Intratympanic dexamethasone injection in Meniere's disease

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Aim
The aim of the study was to investigate the role of intratympanic (IT) dexamethasone in the treatment of medically refractory Meniere's disease (MD) using two different concentrations.
Patients and methods
Twenty-four adults with unilateral MD received a single IT injection of dexamethasone at 4 or 10 mg/ml concentration. Partial or no improvement over the next 1 month following injection necessitated a second injection. Before and after injection, all patients underwent detailed history taking, were evaluated with the Dizziness Handicap Inventory scale, and underwent basic audiological evaluation and assessment of cervical-vestibular evoked myogenic potential. The presence or absence of spontaneous, post-head-shaking, and positional nystagmus was assessed using a video-nystagmography system. Twelve patients served as the control group and were followed up subjectively for 1 month.
Results
Both 4 and 10 mg/ml IT dexamethasone improved all subjective symptoms and pure-tone audiometry thresholds. The cervical-vestibular evoked myogenic potential asymmetry ratio dropped after injection. However, the 10 mg/ml concentration was superior to the 5 mg/ml concentration in improving the signs of disease activity, Dizziness Handicap Inventory scores, and the duration of vertigo attacks. No change was reported by the controls.
Conclusion
IT dexamethasone injection might be helpful in controlling MD in some patients. The 10 mg/ml dexamethasone concentration controls vertigo at both the subjective and objective level. Especially if used early in the course of the disease

Keywords:
intratympanic steroids, Meniere's disease, short-term outcome, vertigo

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Introduction

Meniere's disease (MD) is a chronic disorder affecting the inner ear, characterized by recurrent episodes of spontaneous vertigo, fluctuating sensorineural hearing loss, and tinnitus, often with a feeling of fullness in the ear. Endolymphatic hydrops is accepted as the most possible pathophysiologic mechanism of the disease [1].

At present, no 'gold standard' treatment for MD is available. In fact, an evidence base for the management of patients with MD is sadly lacking [2]. Treatment options include lifestyle modifications, medications such as diuretics [3], vestibular suppressants (Claes and Van de Heyning, 1997) [4], oral steroids [5], and intratympanic (IT) injection of dexamethasone and/or gentamicin [6,7].

When less invasive medical therapies fail to provide symptomatic relief after 6 months, the patient is said to have 'intractable' MD. A more invasive treatment option, such as IT injection of steroid, should be considered [8]. IT steroid is a convenient and easy office-based treatment with minimal side effects, mainly limited to pain, inflammatory middle-ear changes, short-lasting vertigo, and tympanic membrane perforation [9]. The steroid most often used for IT therapy is dexamethasone. Dexamethasone seems to be the best tolerated with the longest half-life of up to 36–54 h [7].

Controversial evidence exists about the effectiveness of IT dexamethasone injection in MD. Specifically, there is uncertainty as to whether IT steroids are better than placebo or no treatment [2]. This controversy may be related to the dosage of dexamethasone used (4, 12, or 24 mg/ml), frequency of injections (single with short-term effect vs. multiple with long-term effect), method of injection, and who and when to inject [9].

The present work was designed to study the short-term role of IT steroids in the treatment of medically refractory MD. The effect of two different concentrations of IT dexamethasone (4 and 10 mg/ml) in controlling MD symptoms was also addressed.

Patients and methods

Patients

Study group

Twenty-four adults with unilateral MD were selected. The criteria for selection included a diagnosis of definite

MD according to the classification of Committee of Hearing and Equilibrium [10]. Failure to achieve benefit from conventional medical therapy for at least 6 months was an important inclusion criterion. The patients had to have no history of steroid therapy, ear operations, or neurological disorders. MRI with contrast was requested, whenever needed, to exclude retrocochlear lesions. Patients were recruited from the ENT Outpatient Clinic in Kobry El Koba Military Hospital during the period Jannuary 2013–December 2013.

