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A study of Intratympanic Dexamethasone Injection in Meniere's Disease (Continuation study)

Adel A.M Nassar, Ahmed E.F. Chedid, Rasha H. El-Kabarity and Sameh M.A. Beshry
ENT Dept. – Audiology Unit, Faculty of Medicine, Ain Shams University, Military Medical Academy
Corresponding author: Sameh M.A. Beshry .email: semsembeshry@gmail.com

ABSTRACT

Background: Meniere's disease is a condition that is thought to arise from abnormal fluid and ion homeostasis in the inner ear. The disease is named for Prospere Meniere, a French physician who was first known victim of this disease and reported that the inner ear could be the source of a syndrome manifesting episodic vertigo, tinnitus and hearing loss. The origin of Meniere's disease is presently controversial. While, in the past, it was felt that endolymphatic hydrops (excess fluid) in the inner ear were responsible for the disease, the most current opinion is that hydrops are just a marker for the Meniere's disease, rather than absolutely being responsible for the symptoms.

Aim of the work: this study aimed to follow up (2 and 2.5 years) the effect intratympanic (IT) dexamethasone in the prognosis of Meniere's disease (MD) with two different concentrations (4 and 10 mg/ml). **Patients and methods:** twenty patients with unilateral Meniere's disease received intra tympanic dexamethasone injection were included in this study ·The studied subgroups were categorized according to the concentration of dexamethasone (4 and 10 mg/ml) used into two subgroups. Detailed history was taken from all patients. They were exposed to Dizziness Handicap Inventory scale, basic audiological evaluation and cervical-vestibular evoked myogenic potential assessment. The presence or absence of spontaneous, post-head-shaking, and positional nystagmus was evaluated using a video-nystagmography system. The patients in the two groups were followed -up for 2 and 2.5 years.

Results: the dosage of 10mg/ml dexamethasone showed more stability in signs and symptoms of Meniere's disease than the dose of 4 mg/ml dexamethasone in follow up study. The long term study of intratympanic (IT) dexamethasone injection in both subgroups shows nearly no improvement as regard pure tone average, speech reception thresholds, word discrimination scores, subjective hearing loss, tinnitus, aural fullness, vertigo interruption with daily activities and vertigo associated symptoms compared to the previous study thesis. **Conclusion:** the long-term study of intratympanic (IT) Dexamethasone injection in both subgroups showed nearly no improvement in most assessments performed.

Keywords: long-term study of intratympanic dexamethasone injection, Meniere′s disease, Dizziness Handicap Inventory scale.

INTRODUCTION

Meniere's disease is a condition that is thought to arise from abnormal fluid and ion homeostasis in the inner ear. The disease is named for Prospere Meniere, a French physician who was first known victim of this disease and reported that the inner ear could be the source of a syndrome manifesting episodic vertigo, tinnitus, and hearing loss[(1)]. The origin of Meniere's disease is presently controversial. While in the past, it was felt that endolymphatic hydrops (excess fluid) in the inner ear were responsible for the disease, the most current opinion is that hydrops are just a marker for the Meniere's disease, rather than absolutely being responsible for the symptoms [(2)].

Many factors appeared to cause endolymphatic hydrops (excess fluid) in the inner ear. The most common causes were: auto-immune reactions, dietary deficiencies, viral infections, allergic responses, autonomic nervous system imbalances, blockage and/or damage to the endolymphatic structures and vascular (circulation) irregularities [(3)]. A wide variety of conservative approaches were established for the initial treatment of Meniere's disease. These included medical therapies in the form of low-salt diet and administration of diuretics, steroids, calcium channel blockers, and vasodilators, and they were useful in regulating the symptoms in 50–70% of patients. For medically intractable Meniere's disease, various surgical techniques had been developed. They had been criticized because of their poor results with respect to the long-term control of vertigo, the definite hearing damage that may be induced, and the morbidity associated with the procedure [(4)].

The use of local intratympanic delivery of aminoglycosides or corticosteroids has been recommended in an attempt to minimize the complications and risks involved in the 3 surgical procedures. The sensorineural hearing loss in Meniere's disease is typically fluctuating and

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progressive. A pattern of low-frequency fluctuating loss and a coincident non changing, high-frequency loss has been reported, as a 'peaked' or a 'tent-like' audiogram. This peak classically occurs at 2 kHz. Over time, the hearing loss flattens and becomes less variable [(5)]. Video nystagmographic recording of eye movements after caloric and rotational stimulation represents the most reliable method for the assessment of vestibular function. Vestibular-evoked myogenic potential (VEMP) testing was a relatively noninvasive method to assess patients with vestibular disorders. VEMPs are believed to be a good indicator of saccular and inferior vestibular nerve function in clinical evaluations. Thus, VEMPs indirectly measure vestibular function through a vestibulocollic reflex [(6)].

