position for 30 minutes, with his/her head turned to the contralateral side of the injection so that the round window could be in direct contact with the middle ear dexamethasone to facilitate its diffusion into the inner ear. The patient was also requested to swallow as little as possible to maintain the fluid in the middle ear space for as long as possible. The injections were repeated weekly to achieve a number of 3 sessions.

Information about vertigo was gathered through a symptoms diary (in which the patient recorded every vertigo spell that lasted ≥20 minutes at the time of occurrence, describing date, duration, and accompanying symptoms) before and after treatment.

Tinnitus loudness and PTA were registered immediately before treatment and 6 months afterwards. Data about tinnitus loudness was collected using a visual analogue scale with scores ranging from 0 to 10 according to increasing intensity of the symptom from the subjective point of view of the patient. Hearing assessment was made using PTA considering the auditory frequencies 250, 500, 1000, 2000, 3000, 4000, and 8000 Hz to determine the stage of the disease as defined by the AAO-HNS Committee [9].

Vertigo spells were compared between the ITD group and the control group in the 6-month period and in the 18-24-month period after their inclusion in the study.

Further analysis was performed in subjects of the ITD group: we compared the number of vertigo spells in the 6-month period prior to ITD with the number of spells in the 6-month period after ITD, and with the number of spells that occurred in the period between 18 and 24 months after injections. We also compared the number of vertigo spells in the month prior to treatment to the number of spells in the first month after treatment. As well, a comparison of the Tinnitus loudness score (immediately prior to ITD with the score obtained 6 months afterwards), and the PTA (immediately prior to ITD with the PTA 6 months after treatment) were performed.

In these comparisons either a Paired t-test or a Wilcoxon Signed Rank Test were performed (the first one if samples were accepted into the Shapiro-Wilk normality test, or the second one if samples failed it). We performed 2 response over time curves. In the first curve, an event was assigned as a decrease in vertigo spells equal to, or higher than, 60% during a 6-month period. In the second curve, an event was assigned as complete remission of vertigo spells during a 6-month period (i.e., once a patient achieves the event, a rise in the curve is registered).

To determine whether the response was influenced by any personal feature of the patient, we compared the percentage of decrease in vertigo spells with respect to the number of spells before treatment by stratifying 3 features of the disease: (1) stage of MD (as proposed by the American Academy of Otolaryngology-Head and Neck Surgery [9] in 1995, based on the arithmetic mean of the pure-tone thresholds at 0.5, 1.0, 2.0, and 3.0 kHz using the worst audiogram during the 6-month interval before treatment. The stages were classified as follows: stage I, a 4-tone average of less than 26 dB; stage II, 26 to 40 dB; stage III, 41 to 70 dB; and stage IV, more than 70 dB), (2) years from disease onset (defined as the number of years since the first vertigo spell), and (3) the mean number of vertigo spells

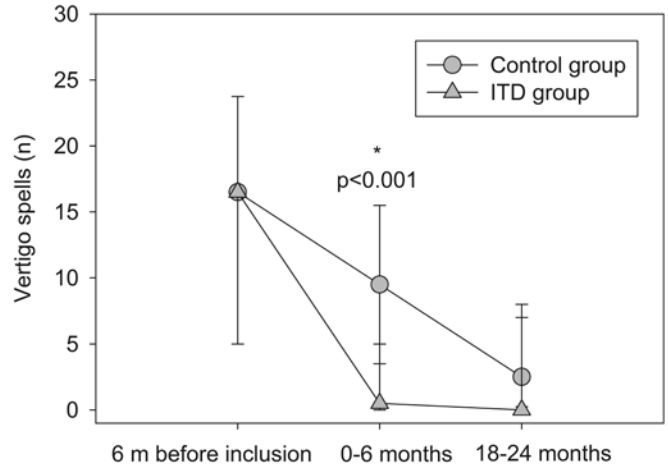

Figure 1. Comparison of the number of vertigo spells between subjects treated with ITD and control subjects