Control group

Twelve adult patients with unilateral MD matched the study group in all selection criteria. They were only assigned for lifestyle modification and salt restriction as a treatment option. As reported by Phillips and Westerberg [2], there was significant placebo effect and spontaneous resolution in MD.

Verbal consent was taken from all patients before participation in the study. The study protocol was approved by the Ain Shams University Ethics Committee.

Procedures

All patients underwent detailed history taking. Both hearing loss and severity of tinnitus were subjectively rated from 0 to 100% and from 0 to 10, respectively. The interruption of daily activities caused by vertigo was rated 0–100% [2].

The physical, emotional, and functional aspects of vertigo symptoms were evaluated according to the Dizziness Handicap Inventory (DHI) scale (Arabic version) [11]. The total score evaluated the disability and feelings of anxiety and depression. Jacobson and Newman [12] categorized vertigo patients according to the total DHI score as follows: score of 0–15, no activity limitation; more than 16 to 27, mild activity limitation; more than 28 to 45, moderate activity limitation; 46 or more, severe activity limitation.

Basic audiological evaluation

Pure-tone audiometry, speech audiometry using Arabic Phonetically-balanced (PB) words was performed in a sound-treated room (model IAC, series 120, IAC acoustics, New York, USA) using the two-channel audiometer (Orbiter, model 922, Madsen Orbiter, GN autometrics, Denmark). The middle-ear functions were assessed with tympanometry using the immittancemeter (GSI, model 38, Grason Stadler GSI, USA).

Vestibular workup

The study group patients were assessed for the presence or absence of spontaneous, post-head-shaking, and positional nystagmus using the four-channel VNG-MicromedicalTechnology (version 4, USA). The protocol of testing followed that described by Shepard and Telian [13]. Cervical-vestibular evoked myogenic potential (c-VEMP) was recorded from the sternocleidomastoid muscle using the two-channel evoked potential system (Audera, model 091090, Grason Stadler Audera, USA). The protocol of testing followed that described by Colebatch [14]. The latency of P13, N23, amplitude, and asymmetry ratio (AR) were calculated. The AR was calculated as: $100(A_u\text{-}A_a)/(A_u\text{+}A_a)$, where A_a is the amplitude of affected ear and A_u is the amplitude of unaffected ear (Kingma and Wit, 2011) [15].

Intratympanic steroid injection

Study group patients underwent IT injection of dexamethasone with a spinal needle 22×3.5¢. The procedure for IT dexamethasone injection followed that described by Boleas-Aguirre *et al.* [16]. All subjects were injected by the same physician (the 3rd author) to decrease the confounding factors. Two concentrations of IT dexamethasone were used in the present study (4 and 10 mg/ml). The 4 mg/ml dose was readily available in the Egyptian market. The 10 mg/ml dose was specifically prepared for this study by a professional pharmacist. This concentration was tested to study its efficacy as both 12 and 24 mg/ml doses were no longer available in the Egyptian market.

According to the concentration of dexamethasone injected, the study group was divided into subgroup A and subgroup B. Subgroup A comprised 12 patients who received 4 mg/ml IT dexamethasone and subgroup B comprised 12 patients who received 10 mg/ml IT dexamethasone. The participants were randomly assigned to either of the subgroups.

The protocol for IT injection began with a single IT injection of dexamethasone. Follow-up of the study subgroups for subjective control of vertigo was carried out for 1 month. If there were no attacks of vertigo reported in that month, no further IT dexamethasone injection was recommended. Another dose of the same concentration of IT dexamethasone injection was offered to the patients who demonstrated subjectively no improvement or partial improvement during the next 1 month after the first IT dexamethasone injection.

The study group patients were evaluated before the first IT dexamethasone injection and 1 month after the last injection on the basis of the above-mentioned parameters. According to Dallan *et al.* [17], the criteria of improvement were at least 10 dB improvement in

the pure-tone average and/or at least 15% improvement in the word discrimination score. The control group was also subjectively evaluated after 1 month through history and DHI.