The present work was designed to assess the effectiveness of intratympanic (IT) dexamethasone injections with different concentrations in controlling signs and symptoms of medically refractory Meniere's disease patients [(7)].

PATIENTS AND METHODS

PATIENTS

Twenty patients with unilateral Meniere's disease who received intra tympanic dexamethasone injection were included in this study. They were categorized according to the concentration of dexamethasone used into two subgroups:

- **Subgroup A:** 10 subjects intratympanically injected with 4 mg/ml dexamethasone.

Subgroup B: 10 subjects intratympanically injected with 10 mg/ml dexamethasone). Follow up of the patients for subjective control of vertigo was done for 2 years and 2.5 years.

METHODS

All patients were 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% .

The physical, emotional, and functional aspects of vertigo symptoms were evaluated according to the Dizziness Handicap Inventory (DHI) scale (Arabic version) [(8)].

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 [(9)].

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-Micromedical Technology (version 4, USA). Cervical-vestibular evoked myogenic potential (c-VEMP) was recorded from the sternocleidomastoid muscle using the two-channel evoked potential system [(1)]. The latency of P13, N23, amplitude, and asymmetry ratio (AR) were calculated. The AR was calculated as: 100(Au -Aa)/ (Au +Aa), where Aa is the amplitude of affected ear and Au is the amplitude of unaffected ear [(10)].

The study was approved by the Ethics Board of Ain -Shams University.

Data obtained were exposed to statistical analysis using SPSS V17 package, through the tests the mean, standard deviation, student t- test, Paired t-test, Chi-square, and Linear Correlation Coefficient.

RESULTS

- **Results of Basic Audiological Tests**

Table 1 showed that there was a mild improvement regarding pure tone average (PTA) and word discrimination score (WDS) in subgroup B (10%) more than subgroup A (0%).

Table 1: prognosis of patients of both studied subgroups post ITPS as regards pure tone average (PTA) and word discrimination score (WDS) after FU2 compared to FU1

	Subgroup A			Subgroup B		
	Improved	The same	Deteriorated	Improved	The same	Deteriorated
PTA	0 (0 %)	10 (100%)	0 (0%)	1 (10%)	9 (90%)	0 (0%)
WDS	0 (0 %)	10 (100%)	0 (0%)	1 (10%)	9 (90%)	0 (0%)

Table 2 showed no statistically significant difference as regarding the difference in the basic audiological test results (pure tone average "PTA", word discrimination score "WDS", and Speech Reception Thresholds "SRT" for both studied subgroups between FU1 and FU2.

Table 2: mean (X), Standard deviation (SD) and T-test for the difference in the basic audiological test results for both study subgroups between FU1 and FU2

	Subgroup A		Subgroup B		t.value	P –value
	X	SD	X	SD		
4 KHz	0.27	1.13	0.27	0.44	0.571	>0.05
8 KHz	0.78	1.20	- 0.82	0.33	0.699	>0.05
Pure tone Average	0.20	0.90	0.25	0.40	0.360	>0.05
SRT	0.89	0.51	0.28	0.47	0.493	>0.05
WDS %	0%	0	0%	0.02	0.701	>0.05

Table 3 showed that the most common audiometric pattern in both study subgroups was the steeping curve and also all the audiometric patterns in each subgroup have the same values during the studied period.

Table 3: audiometric configuration in the both study subgroups after FU1 & FU2

	Subgroup A			Subgroup B		
	Basal	FU1	FU2	Basal	FU1	FU2
Flat	10%	10%	10%	20%	20%	20%
Rising	10%	10%	10%	10%	10%	10%
Peaked	10%	10%	10%	20%	20%	20%
Steeping	70%	70%	70%	50%	50%	50%

IMMITTANCEMETRY RESULTS

- **Tympanometry**
  Both subgroups showed bilateral type A tympanogram reflecting bilateral normal midlle ear function.
- **Acoustic reflex:**
  Acoustic reflexes in all the patients of both subgroups were elicited when expected to be present.
- **Vestibular test results**
  VNG test was performed for both subgroups 2 and 2.5 years after the last intratympanic injection of dexamethasone. The prescience of spontaneous, post head shaking and positional nystagmus were assessed.
- **Videonystagmography (VNG) test:**
  Table 4 showed no statistically significant difference in the VNG subtests results for both studied subgroups between FU1 and FU2.

