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Food-induced stimulation of the antisecretory factor to improve symptoms in Meniere's disease: our results

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Abstract

Purpose Specially processed cereals (SPC) that increase endogenous antisecretory factor (AF) synthesis have been proposed to improve symptoms of Meniere's disease (MD) with controversial results. The aim of this study was to evaluate the effects of SPC in patients with definite unilateral MD and compare the results to a treatment protocol with intravenous glycerol and dexamethasone.

Methods Thirteen patients with unilateral MD were treated with SPC and 13 patients were treated with intravenous glycerol and dexamethasone for 12 months. Audio-vestibular evaluation was performed before (T0) and at the end of the treatments (T12). The number of vertigo spells were evaluated before and after therapy and the Efficacy Index (EI) was calculated. Questionnaires for hearing loss (HHIA), tinnitus (THI) and quality of life (TFL) were administered.

Results EI decreased in the SPC group in the second semester compared to the first although not significantly ($p=0.6323$). There was a significant reduction for THI score in the SPC group at T12 ($p=0.0325$). No significant differences were found between the two groups at T0 ($p=0.4723$), while a significant difference was found at T12 ($p=0.0041$). Quality of life showed an improvement in daily activities in the SPC group compared to infusion therapy group.

Conclusion Our study shows a reduced number of vertigo attacks and a positive effect on the discomfort generated by tinnitus and quality of life in patients with unilateral MD treated with SPC and when compared to patients treated with intravenous glycerol and dexamethasone. No effects on hearing thresholds were noted in both groups.

Keywords Meniere's disease · Specially processed cereals · Endogenous antisecretory factor · Vertigo · Hearing loss

Introduction

Meniere's disease (MD) is an inner ear disorder characterized by recurrent attacks of vertigo accompanied by fluctuating sensorineural hearing loss (SNHL), aural fullness and tinnitus [1]. Current evidence suggests that the pathophysiological mechanisms that underlie typical symptoms of MD is the presence of endolymphatic hydrops (EH) in the inner ear, resulting in the distension of the Reissner's membrane and the semicircular canals [2, 3]. Histopathological findings have suggested that possible causes of EH include overproduction of endolymph and/or a decrease in the absorption of endolymph. However, EH alone cannot explain the pathophysiology of cochlear and vestibular symptoms; accumulating evidence suggests that the causes of MD symptoms are multifactorial and involve different pathogenic mechanisms [4–7].

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Several therapeutic options for MD have been proposed [8–11]. The first-line treatment commonly includes dietary modifications such as restriction of salt, caffeine and alcohol intake followed by drugs both for acute attacks (dimenhydrinate, benzodiazepines), and as a prophylactic therapy (betahistine, βblockers, diuretics).

In the last decade, the use of specially processed cereals (SPC) has been proposed to increase endogenous antisecretory factor (AF) synthesis to improve symptoms of MD with controversial results [12–15]. AF is a 41 kDa protein, originally characterized as a pituitary substance, that acts as a regulator of water and ion transport across the cellular membrane [16, 17]. Immunohistochemical studies [14, 15] have demonstrated the presence of AF in the rat's inner ear and in the man's saccule; evidence showed that endogenous AF activity increases after exposure to bacterial toxins and can be also induced in humans and animals by a diet with SPC [18, 19]. Clinical studies have shown that intake of SPC can improve symptoms of patients with diarrhea as well as patients affected by inflammatory bowel diseases [17], endocrine diarrhea [18], and mastitis [20].

The aims of this study were a) evaluate the effects of endogenous AF synthesis increase using SPC in a sample of patients with definite unilateral MD not responsive to dietary restrictions and pharmacological treatment on hearing, tinnitus, vertigo, and quality of life and b) compare the results to a treatment protocol of intravenous glycerol and dexamethasone.

Materials and methods

Patients

Twenty-six (8 males and 18 females) patients with a diagnosis of definite MD according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) criteria presenting to the audiology service of the Department of Otolaryngology of University of Salerno and the Audiology Unit of the University of Magna Graecia between January 2017 and January 2018 were enrolled in this multicenter prospective cohort study.

