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ORIGINAL ARTICLE

Comparison between mesoglycan and betahistine in the treatment of vertigo and dizziness in elderly patients

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ABSTRACT

BACKGROUND: The cochlear and the vestibular anatomical structures are very sensitive systems to modification on blood perfusion pressure. However, the relationship between the systemic circulation and inner ear ischemia seems to be more complex than frequently considered. In clinical practice, many drugs have been used to improve dizziness of vascular origin and it seems that all drugs have similar effects. Betahistine and mesoglycan are the most frequently used drugs but their prescription is empirical, and it is not possible to differentiate how and when to prescribe one or the other; frequently the prescription of one or the other depends only on the personal experience of the physician and not on a precise clinical indication or a specific desired effect.

METHODS: To clarify the different effects of the two drugs, in this paper we have evaluated clinical outcomes collected by 39 vestibology centers on 819 patients with dizziness, at the first visit and at 3 and 6 months, comparing three treatment groups: with betahistine or mesoglycan alone or with both drugs. Patients underwent evaluation of hearing threshold, videonystagmoscopy (VNS) for spontaneous, positional and vibration-induced nystagmus, Head Impulse Test (HIT), Head Shaking Test (HST), clinical diary and Dizziness Handicap Inventory (DHI).

RESULTS: There were 425 women (56.0%), and the mean (standard deviation) age was 70.7 (22.9) years. Vertigo was reported by 30.7% of patients, dizziness by 36.7% and both vertigo and dizziness by 32.6%.

CONCLUSIONS: Our paper demonstrates that the mesoglycan contribute to reactivate the neural connections, re-establishing the vestibular network better than the bethaistine that instead reduce the vestibular function improving the symptom, but is not useful towards the healing of the disease.

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KEY WORDS: Mesoglycan; Betahistine; Vertigo.

Dizziness and vertigo affect 20% to 30% of the general population.[1] Vertigo is a subtype of dizziness, defined as an illusory sensation of movement, which may occur in peripheral and/or central vestibular disorders. Vertigo may be of peripheral-labyrinthine, central-vestibular, psychogenic or of physiologic origin.[2]

Recent studies have focused on the vascular origin of inner ear disorders. In fact, Keller *et al.*[3] observed an association between acute myocardial infarction and sudden sensorineural hearing loss. Moreover, cardiovascular risk factors have been found to be associated with hearing impairment,[4] and white matter abnormalities appear to likely contribute to the development of dizziness.[5] However, this is still a matter of study, as the relationship between the systemic circulation and inner ear conditions seems to be more complex than frequently considered.[6] A possible explanation of this association could be the anatomical structure of the inner ear. This system closely depends on the cochlear perfusion pressure. If the mean arterial pressure decreases, endothelial damage may be produced,[7] due to a state of hypoxia. This leads to metabolic damage in the cochlear cells and thus to the classical cochleovestibular

symptoms, such as tinnitus, hearing loss and vertigo or instability. From these observations, a drug able to correct the hemodynamic and metabolic imbalances could be very useful for the treatment of inner ear disorders, both alone and in combination with other drugs. In particular, glycosaminoglycans (GAG), which are essential constituents of the endothelium and the vessel walls, may have an antithrombotic function. It has been shown[8] that sulodexide (a GAG) in combination with melatonin could be an interesting treatment option for patients suffering from central or sensorineural tinnitus. This result was confirmed by the study of Ferrari *et al.*.[9] Another natural GAG is mesoglycan, which is composed of heparan sulphate, dermatan sulphate, electrophoretic slow-moving heparin and variable and minimal quantities of chondroitin sulphate. Data on antithrombotic and profibrinolytic activities of the drug show that mesoglycan may be useful in the management of vascular diseases.[10] A recent study[11] showed that mesoglycan significantly improves the cochleovestibular symptoms and the quality of life of patients suffering from tinnitus, peripheral vertigo and instability. Also, in previous studies the efficacy of mesoglycan in improving inner ear microcirculation has been observed, in particular in tinnitus[12] and dizziness.[13] Betahistine dihydrochloride (betahistine) is currently used in the management of vertigo and vestibular pathologies with different etiologies. This drug appears to be effective in treating vertigo in routine clinical settings, with persistent results for 2 months after treatment cessation.[14] Betahistine is a structural analogue of histamine. It has been shown[15] that all four types of histamine receptors (H1R, H2R, H3R, and H4R) are present in the mouse inner ear, thus supporting the hypothesis that histamine plays a physiological role in it. It is proposed that the mechanism of action of betahistine is to reduce peripherally the asymmetric functioning of the sensory vestibular organs in addition to increasing vestibulocochlear blood flow by antagonizing local H3 heteroreceptors.[16]