Results

The study and control groups were matched in age, sex, and duration of illness with no statistically significant difference between them ($P > 0.05$). The mean age was 46.83 ± 11.95 years in subgroup A and 43.08 ± 13.45 years in subgroup B, whereas the control group had a mean age of 45 ± 13 years. Male sex was common with a frequency of 83, 75, and 60% in subgroup A, subgroup B, and the control group, respectively. The duration of disease ranged from 6 to 120 months in the study patients, with a mean of 33 months in subgroup A and 29 months in subgroup B.

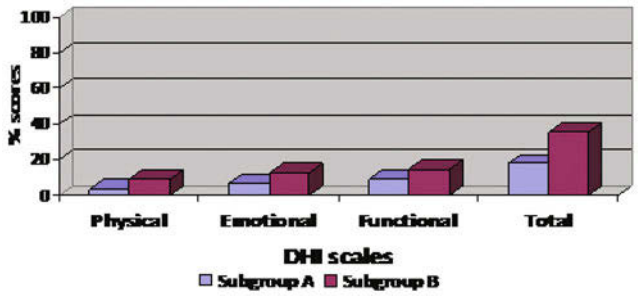
All study group patients received IT steroids with no serious side effects, except for pain and discomfort reported by a few. Six out of 24 (25%) patients received a second injection during the 1-month follow-up. Three patients were from subgroup A and the other three belonged to subgroup B.

Subjective symptoms

Before IT injection all study group patients (100%) experienced intractable vertigo that interfered with daily activities, as well as hearing loss and tinnitus. After receiving dexamethasone injection, only two (16.67%) patients from subgroup A and one (8.3%) patient from subgroup B experienced vertigo. The mean duration of vertigo attacks dropped from 5.98 to 0.06 h in subgroup A and from 20.26 to 0.007 in subgroup B. The mean score for interruption of daily activities decreased from 85 ± 24 to 9 ± 22% in subgroup A and from 87 ± 28 to 4 ± 14% in subgroup B. Both the change in duration of vertigo attacks and the interruption of daily activities score were statistically significant in each subgroup after injection ($P < 0.05$).

The total DHI scores improved after injection in 10 (83%) patients of subgroup A and in all (100%) patients of subgroup B. The mean total DHI score dropped from 54 ± 19.7 to 35 ± 20% in subgroup A and from 63 ± 12.8 to 27 ± 21% in subgroup B. The degree of improvement was statistically significant in each subgroup ($P < 0.05$). Both subgroups had severe activity limitation before IT injection. This changed after injection to moderate activity limitation in subgroup A and mild activity limitation in subgroup B. Obviously, the magnitude of improvement in all items and total score was greater in subgroup B (Fig. 1). The functional scale scores were

Figure 1



Mean of differences in the Dizziness Handicap Inventory (DHI) scale scores in the study subgroup before and after injection.

the highest of the subscales in all study patients before and after injection, reflecting the degree of disability experienced during life.

In terms of subjective hearing loss, eight (66.67%) patients of subgroup A and nine (75%) patients of subgroup B reported better hearing sensitivity after IT injection. The subjective hearing loss mean score dropped from 60 ± 0.24 to 38 ± 0.15% in subgroup A. Similarly in subgroup B, it dropped from 73 ± 0.12 to 43 ± 0.25%. The difference reached statistically significant difference in each subgroup ($P<0.05$).

Reduced tinnitus severity was experienced by 11 (91.67%) patients of subgroup A and seven (58%) patients of subgroup B following IT injection. However, two (16%) patients of subgroup B reported complete absence of tinnitus. The mean tinnitus score changed from 7 ± 2 to 3.9 ± 2.2 in subgroup A and from 7.3 ± 2 to 3.9 ± 3 in subgroup B with statistically significant difference in each subgroup ($P<0.05$). Aural fullness was reported by 10 (83%) patients from each study subgroup before injection. It disappeared totally from five (50%) and seven (70%) patients of subgroups A and B, respectively, following intra-tympanic steroid (ITPS). The absence of aural fullness was statistically significant in each subgroup.