Inclusion criteria were age between 18 and 65 years and a clinical diagnosis of unilateral MD according to the Barany Society criteria [21] not responsive to dietary restrictions (salt, caffeine and alcohol intake) and pharmacological treatment (betahistine, 48 mg/day). Exclusion criteria were patients with a clinical diagnosis of bilateral MD, ipsilateral or contralateral middle ear pathology, previous treatment with intratympanic steroids, contralateral SNHL (Pure Tone Audiometry—PTA bone threshold ≥ 35 dB HL), retrocochlear pathology, previous ear surgery, previous intake of SPC.

The study was approved by the local Ethic Committee of the University of Magna Graecia (2017) and the University of Salerno (2018) and was performed in accordance with the Helsinki Declaration and its amendments. Informed consent was obtained from all the participants.

Experimental treatment

The patients were divided into two groups: the first group included 13 patients (10 females and 3 males, mean age 51.8 ± 15.4 years) that were treated with SPC-Flakes, Piam Farmaceutici S.p.A, Italy (SPC group); the second group included 13 patients (9 females and 4 males, mean age 53.76 ± 12.6) that were treated with infusion therapy consisting of 10% glycerol, 250 ml/day in 200 ml/h infusion rate and dexamethasone 8 mg/2 ml per day in single bolus and pantoprazole 40 mg per day diluted in 100 mL of 0.9% sodium chloride (infusion therapy group). Patients in the SPC group took cereals twice a day at a dose 1 g/kg of body weight/per day in accordance with previous studies [12, 14, 15] and with the recommendation by the manufacturer of SPC for 30 consecutive days each other month for six cycles. Patients in the infusion therapy group were treated each month for 3 consecutive days. Total duration of treatment for both groups was 12 months.

Audio-vestibular evaluation

All patients underwent an anamnestic interview, full ENT examination, an audio-vestibular test battery with pure tone audiometry (PTA), acoustic immittance test and vestibular bed-side examination. All patients were asked to self-compile a clinical report with the number of vertigo spells for the entire duration of the study (18 months).

Audio-vestibular examination was performed before starting therapy (T0) and after 12 months (T12).

PTA (Piano Clinical Audiometer Inventis, Padua, Italy) was measured at frequencies of 125, 250, 500, 1000, 2000, 3000, 4000, and 8000 Hz; data from the frequencies 500, 1000, 2000 and 4000 Hz were used in the study.

Acoustic immittance measures were performed to measure the functional integrity of the eardrum and middle ear anatomy using tympanometry tests and acoustic stapedial reflex tests (AT 235 Tympanometer Interacoustics, Denmark).

Vestibular examination included eye movement evaluation with and without fixation by videonystagmoscopy with video-oculography goggles (GN Otometrics, Taastrup, Denmark). The patient was evaluated in the sitting position and in six different positions according to a standardized procedure (upright, gaze straight ahead, supine position with head elevation 30° nose up, supine position with head elevated 30° and head turned 45° left, supine

position with head elevated 30° and head turned 45° right, backwards head hanging position with head turned 45° towards the right, backwards head hanging position with head turned 45° towards left.

Vertigo spells were elaborated based on the self-compiled clinical report calculating the efficacy index (EI) 6 and 12 months after beginning of therapy. The EI for the first semester of therapy was calculated using the formula $[Y/X \times 100]$ where (Y) is the mean of the number of vertigo spells/month during the first 6 months of therapy and (X) is the mean of the number of vertigo spells/month for a 6 month-period before starting treatment (pretreatment period). The EI for the second semester of therapy was calculated using the formula $[Z/X \times 100]$ where (Z) is the mean of the number of vertigo spells/month during the last 6 months of therapy and (X) is the mean of the number of vertigo spells/month for the pretreatment period. Based on the result obtained, the patients were divided into six classes according to the AAO-HNS criteria (Table 1).