Table 4: Chi-Square and P value between the difference in the VNG subtests results for both study subgroups between FU1 and FU2

Groups	VNG test						X^2	P-value
	Spontanous		Post head shaking		Positional			
	N	%	N	%	N	%		
Subgroup A	1	10%	1	10%	10	10%	1.105	>0.05
Subgroup B	0	0%	0	0%	0	0%	0	> 0.05

- **Cervical-Vestibular Evoked Myogenic Potentials results (C-VEMP):**
  C-VEMP was done for all patients of both study subgroups. All the waves were of good morphology. P 13 latency and N 23 latency and asymmetry ratio were measured in both study subgroups after FU1 &FU2.

Table 5: mean, SD, and ANOVA test for the latency of P13 in both studied subgroups after FU1 and FU2

	P13						F	P-Value
	Basal		FU1		FU2			
	Mean	SD	Mean	SD	Mean	SD		
Subgroup A	17.61	2.52	17.65	2.55	17.80	2.80	0.210	>0.05
Subgroup B	17.94	3.63	18.22	4.02	18.40	4.15	0.443	>0.05

Table 6: mean (X), Standard deviation (SD) and ANOVA test for the latency N23 of both studied subgroups between FU1 and FU2

	N 23						F	P Value
	Basal		FU1		FU2			
	Mean	SD	Mean	SD	Mean	SD		
Subgroup A	25.91	2.54	26.33	2.90	26.88	3.11	0.221	>0.05
Subgroup B	25.64	3.71	26.22	4.11	26.75	4.31	0.348	>0.05

Table 5&6 showed no statistically significant difference as regarding the VEMP latency of P 13 and N23 in both studied subgroups after FU1 and FU2.

Table 7 showed no statistically significant difference in the amplitude asymmetry ratio of both studied subgroups between FU1 and FU2.

Table 7: mean (X), Standard deviation (SD) and T-test for the difference in the amplitude asymmetry ratio of both studied subgroups between FU1 and FU2

	Subgroup A		Subgroup B		t.value	P value
	X	SD	X	SD		
Asymmetry ratio Difference	2%	0.02	3%	0.03	0.248	>0.05

QUESTIONNAIRE DATA RESULTS

- **Dizziness Handicap Inventory (DHI) scale:**

Both studied subgroups were evaluated after FU1 & FU2 as regarding the Dizziness Handicap Inventory scale (physical, emotional, functional aspects and the total score).

Table 8 showed no statistically significant difference for the difference in the Dizziness Handicap Inventory scale of both studied subgroups

Table 8: mean (X), Standard deviation (SD) and T-test for the difference in the Dizziness Handicap Inventory scale of both studied subgroups between the FU1 and FU2

Test	Subgroup A		Subgroup B		t. value	P value
	X	SD	X	SD		
Physical	0.07	0.11	0.25	0.61	0.029	>0.05
Emotional	0.22	0.15	0.32	0.05	0.124	>0.05
Functional	0.11	0.05	0.2	0.24	0.411	>0.05
Total	0.18	0.07	0.32	0.34	0.703	>0.05

- **The Personal Questionnaire**

Both studied subgroups were evaluated after FU1 and FU2 as regards subjective hearing loss (%), tinnitus severity score (scale from 0 to 10), presence of aural fullness and vertigo characteristics (frequency of attacks (in hours), duration of attacks (in minutes), and presence of vertigo associated symptoms)

Table 9 showed no statistically significant difference for subjective hearing loss, tinnitus severity and vertigo characteristics in subgroup A after FU1 and FU2.

Table 9: mean (X), standard deviation (SD) and P value for subjective hearing loss, tinnitus severity and vertigo characteristics in subgroup A after FU1 and FU2

		Subgroup A						t.value	P value
		Basal		FU1		FU2			
		X	SD	X	SD	X	SD		
Subjective hearing loss		38%	0.25	40%	0.17	42%	0.18	0.0673	>0.05
Tinnitus		3.91	3.13	3.95	2.25	3.96	2.30	0.624	>0.05
Vertigo	Frequency	0.83	3.46	0.85	2.42	0.88	2.45	0.457	>0.05
	Duration (hours)	0.06	0.02	0.08	0.16	0.18	0.18	0.514	>0.05
	Interruption with daily activitie	9%	0.22	10%	0.24	10%	26%	0.615	>0.05

Table 10 showed no statistically significant difference in the percentage of the patients with aural fullness among both studied subgroups between FU1 and FU2.

