Meniett device in Meniere disease: Randomized, double-blind, placebo-controlled multicenter trial

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MENIETT® DEVICE IN MENIÈRE'S DISEASE: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED MULTICENTER TRIAL

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ABSTRACT

OBJECTIVE: To evaluate the efficacy of Meniett® low-pressure pulse generator in Menière's disease.

STUDY DESIGN: Randomized, double-blind, placebo-controlled, multicenter trial carried out in seventeen academic medical centers.

METHODS: One hundred twenty-nine adults presenting Menière's disease (AAO-HNS criteria) not controlled by conventional medical treatment were included. The protocol included three phases: 1) placement of a transtympanic tube and evaluation of its effect; if resolution of symptoms, the patient was excluded; 2) randomization: 6-weeks treatment with Meniett® or placebo device; 3) removal of the device and 6-weeks follow-up period. The evaluation criteria were: the number of vertigo episodes (at least 20 minutes with a 12 hours free interval), and the impact on daily life assessed by self-questionnaires.

RESULTS: Ninety-seven patients passed to the second phase of the study, 49 and 48 patients received the Meniett® device or the placebo device, respectively. In the placebo group, the number of vertigo episodes decreased from 4.3 ± 0.6 (mean ± SEM) during the first phase to 2.6 ± 0.5 after 6 weeks of treatment, and to 1.8 ± 0.8 after the removal of the device. Similar results were observed in the Meniett® group: 3.2 ± 0.4 episodes during the first phase, 2.5 ± after 6 weeks of Meniett® treatment, and 1.5 ± 0.2 after the third phase.

CONCLUSION: An improvement of symptoms is evidenced in all patients, with no difference between the Meniett® and the placebo groups. The decrease in number of vertigo episodes could be explained by an effect of the medical care.

KEYWORDS: Transtympanic tube; inner ear; placebo; endolymphatic hydrops; vertigo

LEVEL OF EVIDENCE: 1b

INTRODUCTION

Menière's disease is a chronic illness that affects approximately 0.2% of the world's population. The estimated annual incidence of the disease is 2/1000 [1]. Its origin is an imbalance in inner ear hydrodynamics. Of as yet poorly understood physiopathology, this syndrome is characterized by sudden and repeated vertigos, hearing loss, feeling of pressure in the ear, and tinnitus [2]. Vertigo can last hours or even days, during which time the patient is often bedridden. The disease can have a significant effect on quality of life including a not insignificant risk of workplace injury [3].

Because of the natural history of Menière's disease, benefit of each treatment should be compared to a spontaneous improvement, and to the well-known placebo effect. Symptoms have for long time been treated by medications such as Betahistine, steroids and diuretics, and yet their effect on hearing loss and on the long-term evolution of the disease has not been established[4]. In severe cases, resistant to medical treatment, chemical or surgical labyrinthectomy is considered, but a debate on the risk-benefit ratio still exist [5-8]. Therefore, effective, less invasive, treatments are eagerly awaited.

In this context, it has long been shown that changes in local pressure in the middle ear could have a positive effect on Menière's disease [9-12]. *In vivo* studies showed that the insertion of a transtympanic tube could reduce the development of endolymphatic hydrops, resulting in an improvement of symptoms [13]. A similar effect was also noticed in patients with Menière's disease [14], where it has been shown that the inner ear hydrodynamic system balance could be corrected with low-pressure air pulses in the middle ear. The development of the miniaturized, portable device Meniett® may provide the accessibility of this treatment [15-19]. The results of an initial placebo-controlled study with the Meniett® device developed by Medtronic Xomed, have been positive and the trial was able to document the ease of use and

safety of the device [19].

The present prospective, multicenter, double-blind placebo controlled study aims to validate the effectiveness, and to assess the benefits of the Meniett® device on number of vertigos, and on quality of life of patients affected by Menière's disease. Additionally, the introduction of a run-out period should permit to estimate the possible residual effects of this method. Considering both the spontaneous and unpredictable occurrence of Menière's disease and the difficulty in predicting its natural evolution over a given period, a controlled trial is crucial. Moreover, as the use of the Meniett® device requires the insertion of a transtympanic tube, it is necessary to demonstrate that its effectiveness is not a result of the only transtympanic tube effect.