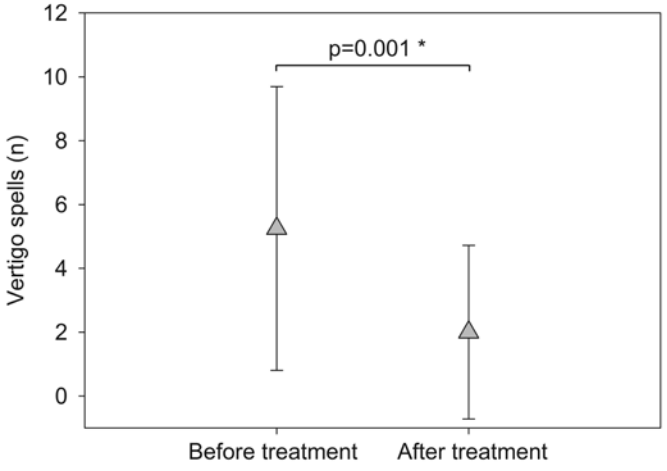

Figure 2. Comparison of the number of vertigo spells in the month prior to ITD injections with such spells in the first month after treatment

per month before treatment (defined as the total number of vertigo spells within 6 months before treatment, divided by 6). Comparisons were performed using a Z-Test for difference of proportions.

Data obtained were analyzed using the statistical program SigmaPlot (Systat Software; San Jose, CA, USA).

RESULTS

Forty-eight patients with MD were selected for this survey. The demographics and audiological data of the ITD group and the control group are summarized in Table 1.

During this study, all patients were kept on a caffeine- and salt-restricted (up to 1500 mg of salt/day) diet and continued receiving systemic treatment that included the administration of betahistine and/or torasemide. Out of 24 patients in the ITD group, 18 (75%) received only betahistine (5 received 32 mg/day, 9 received 48 mg/day, and 4 received 64 mg/day) and 6 (25%) received different dosages of betahistine (4 received 48 mg/day and 2 received 64 mg/day), accompanied with 2.5 mg of torasemide. Among the 24 patients of the control group, 11 (45%) received only betahistine (3 received 32 mg/day, 6 received 48 mg/day, and 2 received 64 mg/day) and 13 (55%)

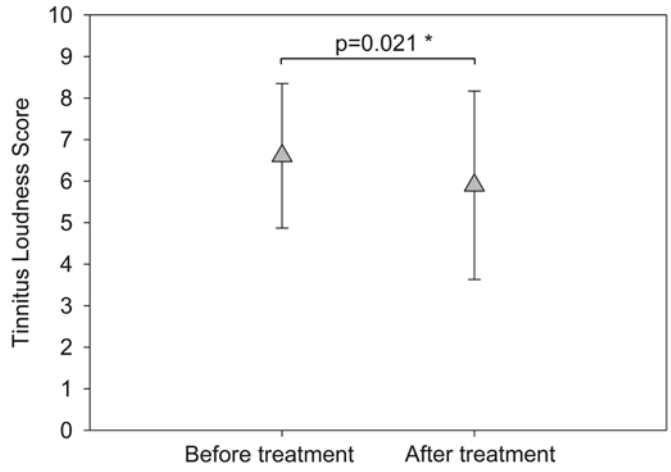

Figure 3. Comparison of the Tinnitus loudness score before ITD injections and 6 months later

Table 1. Summary of demographic and audiological features of the patients

	Cases (n=24)	Controls (n=24)	p
Age (years)	57.3±12.1*	54.5±12.0	0.424
PTAa (dB)#	71.1±19.9	64,6±21.9	0.292
Years from disease onset	6.5±6.3	3.5±3.8	0.052
Vertigo spells in the past 6 months	17.3±12.8	17.3±12.8	1.000

*Data are expressed as mean±standard deviation: SD; PTAa: average pure-tone audiometry from 250 to 8000 Hz.

received different dosages of betahistine (11 received 48 mg/day and 2 received 64 mg/day), accompanied with 2.5 mg of torasemide.

A significant difference (p<0.001) in the number of vertigo spells was observed in the 6-month period after inclusion when comparing the ITD group with a median of 0.5 spells (CI 25-75%: 0-5) and the control group with a median of 9.5 spells (CI 25-75%: 3.5-15.5). No differences were observed in the 18-24-month period (Figure 1).