Table 10: Chi-Square test and P value for the difference in the percentage of the patients with aural fullness among both studied subgroups between FU1 and FU2

Aural Fullness	Subgroup A	Subgroup B	Chi-Square test	P value
Difference	1%	0%	0.21	> 0.05

DISCUSSION

The present study was conducted on twenty patients diagnosed with definite Meniere's disease. They were catecorized into two subgroups according to the injected dose of intratympanic (IT) dexamethasone. Follow up of the patients was done 2 and 2.5 years after the last injected dose of (IT) dexamethasone. Both subgroups were matched in age with a mean age of 48.8 and 45.15 years in subgroup A and B respectively . Similary, **Hain** [(11)] reported that the mean age of Meniere's disease patients ranged between 40 and 60 years.

Our results showed that IT dexamethasone injection either in a dose of 4 mg/ml or 10 mg/ml had increased the percentage of patients with steeping curve signifying that the effect of IT dexamethasone on lower frequencies is better than the higher frequencies. This can be attributed to the presence of higher concentration of dexamethasone in the low frequency apical region of the cochlea rather than the high frequency basal region after its IT injection [(12)]. **Kotimaki** [(13)] reported that ascending or low-frequency rising configurations are common in the early (duration of the disease< 2 years) stage of Meniere's disease, whereas patients with advanced disease have nearly flat or steeping audiograms. **Young *et al.*** [(14)] reported that rising or steeping curve was found in 83% of the stage I (pure tone average of 0.5, 1, 2, 3 KHz less than 26 dB) ears and in 75% of the stage II (pure tone average of 0.5, 1, 2, 3 KHz from 26 to 40 dB) ears. In contrast, peak- or flat-type hearing loss was found in 62% of the stage III (pure tone average of 0.5, 1, 2, 3 KHz from 41 to 70 dB) ears and in 100% of the stage IV (pure tone average of 0.5, 1, 2, 3 KHz more than 70 dB) ears, indicating a significant relationship between the types of hearing loss and the stage of Meniere's disease.

In comparison between FU1 and the FU2, the percentage of all types of nystagmus in both subgroup A increased by one patient (10%) while, the percentage of all types of nystagmus in both subgroup B remained the same values reflecting more stability and vertigo control of patients in subgroup B than subgroup A with no statistical significant difference as shown in the present results.

This agrees with results **of Hamid** [(15)] who reported 90% control of vertigo in 60 Meniere's disease patients followed for 2 years after intratympanic dexamethasone.

Barrs *et al.* [(16)] also reported control of vertigo in 16 (47%) of 34 patients with intractable Meniere's disease-Their patients achieved control of vertigo with one or more courses of intratympanic injections of corticosteroids followed for 2 years after ITP .

The above results were explained by **Hamid** [(17)] who reported that the improvement of vertigo after ITPS can be attributed to the regulation of the vestibular endolymphatic ion potential through controlling the recycling of K^+ and establishment of the blood labyrinthine barrier responsible for ion homeostasis.

C-VEMP was obtained from all patients in both studied subgroups. No statistical significant difference was observed in C-VEMP wave latencies (P13-N23) after FU1&FU2 in both subgroups as shown in the present results. The mean of difference in the latency of P13 and N23 between FU1 and FU2 was 0.15 and 0.55 respectively in subgroup A while the mean in subgroup B was 0.18 for P13 and 0.53 for N23 with no statistically significant difference.

Young *et al.* [(13)] reported that normal C-VEMP latency denotes that the sacculocollic reflex retains normal velocity conduction in the early stage of Meniere's disease. **Murofushi *et al.*** [(18)] reported that latency was seldom used for the evaluation of VEMP and prolonged VEMP latencies, especially prolonged p13, would strongly suggest lesions in the vestibulospinal tract and it is unlikely that prolonged VEMP latencies are a sign of inner ear lesions. They found that patients who had MD hardly showed any prolongation of VEMP latency, whereas many patients showed decreased amplitudes or absent responses. Results of the present study showed that the mean of the difference in the asymmetry ratio between FU1 and FU2 was 2% & 3% in subgroup A and subgroup B respectively with statically insignificant difference

Kingma *et al.* [(10)] reported that the diagnostic value of VEMP amplitude asymmetry measurement in individual patients is low, because

of the large overlap of the VEMP amplitude asymmetry range for unilateral Meniere's patients with that for normal subjects.