MATERIALS AND METHODS

This study was a multicenter (17 centers: see Acknowledgements), randomized, double-blind, placebo controlled study. The protocol was approved by the local institutional boards.

Patients' selection

An analysis with power calculation was performed for the study design.Given the lack of published data concerning the evolution of vertigos following placement of a t-tube, the calculation was made considering the percentage of subjects who are free of symptom. Based on the results of previous studies[14, 20], the percentage of patients that no longer experience vertigo following drain placement was estimated between 50 and 66. Thus, the number of 47 patients per group was adapted to detect a possible variation of 30% of the Meniett® over the placebo device (alpha risk 5%, beta risk 20%, two sided test).

After giving their written consent, all patients underwent complete ENT examination, audiometry, and videonystagmometry were realized to confirm the diagnosis. All patients were adults over 18 years old age, affected by a stage 2, or greater, unilateral definite Menière's disease, according to the AAO-NHS criteria [2]. They were included if they experienced at least two episodes of rotatory vertigo in the preceding two months (vertigo lasting at least 20 minutes, with a free interval of 12 hours), with or without associated tinnitus, and/or a sensation of fullness in the ear. Moreover, the impact of vertigo on the patient's daily life had to be at level 3 at least on the functionality level according to AAO-HNS criteria. Patients having undergone surgical treatment or chemical labyrinthectomy for Menière's disease were excluded.

Phases of the protocol

The clinical protocol comprised three phases (Figure 1).

First phase: Placement of the transtympanic tube associated to the complete withdrawn of any anti-vertigo treatment, afterwards a period of eight weeks maximum (56 days), with recording of the number of vertigo episodes. The objective was to ensure the washout of any earlier anti-vertigo treatment, and to document the onset of at least two episodes of vertigo. This phase had a mean duration of 33 days (median: 28 and 29 days, in placebo and Meniett® groups, respectively). If patients had at least two episodes of vertigo, they were included in the second phase.

Second phase: In this phase of the duration of six weeks (45 days) the patients were randomly assigned under double-blind conditions to receive either the Meniett® device or a placebo device. Randomization was performed by blocks of four. Each center received a block of four devices (2 Meniett® and 2 Placebo). If necessary, according to the rate of inclusion in a given center, more blocks of four devices were attributed to the center. The boxes were randomly numerated and the physician did not know their content, and had to distribute them to the patients. The placebo was identical in all aspects to the active device, but did not generate pressure pulses. The patients were instructed to use the device three times daily for 15 minutes each, the pressure pulsed waves were at a frequency of 6 Hz and a maximum pressure of 12 cm/H_20. Patients were seen at 3 weeks (day 21 ± 3), and at the end of the six weeks period (day 42 ± 3).

Third phase: At the end of second phase, the Meniett® or the placebo devices were removed and the evolution of the number of vertigo attacks was observed for an additional six-week period. Also in this phase the patients were seen at 3 weeks (day 21 ± 3), and at the end of the six weeks period (day 42 ± 3).

Assessment parameters

At each visit the permeability of the transtympanic tube was verified.

During the three phases, the patients were asked to record on a journal all the attacks that they had during the day, and their duration, the patients had to score the vertigo attacks by mean of a visual analog scale (VAS) going from 1: very weak vertigo, to 10: unbearable vertigo attack.

The main assessment criteria of the therapeutic impact of the Meniett® device were the total number of vertigo episodes lasting at least 20 minutes during each study phase. Two successive episodes were considered as distinct if they occurred at a minimum asymptomatic interval of 12 hours, otherwise they were considered as a single episode.

The second parameter was the evolution of the impact of vertigo on daily life evaluated with the AAO-HNS scale.

Randomization and Statistical analysis

Data are given as means ± SEM. To test the homogeneity of the two study groups a Chi-squared test was performed for age and sex, or t-test for mean comparison.Two way ANOVA (factors: treatment and time) followed by a Tukeys's HSD post-hoc test, was used to analyze the influence of Meniett® or Placebo device and time over the vertigo episodes.