The aim of the study was to compare the efficacy of mesoglycan and betahistine, alone and in combination, in elderly patients with dizziness and vertigo.

Materials and methods

Study design and population

This is a randomized clinical trial performed in elderly patients with dizziness and/or vertigo. Inclusion criteria were: 1) patients aged 60 years or more; 2) subjects with a diagnosis of dizziness, vertigo, or both; 3) presence of cardiovascular risk factors. Exclusion criteria were: 1) diagnosis of Menière's disease, according to the established diagnostic criteria;[17] 2) presence of current or previous neurological disorders; 3) presence of psychiatric disorders; and 4) treatment with anticholinergics, antihistamines, benzodiazepines, calcium channel antagonists and dopamine receptor antagonists.

Informed consent was obtained from each participant in accordance with the Declaration of Helsinki. Patients were randomly assigned to one of three treatment groups: A=betahistine 24 mg 2 per day; B=betahistine 24 mg 2 per day + mesoglycan 50 mg 2 per day; C=mesoglycan 50 mg 2 per day. The treatment lasted 3 months in each group.

Data collection

Data were collected at baseline, and after 3 and 6 months. At baseline, collected data were: 1) demographic data; 2) presence of tinnitus; 3) instability, following unilateral or bilateral vestibular injury or benign paroxysmal positional vertigo (BPPV) 1 month after 1st symptom; 4) recurrent vertigo and number of episodes; 5) paroxysmal vertigo during the last 6 months; 6) migraine; 7) acute loss of vestibular function; and 8) vascular risk factors (diabetes, smoking, familiarity, BMI>30, dyslipidemia, low physical activity, hypertension). Moreover, data were collected on hearing threshold for 250, 500, 1000, 2000, and 4000 HZ, in the presence of spontaneous, positional, and vibration-induced nystagmus, measured using infra-red video goggles and on the presence of BPPV. For measuring directional asymmetries in vestibular responses the positivity to the Head Impulse Test (HIT) and the Head-Shaking Test (HST) was recorded. Patients filled in the validated Italian version of the Dizziness Handicap Inventory (DHI),[18] which measures the impact of vertigo on patient quality of life. The test consists of 25 questions summed up on three scales: functional (9 questions), emotional (9 questions) and physical (7 questions). At 3- and 6-month follow-up, measurement of nystagmus, BPPV, HIT, HST, and DHI were repeated. After 6 months, the outcome was evaluated by both the patient and the clinician as "improved," "unchanged," and "worsened."

Statistical analysis

Categorical data were described as percentages and continuous variables as mean and standard deviation. Outcome variables (*i.e.* nystagmus, HIT, and HST) were considered as dichotomous variables (presence/absence), and mean values of DHI were calculated. The mean hearing threshold for 250, 500, 1000, 2000, and 4000 HZ was calculated for each ear. First, outcome variables were com-

pared in the three treatment groups at baseline, in order to verify if the three groups were comparable. Continuous variables were compared using t-test, and categorical variables using the χ^2 test. Changes in outcome variables from baseline to 3- and 6-month follow-up were then compared in the three treatment groups. Wilcoxon signed-rank test for paired data was used to compare the percentages of positive results at baseline with those at 3 and 6 months, respectively. *T*-test for paired data was used for continuous variables, such as DHI. Moreover, the mean difference between DHI scores at baseline and at 6-month follow-up was compared among the three groups using ANOVA. Clinical evaluation by the patient (PtGA) and the physician (PGA) was reported as "improved," "unchanged" and "worsened" in the three groups. Cohen's κ was calculated to evaluate the concordance between PGA and PtGA. A risk factor score was calculated, according to the presence of diabetes, smoking, dyslipidemia, and hypertension (the score was 0 for absence of risk factors, 1 for one risk factor, etc.).