To put forward the short-term effect, we compared the vertigo spells in the month prior to treatment with such spells in the first month after treatment. We found a significant decrease in vertigo spells (5.2±4.4 to 2.0±2.7; p=0.001) (Figure 2).

The Tinnitus loudness score exhibited a slight, but statistically significant, improvement (6.6±1.7 to 5.9±2.2; p=0.021) 6 months after the treatment (Figure 3).

The hearing level did not change in any of the 7 frequencies studied when the audiograms before and 6 months after treatment were compared (p>0.05 in every frequency) (Figure 4).

Considering that a goal of this study was to determine the monthly response to ITD regarding vertigo spells, we performed a response over time curve with an event assigned as a ≥60% decrease in vertigo spells during a 6-month period. We found that 70.8% of patients achieved this criterion in the first 6 months after treatment (Figure 5).

In the ITD group, 5 patients did not accomplish the complete 24 month follow-up, due to the necessity of additional treatment (2 of

Table 2. Percentage of decrease in vertigo spells after ITD injections stratified by the disease stage

Stage	n	1 month (%)	0-6 months (%)	18-24 months (%)
I	-	-	-	-
II	2	100	100	100
III	12	88.5	77.7	63.1
IV	10	87.7	85.8	71.3

*Percentage of decrease in vertigo spells: proportion of reduction of vertigo spells with respect to the number of such spells prior to treatment.
ITD: intratympanic dexamethasone treatment

Table 3. Percentage of decrease in vertigo spells after ITD injections stratified by years from disease onset

Years from disease onset	n	1 month (%)	0–6 months (%)	18–24 months (%)
≤7	17	87.1	84	74.2
>7	7	89.8	82.4	60.5

*Percentage of decrease in vertigo spells: proportion of reduction of vertigo spells with respect to the number of such spells prior to treatment.
ITD: intratympanic dexamethasone treatment

Table 4. Percentage of decrease in vertigo spells after ITD injections stratified by mean number of vertigo spells per month prior to treatment

Vertigo spells/month	n	1 month (%)	0–6 months (%)	18–24 months (%)
≤1	11	87	84	59.8
1.1-3	7	91.1	86.6	100
>3	6	95.6	60.8	91.3

*Percentage of decrease of vertigo spells: proportion of reduction of vertigo spells with respect to the number of such spells prior to treatment.
ITD: intratympanic dexamethasone treatment

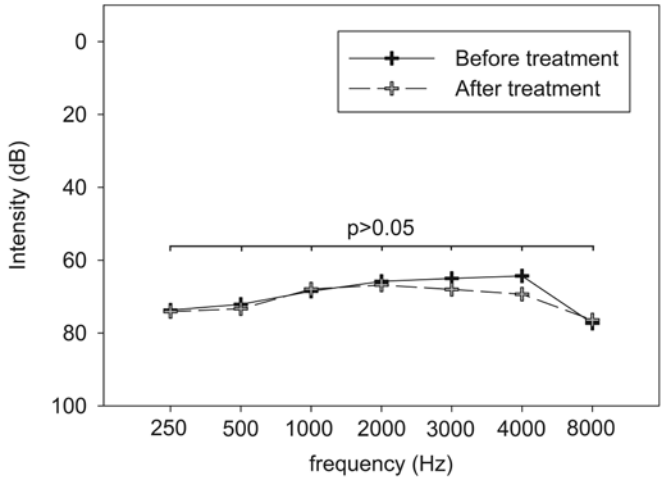

Figure 4. Comparison of the pure-tone audiometry before ITD injections and the pure-tone audiometry 6 months later

them required a second round of 3 sessions of ITD injections, another 2 patients required chemical labyrinthectomy with ITG therapy, and 1 patient underwent a surgical labyrinthectomy). In the control group, 2 patients required additional treatment (both of them underwent chemical labyrinthectomy with ITG therapy).