All the statistical analysis was performed using IBM SPSS for Windows (V22.0, SPSS inc., Chicago, Illinois, USA). For all comparisons $p<0.05$ was considered as significant.

RESULTS

Characteristics of the population

One hundred twenty-nine patients were enrolled and had a transtympanic tube insertion.

Among them, 32 patients (26%) showed the complete absence of vertigo during the first phase of six weeks. Therefore, 97 patients were included in the second phase: after the randomization 49 were treated with the Meniett® device, and 48 with the placebo device. Considering the clinical data of the population (sex ratio, age, weight, height, body mass index, blood pressure), the two groups were homogeneous (Table 1).

The duration of Menière's disease ranged from 0.22 to 24.5 months (mean 5 ± 0.81 months), and from 0.15 to 26.5 months (mean: 7 ± 0.97 months), in placebo and Meniett® groups, respectively. The number of vertigo episodes, including dizziness, during the previous six months was comparable in the Meniett® group (36 ± 4.6, range: 4-180, median: 30) and in the placebo group (28 ± 3.0, range: 3-72, median: 23). The impact of vertigo estimated by the patient on the AAO-HNS scale, was 4.3 ± 0.10 (range: 3-5, median: 4) in the placebo group, and 4.5 ± 0.093 (range 3-5, median: 5) in the Meniett® group.

Evolution of the number of vertigo episodes > 20 minutes during the different phases

A decrease of the number of the vertigo lasting more than 20 min occurred in both groups in the second phase compared to the first one, and persisted during the third phase when the devices were removed (Figure 2). In the placebo group the number of vertigo episodes decreased from 4.3 ± 0.6 during the first phase, to 2.6 ± 0.5 after 6 weeks of treatment, and to 1.8 ± 0.8 after the third phase. Similar results were observed in the Meniett® group: 3.2 ± 0.4 episodes during the first phase, 2.5 ± after 6 weeks of Meniett® treatment, and 1.5 ± 0.2 after the third phase. A decrease of vertigo episodes was observed in both group if comparing the first phase to the end of the second phase, and if comparing the episodes recorded after the first 21 days of the second phase and the third phase (Figure 2, Tukeys's HSD post-hoc test). However, there was no significant difference between the 2 study groups at all the phases of the study (Two-ways ANOVA, $F=2.57$ $p=0.11$).

Considering the individual evolution, a decrease of the number of vertigo episodes, was observed in both groups during the second and the third phase, compared to the first phase. Table 2 shows the number of patients that have improved, worsened, or that were stable for each period of 21 days. No difference was found between the two groups (Fisher's exact test), and overall the 10% of patients aggravated their symptoms, the 30% were stable, and the 60 % improved their symptoms. It should be noticed that fivepatients interrupted the treatment after the end of the second phase (3 placebo, 2 Meniett®), and 15 during the third phase (9 placebo, 6 Meniett®).

Evolution of short duration vertigo and dizziness

The number of the short duration vertigos (5-20 min), and the number of dizziness episodes (vertigos of less than 5 min duration) remained stable in both groups during the three phases (Table 3). The decrease of the number of 20 min lasting vertigo during the treatment and the run-out periods was clearly not associated to an increase in shorter vertigos or dizziness.

Impact of vertigo in daily life

Concerning the impact of vertigo on quality of life, whatever the treatment, Meniett® or placebo, the quality of life of the patient was improved, and this, even after the treatment was removed, with no significant difference between the two groups of patients (Table 4).

DISCUSSION

This study demonstrates that patients with Menière's disease could be improved in terms of number of vertigo episodes after placement of transtympanic tube, and after Meniett or placebo treatment without significant difference between these two later groups.

The improvement of the symptoms was evidenced immediately after the placement of the transtympanic tube, indeed after the first phase the 26% of patients were excluded from the study for absence of vertigo episodes. A transtympanic tube effect has been first evidenced in guinea pigs [21], where the middle ear ventilation reduced the development of endolymphatic hydrops induced by the blockage of the endolymphatic duct. The authors proposed that the inhibition of hydrops was due to pressure release into the middle ear and/or improved oxygenation of the middle and inner ears. In patients with Menière's disease, Barbara et al. [17] evidenced a major effect of the transtympanic tube, the number of vertigo decreasing from 9 to 1 after a 40-day period.