Results

The study population included 819 patients, coming from 39 Italian vestibology centers. The study population is described in Table I. There were 425 women (56.0%), and the mean (standard deviation) age was 70.7 (22.9) years. Vertigo was reported by 30.7% of patients, dizziness by 36.7% and both vertigo and dizziness by 32.6%. Vertigo was reported as recurrent in 57.2% of cases, with 2-3 episodes in the past year reported by 31.6% of patients. 22.8% of patients reported migraine.

Spontaneous nystagmus was observed at baseline in 23.6% of patients, positional nystagmus in 33.9%, and vibration-induced nystagmus in 28.8%. The risk factor which was reported most frequently was hypertension (67.6%), followed by BMI of 25 or more (62.2%), dyslipidemia (52.8%) and smoking (40.1%) (Figure 1). Each treatment group included 273 patients. At baseline, no differences were observed in the three groups for all the considered variables. Sex, age, inclusion criteria, risk factors, the presence of nystagmus and the mean hearing thresholds were homogeneous in the three groups (always P>0.05, results not shown). A significant decrease of the presence of spontaneous, positional, and vibration-induced nystagmus was observed in all treatment groups (Figure 2) with P<0.001 (from Wilcoxon signed-rank test for paired data) for the comparisons "baseline *vs.* 3-month follow-up" and "baseline *vs.* 6-month follow-up." The decrease was comparable in the three groups A significant decrease of the prevalence of HIT and HST positivity from baseline to follow-up was observed in all treatment groups (Figure 3), with no significant differences among groups. For example, the difference between the prevalence of HIT at baseline and 6-month follow-up was 20.7 in group A, 21.7 in group B, and 18.9 in group C. The

TABLE I.—*Description of the study population at baseline.*

Population at baseline	N.	%
Male	334	44.0
Female	425	56.0
Dizziness	253	36.7
Vertigo	212	30.7
Dizziness + vertigo	225	32.6
Instability 1 month after 1st symptom	455	64.3
Instability following vestibular damage or VPPB	434	59.7
Migraine	165	22.8
Acute loss of vestibular function	140	19.3
Recurrent vertigo	411	57.2
Paroxysmal vertigo	310	43.4
Spontaneous nystagmus	175	23.6
Positional nystagmus	217	33.9
Vibration-induced nystagmus	145	28.8

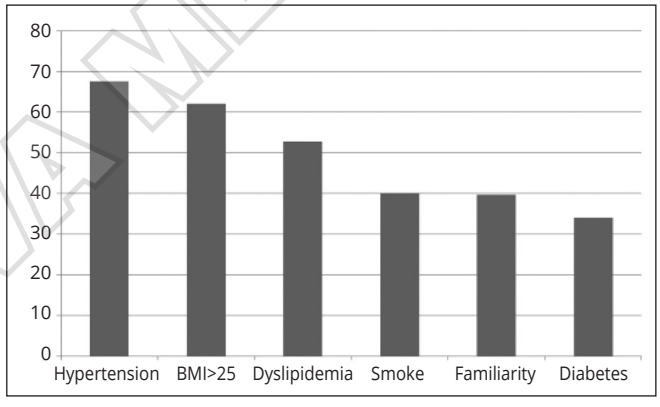

Figure 1.—Frequency of risk factors in the study population.