On comparing the 10 mg/ml concentration of dexamethasone over the 5 mg/ml concentration, we found no statistically significant difference in subjective hearing loss, tinnitus, and aural fullness between the two subgroups ($P > 0.05$). However, the 10 mg/ml dexamethasone concentration was superior to the 5 mg/ml concentration in improving the duration of vertigo attacks after ITPS ($P < 0.05$). It was noted that no patient worsened at the subjective level.

With regard to the control group, all (100%) patients reported vertigo, hearing loss, and tinnitus. After 1 month of lifestyle modification and salt restriction, no

patient reported improvement in either the symptoms or DHI scores, and the condition of two patients worsened. The mean score of interruption of daily activities was 80 ± 15% at the start of the study, which changed to 75 ± 12% after 1 month. The mean total DHI score was initially 60 ± 11%, and become 57 ± 15% at the end of the study. The mean subjective hearing loss score was 54 ± 0.4% and the mean tinnitus rating score was 6.5 at the beginning of the study. It changed to 53 ± 2.6 and 7 ± 3, respectively, after 1 month. The difference in scores was statistically nonsignificant ($P > 0.05$).

Basic audiological evaluation

As all study patients were selected with unilateral MD, the results of the affected ear are revealed. The PTA before IT dexamethasone injection in both subgroups is shown in Fig. 2. Based on the four-tone average of hearing at 0.5, 1, 2, and 4 kHz [18], the study and control patients were in stage 3 MD. Stage 3 implies a four-tone average between 41 and 70 dB. Despite the improvement in PTA thresholds after IT injection, the four-tone average stage did not differ. The word recognition scores (WRS%) were 80 ± 0.2 and 64 ± 0.2% for subgroups A and B, respectively, before injection.

Following injection of 4 mg/ml IT dexamethasone, the PTA thresholds improved in six (50%) patients in subgroup A and in five (42%) patients in subgroup B on using a dose of 10 mg/ml IT dexamethasone. Better WRS% was obtained by one (8%) patient in subgroup A and by two (17%) patients in subgroup B. The mean WRS% after injection was 85 ± 0.1 and 75 ± 0.2% in subgroups A and B, respectively. No patient deteriorated in PTA or WRS.

The degree of improvement in PTA and WRS was statistically significant in each subgroup. However, considering the criteria of Dallan *et al.* [17] for improvement, the change in PTA could be an improvement only with the 10 mg/ml concentration and in particular at low frequencies. Statistically, the degree of improvement in PTA thresholds in relation to the dose of injected dexamethasone was not significant (Table 1). This might be related to the limited number of patients in the study.

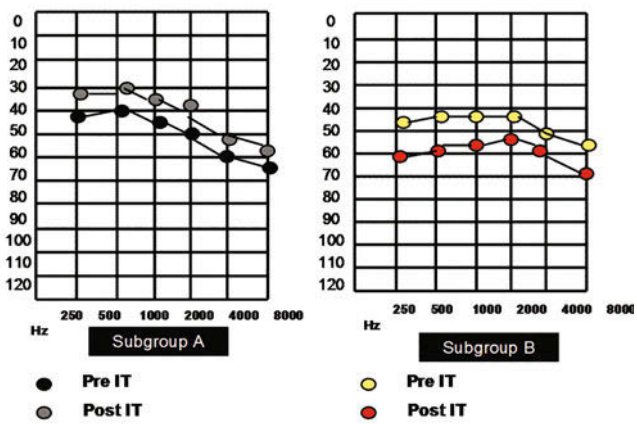
Obviously, the steeping audiometric configurations were common before and after IT injection. In subgroup A, the percentage of steeping curve was 67% before injection, which rose to 75% after injection. Similarly, in subgroup B, it was 42%, which changed to 50% after treatment. The rise in the flat curve and the peaked curves showed variable percentage in both subgroups before and after injection (Figs 3 and 4).