During the subsequent phase of the study an overall improvement in the number of vertigo episodes was evidenced, without difference between the group treated with middle ear pressure therapy by Meniett®, and the group that received a placebo device. Moreover, this improvement persisted about one month and half after the end of the treatment, and after the third phase, the 60% of all the patients showed an improvement in symptoms, suggesting a positive effect of the transtympanic tube, and/or of the medical care in general.

These observations lead to pose some questions concerning the diagnosis of Menière's disease. The clinical diagnosis of Meniere's disease is universally accepted to be based on the AOS-HNS criteria. Nevertheless an instrumental diagnosis of endolymphatic hydrops can be realized by mean of electrocochleography (ECoG) [22,23]. Although for some authors the only reliable diagnosis of Meniere's disease is clinical [24], the symptoms of the disease are very variable and heterogeneous, and to assess the effectiveness of a device, an objective instrumental finding concerning the condition of the inner ear appears to be necessary. A weakness of the present study is the lack of an objective assessment of inner ear status at the inclusion phase, for example by means of ECoG. Indeed the diagnosis of Menière's disease was defined only by clinical parameters as recommended by AAO-NHS, and we can

hypothesize that some patients did not have an active endolymphatic hydrops. Considering the whole population at the end of the protocol, 60% of them had a decrease in the number of long duration vertigo episodes. This percentage can be considered high and may raise some issues for the patients' selection.

The relationship between the middle ear, easily accessible, and the inner ear pressures changes in connection with endolymphatic approaches has been the subject of several experimental and clinical studies[25]. Most of them support the hypothesis that continuous or intermittent pressure to the middle ear could prevent the development of endolymphatic hydrops (in animal) [26], or improve both the clinical symptoms and the electrophysiological hearing parameters in patients with Menière's disease [27]. Nevertheless, the evaluation of the effectiveness of treatments for Menière's disease incurs in considerable difficulties because of the natural course of the disease, characterized by spontaneous remissions and placebo effect. This may explain the different conclusion of several literature reviews concerning the Meniett® device, some of them assessing a positive effect of this treatment [28,29], others the inefficacy of it [30,31].

Many randomized controlled studies were realized, in order to investigate the expected placebo effect. The first published study [12] reported improvement concerning frequency and intensity of vertigo and also hearing and electrocochleographic recordings in 31 patients compared to 25 who had a placebo device. Unfortunately, these very encouraging results were not reproduced in the following studies. Gates et al[10] studied 67 patients and reported less severe vertigo, fewer days with definite vertigo, and fewer days lost from work, but no difference in hearing and electrocochleographic results between the two groups of patients. One year later, Thomsen at al[9] evidenced an improved functionality level in the 20 treated patients compared to the 20 who received the placebo, but the difference in the frequency of the vertiginous attacks was clearly not significant. However, the central issue is the selection

criteria of the patients. Gates et al. included medical treatment resistant patients and with a median duration of treatment of 4.5 years. The patients in Thomsen's study had variable disease duration, ranging from less than one year to 37 years with a median between 5 and 10. In the present study, the patients had disease duration much shorter, less than two years.
One suggestion could be that local pressure treatment should be indicated, and effective, in case of well-established and resistant disease, at an early stage.

CONCLUSION

The benefit of the treatment assessed in about the 60% of the patients of both study groups, Meniett® or placebo, strongly suggests a positive effect of the medical management in patients suffering from Meniere's disease, independently from the treatment. Nevertheless, because this effect persisted at the end of the active treatment phase, a pressure effect of the transtympanic tube can be suspected. Moreover, this effect has been rapidly evidenced in 32 patients who were not included after the first phase. Further studies are needed to investigate this beneficial effect of the transtympanic tube and to determine patients that would improve their symptomatology by this procedure. Special attention is needed considering the heterogeneity of this disease in order to define the hydrops evolutivity. Indeed, it is clear from this study that the clinical classification is not sufficient, electrophysiological data (ECoG, for example) would be needed to more precisely select the patients.