Self-assessment questionnaires

Self-assessment questionnaires regarding hearing loss (Hearing Handicap Inventory for Adults, HHIA [22]), tinnitus (Tinnitus Handicap Inventory, THI [23]), and quality of life (Functionality Level Scale, FLS, AAO-HNS [21] were administered at T0 and T12.

Statistical analysis

MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org) was used to perform statistical analysis. The t test was used to compare the numerical values within the two groups before and at different treatment timepoints.

Table 1 Efficacy index

Numerical value	Class
0	A
1–40	B
41–80	C
81–120	D
> 120	E
Secondary treatment initiated because of disability from vertigo	F

The numerical value is the ratio of the average number of vertigo spells during the pre-treatment period (6 months) divided by the average number of vertigo spells for the same number of months at the end of the reporting period

Results

Hearing evaluation

PTA thresholds in both groups are shown in Fig. 1. In the SPC group, average PTA was 46.7 dB at T0 and 46.8 dB at T12 ($p = 0.9930$). In the infusion therapy group, average PTA was 51.4 dB at T0 and 52.3 dB at T12 ($p = 0.9233$). No statistically significant changes were seen in both groups between T0 and T12. Furthermore, no statistically significant changes were found between the two groups at T0 ($p = 0.6257$) and at T12 ($p = 0.5468$).

Vertigo spells

The mean of the number of vertigo spells in both groups and the EI are shown for each patient in Table 2.

The EI for the first semester of therapy was 29.9 in the SPC group and 69.4 in the infusion therapy group ($p = 0.0257$). The EI for the second semester of therapy was 22.1 in the SPC group and 68.6 in the infusion therapy group ($p = 0.0586$). When comparing EI score within groups, in the SPC group, the EI decreased in the second semester compared to the first although not significantly ($p = 0.6323$), while remained stable in the infusion therapy group ($p = 0.9744$).

When dividing patients into classes and comparing the two groups according to the AAO-HNS criteria after 6 and 12 months, in the SPC group, eight patients had a class improvement (61.5%), three had no class change (23.1%) and two had a class worsening (15.4%). Among the eight patients who had a class improvement, two patients (25%) had an improvement of 2 classes, six had an improvement of a single class (75%). In the two patients who had a class

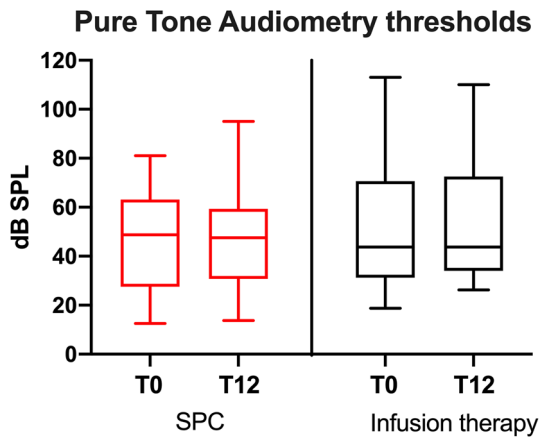

Fig. 1 Pure tone audiometry (PTA) thresholds in the SPC group and in the infusion therapy group before and after 12 months of treatment

Table 2 Mean of vertigo attacks before, during 6 months and during last 6 months of therapy in group I (pt 1–13) and in group II (pt 14–26) calculating also efficacy index (EI) and class of belonging according to the AAO-HNS criteria