Table 1 The mean difference in the PTA thresholds and word recognition scores% before and after intratympanic injection

Frequency in khz	Subgroup A		Subgroup B		*t* value	*P* value
	X	SD	*X*	SD		
0.25 kHz	10.41	9.64	16.71	22	0.91	>0.05
0.5 kHz	10	9.82	14.63	19.42	0.73	>0.05
1 kHz	8.75	8.56	12.54	14.71	0.76	>0.05
2 kHz	10.83	12.93	10.41	13.04	0.08	>0.05
4 kHz	8.33	9.37	6.25	8.56	0.59	>0.05
8 kHz	1.66	6.15	8.33	13.02	1.48	>0.05
Pure-tone average	8.65	7.92	10.94	13	0.52	>0.05
WRS%	5	0.1	11	0.2	1.4	>0.05

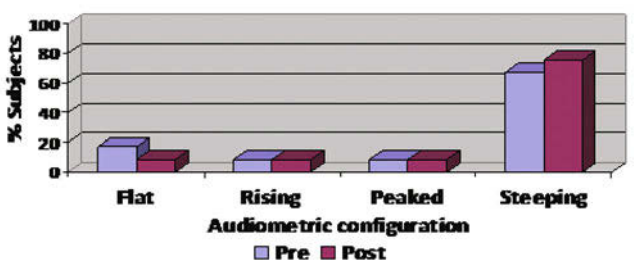
WRS, word recognition score.

Figure 2



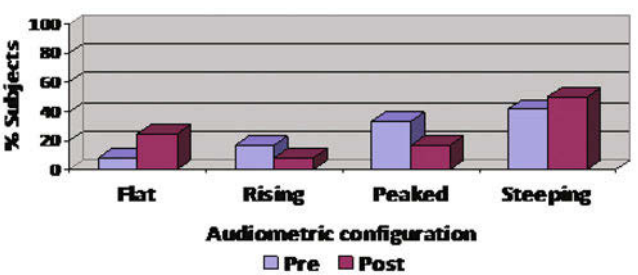
Pure-tone audiometric thresholds in both subgroups before and after intratympanic (IT) steroid injection.

Figure 3



Audiometric configuration in subgroup A before and after injection.

Figure 4



Audiometric configuration in subgroup B before and after injection.

Vestibular workup

The presence of vestibular dysfunction was documented by the VNG before IT steroid injection. The activity of the disease was confirmed by the presence of spontaneous and positional nystagmus. Spontaneous nystagmus was seen in 8.33 and 16.67% of subgroups A and B, whereas positional nystagmus was recorded in 50% of subgroup A and 83.33% of subgroup B. Post-head-shaking nystagmus was also seen in subgroup A (58.33%) and in 83.33% of subgroup B.

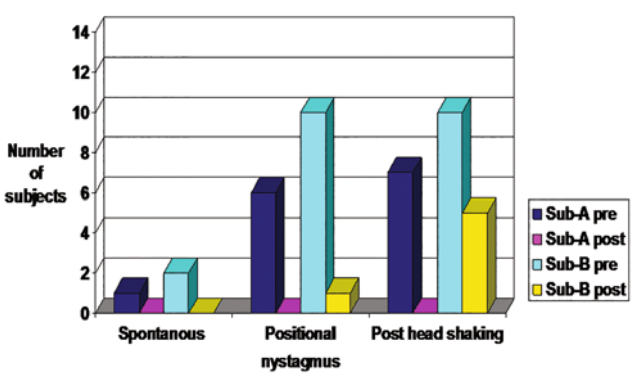
In subgroup A, IT injection of dexamethasone (4 mg/ml) did not change the number of patients with spontaneous, post-head-shaking, or positional nystagmus. However, this number changed significantly after injection of a higher dose of IT dexamethasone (10 mg/ml) in subgroup B (Fig. 5). Spontaneous nystagmus disappeared completely in all patients. Positional nystagmus and post-head-shaking nystagmus decreased by 90 and 50%, respectively. The effect of dose of IT dexamethasone on spontaneous, post-head-shaking, or positional nystagmus was statistically significant, using Fischer's exact test ($P < 0.05$).