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FIGURE LEGENDS

Fig 1. Study design. Mean duration of the first phase: 35 days. The second and the third phase had duration of ~42 days each, and were divided in two periods of ~21 days.

Fig 2. Number of vertigo episodes at the different endpoints for Meniett® and Placebo groups. Values are means ± SEM. Number of patients in parentheses. Two way ANOVA (factors: treatment and time) followed by a Tukeys's HSD post-hoc test. *: $p<0.005$ **: $p<0.03$

Table 1. General characteristics of population

	Age (years)	Sex	Weight (kg)	Height (cm)	BMI (kg/m²)	Blood pressure (mm Hg)
Placebo (n=48)	50 ± 1.9	Men: 47% Women:53%	72 ± 2.2	168 ± 1.4	25.7 ± 2.0	Systolic: 129 ± 0.3 Diastolic: 78 ± 1.5
Meniett (n=49)	52 ± 1.6	Men: 40% Women: 60%	67 ± 1.8	165 ± 1.2	24.8 ± 0.7	Systolic: 127 ± 1.8 Diastolic: 77 ± 1.3

BMI: Body Mass Index. The blood pressure was measured after a 10 minutes period rest. Values are means ± SEM, the number of patients is in parentheses. No difference was observed for these data between the two groups of patients (Chi-squared test for age and sex, and t-test for mean comparison).

Table 2. Evolution of the number of vertigo episodes lasting more than 20 min in patients with placebo or Meniett® device, compared to those recorded during the first phase. The values are number of patients/total

		Placebo	Meniett
Fist Phase			
1st period	Worsening	12/48	16/49
	No change	12/48	8/49
	Improved	24/48	25/49
	Lost	0	0
2nd period	Worsening	10/45	17/47
	No change	9/45	4/47
	Improved	26/45	26/47
	Lost	3	2
Second Phase			
1st period	Worsening	2/36	7/42
	No change	11/36	5/42
	Improved	23/36	30/42
	Lost	9	5
2nd period	Worsening	5/36	2/41
	No change	11/36	12/41
	Improved	20/36	27/41
	Lost	0	1

Table 3. Number of vertigo episodes lasting less than 20 min.

	First phase	Second phase		Third phase
	with tube only ~33 days	1st period ~21 days	2nd period ~42 days	~42 days
N vertigo 5-20 min / 3 weeks				
Placebo	0.7 ± 0.38 (48)	1.0 ± 0.32 (48)	0.4 ± 0.20 (45)	0.05 ± 0.036 (36)
Meniett	0.5 ± 0.19 (49)	0.7 ± 0.19 (49)	0.4 ± 0.16 (47)	0.2 ± 0.08 (41)
N vertigo < 5min / 3 weeks				
Placebo	0.4 ± 0.16 (48)	1.2 ± 0.72 (48)	2.0 ± 1.01 (45)	0.5 ± 0.23 (36)
Meniett	0.6 ± 0.46 (49)	0.7 ± 0.40 (49)	1.3 ± 0.67 (47)	0.4 ± 0.20 (41)

Values are means ± SEM, the number of patients is in parentheses.

During the 3rd phase, after the removal of the device, the number of the vertigo episodes lasting less than 20 minutes were collected during the whole 1st+2nd period (ie ~45 days). For easier comparison with the previous phases, the indicated data was the number of vertigo registered during the 3rd phase expressed on a 21-day period.For easier comparison between the different columns, the numbers of vertigos during the run out period are referred to a 3-week period.

Table 4. Impact of vertigo in daily life

	Initial	End of first phase	End of second phase ~42 days	End of third phase ~42 days
Placebo	4.3 ± 0.10 (48)	4.0 ± 0.12 (48)	2.6 ± 0.21 (45)	2.8 ± 0.22 (36)
Meniett	4.5 ± 0.09 (49)	4.2 ± 0.12 (49)	2.8 ± 0.21 (47)	2.8 ± 0.25 (41)

Values are means ± SEM, the number of patients is in parentheses.

The impact of the vertigo was estimated by the patient on the VAS scale.