The Mean of difference in the Dizziness Handicap Inventory scale of both studied subgroups and B between FU1 and FU2 was with statistically insignificant

Phillips *et al.* [19] reported that the total score of DHI was 60.4 prior to intratympanic injection and decreased to 41.3 post intratympanic injection with a dosage of 4 mg/ml with mean of difference equals 19.1, the improvement in the total score of DHI was achieved in 82% of patients and the improvement in the functional level was achieved in 90% of patients. Both studied subgroups were evaluated as regarding degree of subjective hearing loss, tinnitus, prescence of aural fullness and vertigo (frequency, duration, interruption with daily activities and prescence of associated symptoms) after the first and second continuation studies. The Mean (X) for the difference in the subjective hearing loss, tinnitus and vertigo characteristics of both studied subgroups between FU1 and FU2 showed no statistically significant difference in.

This disagrees with results of **Itoh and Sakata** [20] who reported that the improvement in tinnitus post ITPS was achieved in 74% of patients, but disagrees with **Garduno-Anaya *et al.*** [21] who reported that the improvement of tinnitus was achieved in 48% of patients only .

Mandal [22] reported that during the early stage of Meniere's disease hearing loss occurs mainly during the attack. Moreover; during the middle stage of the disease, hearing fluctuates, but never returns to normal, while at the late stages hearing loss may reach severe degree at all frequencies to the point where it is difficult to recognize speech. There is no longer fluctuation in hearing levels as the hair cells of the inner ear have been destroyed. Around 40% people have both ears affected during the late stage of the disease. Although patient may feel that his hearing is useless, it is rare for an ear to become completely deaf.

Regarding vertigo, the result in the present study was in agreement with the results obtained by **Garduno-Anaya *et al.*** [21] who reported that the complete control of vertigo was achieved in 82% of patients post intratympanic injection with a dosage of 4 mg/ml.

Boleas *et al.* [23] reported that the complete control of vertigo was achieved in 91% of patients post ITPS with a dosage of 12 mg/ml (but with variable number of injections). Phillips et al. (2011) reported that the improvement in vertigo was 90% post ITPS. On the other hand, **Casani *et al.*** [24] reported that complete vertigo control was achieved in 43% only and substantial vetigo control achieved in 18% post ITPS with a dosage of 4mg/ml. **Silvestern *et al.*** [25] reported that no improvement occurs in vertigo post ITPS.

However, there is no change in data of aural fullness in both subgroups between FU1 and FU2 in results of the present study.

This agrees withresults of **Silvestern *et al.*** [25] who reported that the improvement in aural fullness post ITPS was achieved in 68.6% of injected patients, but slightly differs with results of **Garduno-Anaya *et al.*** [21] who reported that the percentage of Meniere's patients who had improved aural fullness post ITPS with a dosage of 12 mg/ml was 48%.

Mandal [22] reported that aural fullness usually starts during the early stage of Meniere's disease and remains or worsens during the middle stage. Also it may be worse before and during a vertigo attack, while during the late stage aural fullness may be stronger and more constant.

CONCLUSION

Intratympanic (IT) dexamethasone injection is one of the most effective therapeutic approaches in the management of Meniere's disease as regards hearing loss, tinnitus, aural fullness, vertigo and in improvement of the Dizziness Handicap Inventory scale (DHI) in Meniere's patients. The dosage of 4 mg/ml IT dexamethasone was nearly effective as the dosage of 10 mg/ml IT dexamethasone in improving the Meniere's disease in pure tone average, speech reception thresholds, word discrimination scores, subjective hearing loss, tinnitus, aural fullness, vertigo interruption with daily activities and vertigo associated symptoms. The dosage of 10mg/ml dexamethasone gives more stability in signs and symptoms of Meniere's disease than the dose of 4 mg/ml dexamethasone in follow up study. The long term study of intratympanic (IT) dexamethasone injection in both subgroups shows nearly no improvement as regard pure tone average, speech reception thresholds, word discrimination scores, subjective hearing loss, tinnitus, aural fullness, vertigo interruption with daily activities and vertigo associated symptoms compared to the previous study thesis**.**

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