c-VEMP was recorded in all patients. P13, N23 waves showed good morphology and were within the normal latency range. No statistically significant difference existed between the two subgroups before and after injection in c-VEMP wave latencies (P13–N23). The mean AR dropped from 30 to 18% in subgroup A and from 33 to 31% in subgroup B after injection. This change was statistically nonsignificant in both groups ($P > 0.05$).

Discussion

The improvement in vertigo following steroid injection agreed with the observation of many studies. Garduño-Anaya *et al.* [19] reported complete control of vertigo in 82% of patients using 4 mg/ml dexamethasone. Boleas-Aguirre *et al.* [15] achieved vertigo control in 91% of patients with a dosage of 12 mg/ml (but with variable number of injections). Similarly, Itoh and Sakata [6] and Phillips and Westerberg [2] showed vertigo relief in 80 and 90% of patients, respectively. In contrast, a lower rate of vertigo control, 43% with a dosage of 4 mg/ml, was reported in Casani *et al.* [20]. ElBeltagya *et al.* [21] reported improvement in 31% of patients. No improvement after IT was documented by Silverstein *et al.* (1998) [22].

Figure 5



Types of nystagmus in the study subgroups.

The results of DHI in the present study matched those of Phillips and Westerberg [2]. They reported that the total score of DHI was 60.4 before injection, which dropped to 41.3 after injection using a dose of 4 mg/ml. The improvement in the mean total score of DHI was achieved in 82% of patients, with better functional scale in up to 90% of patients. Similar to the current work, ElBeltagya *et al.* [21] showed that the activity limitation on the DHI scale dropped after injection to mild to moderate in the majority of patients.

In agreement with the subjective improvement in hearing loss seen in this study, Lu *et al.* [23] showed that 66.7% of patients had subjectively improved hearing after injection with a dosage of 4 mg/ml no one deteriorated. A statistically significant improvement in mean hearing loss (35 vs. 10%) was reported by Phillips and Westerberg [2]. Garduño-Anaya *et al.* [19] reported improvement in only 35% of patients.

The improvement in tinnitus in this study was similar to that seen by Itoh and Sakata [6]. They achieved tinnitus relief in 74% of patients after IT injection. Lower rates of tinnitus relief (33 and 48%) were reported by Lu *et al.* [23] and Garduño-Anaya *et al.* [19]. Moreover, Huang *et al.* [24] reported that the improvement in tinnitus occurred in 38% of patients, and was 38.4% in the study by ElBeltagya *et al.* [21].

The present study showed improved aural fullness in a significant proportion of patients. Silverstein *et al.* [25] and ElBeltagya *et al.* [21] reported that the improvement in aural fullness after IT injection was achieved in 68.6 and 61.5% of injected patients, respectively. This differed from the results of Garduño-Anaya *et al.* [19], who stated that the condition of 48% of patients with aural fullness had improved using the 12 mg/ml IT concentration.

Objectively using PTA, the proportion of improved patients in the present study matched that of Hillman *et al.* [26] and Casani *et al.* [20]. They reported improved hearing thresholds after IT injection in 40, 33, and 57% of patients, respectively. Higher percentage up to 69% was achieved by Huang *et al.* [24]. Hamid and Trune [8] showed that the improvement in hearing

was 90% but he used a dose of 24 mg/ml. Silverstein *et al.* [25] reported that three (15%) patients experienced an improvement (18 dB maximum) after injection. The relatively greater improvement in low frequencies in PTA agreed with the result of ElBeltagya *et al.* [21], who showed that patients in the dexamethasone group had improved low-frequency hearing thresholds.