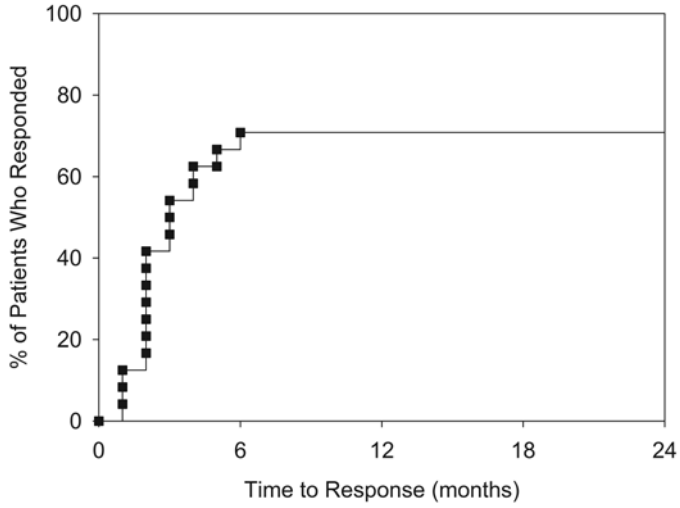

Figure 5. Response over time curve showing patients who achieved a ≥60% decrease in vertigo spells during a 6-month period after ITD injections

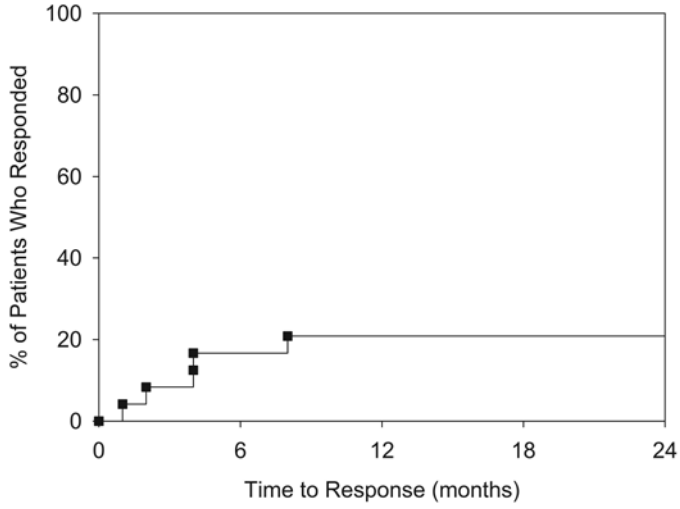

Figure 6. Response over time curve showing patients who achieved a complete remission of vertigo spells during a 6-month period after ITD injections

A second response over time curve was performed with an event assigned as the complete remission of vertigo spells during a 6-month period. We found that 20.8% of patients achieved this second criterion in the first 8 months after treatment (Figure 6).

When stratifying by stage of disease, we found no patients in stage I, 2 patients in stage II, 12 patients in stage III, and 10 patients in stage IV. There were no significant differences in the percentage of decrease in vertigo spells between the compared groups (every stage p>0.05). Data are shown in Table 2.

When stratifying by years from disease onset, 17 patients had ≤7 years since the first vertigo spell and 7 patients had >7 years since the first vertigo spell. There were no significant differences in the percentage of decrease in vertigo spells between the compared groups (every group p>0.05). Data are shown in Table 3.

When stratifying by mean number of vertigo spells per month prior to treatment, 11 patients had ≤1 spells/month, 7 patients had 1.1-3 spells/month, and 6 patients had more than 3 spells/month. There

were no significant differences in the percentage of decrease in vertigo spells between the compared groups (every group p>0.05). Data are shown in Table 4.

No complications (such as tympanic membrane perforations, hearing loss, etc.) were observed after ITD injections.

DISCUSSION

From the data in Figure 1, it is apparent that ITD injections result in a clear decrease in the frequency of vertigo spells when compared to the control subjects in the first 6-month period; however, this effect is not observed in the 18-24-month period.

Additionally, we found that ITD injections achieved an important improvement in vertigo control at least in 70% of the treated patients, but this improvement mainly occurred during the first 2 months. Afterwards, the effect of dexamethasone tapers off. These results are backed up by important facts: the existence of receptors for glucocorticoids in the stria vascularis, and the upregulation of aquaporin 1 mRNA in the cochlea after use of intratympanic glucocorticoids; this effect appears to be dose dependent [10, 11].