Patient	Mean of vertigo spells/month during pretreatment period (*X*)	Mean of vertigo spells/month during the first 6 months of therapy (*Y*)	Mean of vertigo spells/month during the second 6 months of therapy (*Z*)	*Y*/*X* × 100	Class	*Z*/*X* × 100	Class
1	2	1	0	50	III	0	I
2	1	0	2	0	I	200	V
3	3	2	1	67	III	33	II
4	6	2	1	33	II	17	II
5	3	1	0	33	II	0	I
6	2	1	0	50	III	0	I
7	3	1	0	33	II	0	I
8	3	1	0	33	II	0	I
9	4	0	1	0	I	25	II
10	2	0	0	0	I	0	I
11	5	1	0	20	II	0	I
12	3	1	0	33	II	0	I
13	8	3	1	37	II	12	II
14	14	20	30	143	V	214	V
15	9	7	8	77	III	88	IV
16	2	0	0	0	I	0	I
17	3	1	2	33	II	67	III
18	5	0	0	0	I	0	I
19	14	15	7	107	V	50	III
20	4	0	1	0	I	25	II
21	7	10	12	143	V	171	V
22	15	20	13	133	V	87	IV
23	6	2	0	33	II	0	I
24	12	4	8	33	II	50	III
25	20	15	18	75	III	90	IV
26	8	10	4	125	V	50	III

worsening, one patient had only one class worsening (50%) while in the other patient, worsened of 4 classes (50%). In the infusion therapy group, four patients had a class improvement (30.8%), four had no class change (30.8%) and five had a class worsening (38.5%). Among the four patients who had a class improvement, two patients (50%) had an improvement of 2 classes and two of a single class (50%). All the patients who had a class worsening had one class worsening (100%).

Questionnaires

Results of self-administered questionnaires for hearing (HHIA), tinnitus (THI) and quality of life (FLS) before (T0) and after 12 months of treatment (T12) in both groups are shown in Figs. 2 and 3.

In the SPC group, the mean HHIA score was 49.4 at T0 and 39.6 at T12 ($p = 0.4182$). In the infusion therapy group, the mean HHIA score was 57.4 at T0 and 58.7 at T12 ($p = 0.9090$). No statistically significant changes were seen in both groups between T0 and T12. Also, no significant differences were found between the two groups at T0 ($p = 0.4859$) and at T12 ($p = 0.1213$).

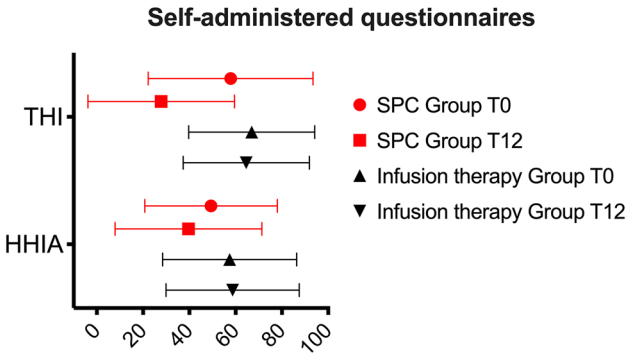

Fig. 2 Self-administered questionnaires for hearing (HHIA), tinnitus (THI) before (T0) and after 12 months of treatment (T12) in the SPC group and in the infusion therapy group

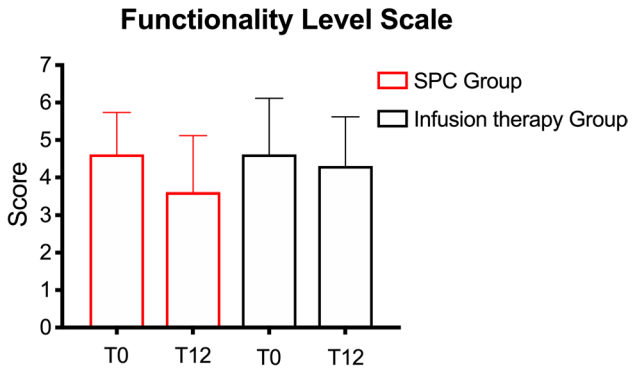

Fig. 3 Self-administered questionnaires for quality of life (FLS) before (T0) and after 12 months of treatment (T12) in the SPC group and in the infusion therapy group

In the SPC group, the mean THI score was 57.8 at T0 and 27.9 at T12, with a significant reduction at T12 ($p=0.0325$). In the infusion therapy group, the mean THI score was 66.9 at T0 and 64.6 at T12 ($p=0.8309$). No significant differences were found between the two groups at T0 ($p=0.4723$), while a significant difference was found at T12 ($p=0.0041$).