The improved clinical picture and PTA following steroid injection might be related to the immunosuppressive effect of dexamethasone on the inner ear. It suppresses the proinflammatory cytokine genes, which leads to inhibition of the cochlear insults responsible for the production of proinflammatory cytokines, chemokines, and reactive oxygen species (nitric oxide, etc.), which are responsible for the deterioration of hearing. The ion homeostasis is controlled by the induction of mineralocorticoid receptor-mediated genes. The IT injection of dexamethasone results in the synthesis of Na^+, K^+-ATPase, and the epithelial sodium channel, leading to regulation of the inner-ear homeostasis [8].

Although statistically nonsignificant, the higher the concentration of the injected steroid, the better the results as regards all symptoms of MD (hearing loss, tinnitus, vertigo, and aural fullness) and even the pure-tone thresholds. This is due to more dexamethasone concentration in the cochlea leading to better immunosuppressive effects and better regulation of the inner-ear homeostasis [7]. However, it appears from most studies that the dose is dependent on what is available on the market instead of the maximal dose of dexamethasone used [27].

In the present study, the steeping audiometric configuration was the most common pattern. This might reflect the progression and the relatively long duration of the disease as reported by Kotimaki [28]. The increase in the proportion of patients with steeping curve following injection highlighted the effect of IT dexamethasone on the low compared with high frequencies. Higher concentration of dexamethasone exists in the low-frequency apical region of the cochlea rather than in the high-frequency basal region, as explained by Salt *et al.* [29].

The effect of the duration of Meniere's disease on the results of ITPS was explored in this study. Significant negative correlation existed between the duration of the disease and the difference in (pure tone average, and speech reception threshold and frequency of attacks) pre- and post-injection. This might highlight that early intervention gives better outcome. The duration of the disease has more effect on the auditory rather than the vestibular system. Hence, early IT injection is recommended for MD patients.

As reported by Hamid and Trune [8], spontaneous nystagmus observed after removing visual fixation by Frenzel glass or video goggles, post-head-shaking nystagmus, and positional nystagmus are all frequently present in the acute or subacute stages of an episode. This was true for patients of the current study. The disappearance of nystagmus in the VNG after injection could be attributed to the control of disease activity. This was achieved through regulation of the vestibular endolymphatic ion potential, which in turn controlled the recycling of K^+ and establishment of the blood labyrinthine barrier responsible for ion homeostasis.

In the present study, the VEMP AR was high in both subgroups and dropped after injection, although nonsignificantly. Glucocorticoids reduce K^+ transport into the endolymph and prevent the formation of new hydrops; thus, the glucocorticoids can stop the deterioration in the saccular function but they cannot improve this function [8]. The normal VEMP wave latencies obtained in this study matched those of Murofushi *et al.* [30]. They found that patients who had MD hardly showed any prolongation of VEMP latency, whereas many patients showed decreased amplitudes or absent responses.

It is important to highlight that a proportion of patients did not show improvement in this study despite IT steroid injection. This can be explained by factors that influence the passage of medication across the round window membrane [29]. They include mechanical obstruction in the middle ear, the integrity of the round window membrane, the degree of inflammation in the round window membrane, and the molecular weight, concentration, liposolubility, and electrical charge associated with specific medications [31].

Conclusion

IT dexamethasone injection might be helpful in controlling MD in some patients. Both the 4 and 10 mg/ml concentration of IT dexamethasone had nearly the same effect in improving MD symptoms. However, the 10 mg/ml concentration was superior to the 4 mg/ml concentration in improving the signs of disease activity 'different types of nystagmus', in improving the scores on the DHI scale, and in improving the duration of vertigo.

Hence, a high dose of IT dexamethasone is recommended when the main complaint of MD is vertigo or when, as early as possible, nystagmus (spontaneous, post-head-shaking, or positional) is present. Nevertheless, either the 4 or the 10 mg/ml concentration can be used when the main complaint

of MD is hearing loss, tinnitus, or aural fullness. The long-term effect of IT dexamethasone injection on MD should be addressed.

Acknowledgements

Conflicts of interest

None declared.

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