Beitz et al. [12] identified aquaporin 1 in the stria vascularis, which synthesizes inner ear fluids and regulates water homeostasis. This leads to the assumption that changes in aquaporin 1 mRNA in the stria vascularis may have an important effect in the regulation of the inner ear fluids and might play a role in endolymphatic hydrops.

Parnes et al. [13] found that intratympanic administration of corticosteroids resulted in a significantly higher inner ear drug level compared with systemic administration, and that concentrations of corticosteroids in the inner ear were higher in the endolymph than in the perilymph when administered via the intratympanic route.

For these reasons, we believe it is important to study the short-term effect of ITD treatment through continuous follow up using a response over time curve.

Current guidelines for reporting results of therapy were developed by the American Academy of Otolaryngology-Head and Neck Surgery in 1985 and amended in 1995 [9]. The method for reporting vertigo control requires calculating the ratio of the number of vertigo spells in the 18-24-month period after treatment, dividing it by the number of vertigo spells in the 6 months before treatment, and multiplying that result by 100. While this method is very useful in assessing response to surgical procedures, it could be insensitive to the short-term effects of ITD treatment. Accordingly, we performed a monthly tracking of vertigo spells to obtain the information of this transient vertigo control.

Although we have followed up with patients until 24 months after treatment, the results obtained for the first few months after injections have shown to be more useful when assessing the effect of ITD. The treatment protocol we used shows effects during the first 6 to 8 months, with a greater impact during the first 2 months after its initiation; this is understandable considering the fact that the effect of dexamethasone in the inner ear tends to taper. In 2014, Martin-Sanz et al. [14] reported a transitory reduction of the endolymphatic hydrops detected by electrocochleography 1 month after ITD injections. The hydrops levels returned to their initial values within a year. Improvements that occurred 24 months after ITD injections were probably not a consequence of this therapy.

The reduction of vertigo spells could result from the natural history of the disease [15]. This is the main reason that justifies the use of a control group with the same characteristics with regard to vertigo spells to avoid the confounding effect of the decrease in the number of vertigo spells that results from the natural course of the disease.

Multiple studies have found progressive reduction in vertigo spells leading to complete recovery within 2 years from onset [16, 17].

In 2001, Barrs [18] injected ITD in patients with intractable MD. More than 80% of cases had at least 1 month of complete remission of vertigo; however, remission decreased to 52% at 3 months, 43% at 6 months and 24% at 24 months. This gradual decrease in the effect is consistent with the results we have found. Therefore, it is reasonable to assume that ITD temporary reduces the disease activity, but does not remove the probability of having further vertigo spells in the future. In contrast, GIT or surgical procedures partially or completely eliminate vertigo spells at the expense of secondary effects, such as loss of labyrinth function that may cause imbalance, disequilibrium disorders, or hearing impairment. Even though there are authors [2] that have found some influence in hearing levels after ITD injections, our treatment protocol showed no changes in the PTA.

One of the main questions that emerged in our study was the influence of the personal features of the patients with MD on the response to therapy, but the stratification we performed showed that: stage of MD, years from disease onset, and mean number of vertigo spells per month did not have any effects on the percentage of decrease in vertigo spells.

Results in our study suggest that ITD treatment is an effective method to control vertigo spells in patients with MD who do not respond to initial treatments and it may decrease the intensity of tinnitus in these patients, but do not have any influence on hearing levels.

Although the natural course of MD can lead to a decrease or complete remission of vertigo, there are periods of the disease in which vertigo control is not appropriately achieved. In those cases, ITD injections provide a valuable tool to accomplish a rapid decrease in vertigo spells.

This therapy is an alternative to chemical or surgical labyrinthectomy thus avoiding the complications these procedures entail. ITD also represents a convenient option for patients who cannot tolerate, or refuse, treatment with systemic corticosteroids due to the side effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of La Fe Hospital, reference number FPNT-07-05-EC-B, approval date February 28th 2012.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.A.; Design - N.A., C.K.; Supervision - H.P., C.M.; Materials - H.P., C.M.; Data Collection and/or Processing - N.A., C.K., V.P.; Analysis and/or Interpretation - N.A., C.K.; Literature Review - N.A., C.K., V.P.; Writing - N.A., C.K.; Critical Review - C.M., H.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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