In the SPC group, the mean FLS score was 4.6 at T0 and 3.6 at T12 ($p=0.0663$). In the infusion therapy group, the mean THI score was 4.5 at T0 and 4.3 at T12 ($p=0.5836$). No statistically significant changes were seen in both groups between T0 and T12. Furthermore, no significant differences were found between the two groups at T0 ($p\geq0.9999$) and at T12 ($p=0.2233$). Taken singularly, when comparing FLS questionnaire at T0 and T12, in the SPC group, nine patients have reported an improvement of their quality of life (69.2%), two reported no change (15.4%), and two complained a deterioration in their quality of life (15.4%). In the infusion therapy group, five patients have noted an improvement of their quality of life (38.5%), seven reported no changes in the quality of life (53.8%), and one reported a deterioration in the quality of life (7.7%) (Table 3).

Table 3 Functionality level scale at T0 and T12 for the SPC group (pt 1–13) and the infusion therapy group (pt 14–26)

Patient	Functionality level scale T0	Functionality level scale T12
1	5	2
2	2	5
3	6	5
4	6	5
5	3	5
6	5	3
7	5	4
8	4	3
9	5	2
10	5	1
11	5	5
12	4	2
13	5	5
14	5	5
15	5	5
16	1	1
17	5	5
18	5	5
19	5	4
20	5	5
21	5	5
22	6	5
23	2	4
24	6	5
25	6	5
26	4	2

Discussion

The aims of this study were (a) evaluate the effects of endogenous AF synthesis increase using SPC in a sample of patients with definite unilateral MD on hearing, tinnitus, vertigo, and quality of life and (b) compare the results to a treatment protocol of intravenous glycerol and dexamethasone. To the best of authors' knowledge, this is the first study comparing SPC treatment to glycerol—a drug commonly used as a diagnostic test in MD but not for therapeutic purposes—in MD patients. Furthermore, this is the first study to evaluate the effects of SPC in MD using questionnaires on hearing, tinnitus, and quality of life.

Our findings show that both SPC and intravenous glycerol and dexamethasone did not improve hearing, as documented by PTA thresholds. This is consistent with other studies [14, 15]. Similarly, no subjective hearing change was reported by patients in both groups at the HHIA questionnaire.

THI score significantly decreased after the end of the treatment in the SPC group, showing a reduced annoyance of tinnitus in these patients. No significant changes were found in the infusion therapy group.

Quality of life, documented by the TFL questionnaire, showed an improvement in daily activities in patients in the SPC group compared to those of the infusion therapy group, although the overall scores were not significantly different. Our results confirm previous studies [13, 15] that report an improvement of the functional level in a significant percentage of patients, as well as in a randomized double-blind placebo-controlled trials [12, 14].

The overall EI in both the SPC and infusion therapy groups did not significantly change before and after treatment and did not differ among groups. However, a larger

number of patients reported a reduction of vertigo attacks as demonstrated by class improvement in the SPC group (61.5%) compared to the infusion therapy group (30.8%).

Study limitations

The present study has several limitations. The main limit is that we did not include a placebo group, as well as it was not possible for the study design to have a randomized double-blind-controlled trial. The number of patients included in the study is low and may have affected the statistical power of our analysis. Further research is required to provide evidence of the effectiveness of SPC in patients affected by MD.

Conclusion

Our study shows a positive effect on the discomfort generated by tinnitus and quality of life and a reduced number of vertigo attacks in patients with unilateral definite MD treated with AF through SPC before and 1 year after therapy, and when compared to patients treated with intravenous glycerol and dexamethasone. No effects on hearing thresholds were noted in both groups. Our preliminary results, although biased by several limitations, are encouraging for the use of AF to decrease the frequency and intensity of vertigo attacks in patients affected by unilateral MD.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee of the University of Naples ''Federico II" (2017) and the University of Salerno (2018) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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