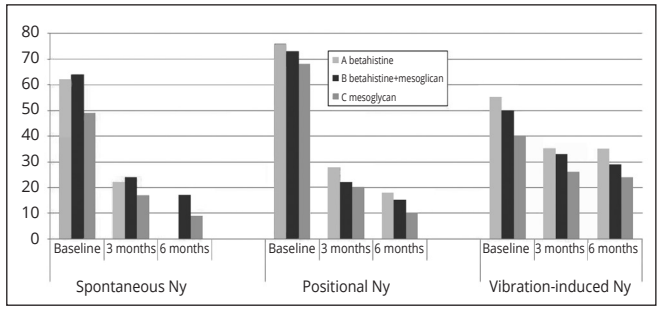

Figure 2.—Presence of nystagmus (N., %) at baseline, at 3-month and 6-month follow-up, in the three treatment groups.

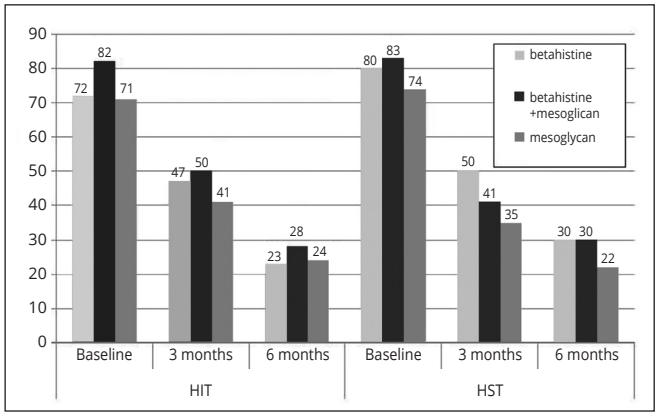

Figure 3.—HIT and HST positivity (N., %) at baseline, at 3-month and 6-month follow-up, in the three treatment groups.

TABLE II.—*Mean (SD) values of DHI scales at baseline, and at 3-month and 6-month follow-up, in the three treatment groups, and comparison between mean values at 6-month follow-up and baseline.*

Scale		Baseline	3 months	6 months	6 months – baseline	P value
Emotional Scale	A	15.8 (10.0)	11.8 (8.9)	8.9 (7.5)	-6.9	
	B	14.9 (9.5)	9.9 (7.1)	7.0 (6.6)	-7.9	
	C	15.5 (9.7)	10.0 (7.7)	7.5 (7.1)	-8.0	0.302
Functional Scale	A	17.2 (9.3)	12.2 (8.1)	9.7 (7.4)	-7.5	
	B	16.8 (8.6)	11.5 (7.4)	7.9 (6.7)	-8.9	
	C	17.2 (9.2)	11.9 (7.8)	8.6 (7.3)	-8.6	0.182
Physical Scale	A	15.1 (11.8)	10.3 (6.5)	8.1 (6.3)	-7.0	
	B	14.2 (6.9)	9.8 (6.5)	7.0 (5.7)	-7.2	
	C	15.4 (7.6)	10.0 (6.8)	7.1 (6.5)	-8.3	0.149

A: Betahistine; B: betahistine+mesoglycan; C: mesoglycan.

same differences for HST were 22.8, 22.6, and 22.9 in the 3 groups, respectively. The mean hearing thresholds were almost the same in the three treatment groups and did not change from baseline to 6-month follow-up. The DHI mean values for the emotional, functional and physical scales significantly decreased from baseline to 6-month follow-up: the mean value of the emotional scale decreased from 15.4 to 7.8, that of the functional scale score from 17.0 to 8.7, and that of the physical score from 14.9 to 7.4. This significant decrease was observed from baseline both to 3-month and 6-month follow-up in the three treatment groups (Table II). The mean difference between mean scores at baseline and at 6-month follow-up was not different among the three groups. PGA was available for 662 patients and PtGA for 660 patients. The majority of patients reported a clinical improvement at the end of the study (Table III). The group with a higher level of reported improvement was C (mesoglycan) (90.0%), followed by B (betahistine + mesoglycan) (89.4%) and A (betahistine) (74.8%). The concordance between the evaluation by the patient and the physician was very high: Cohen's κ=0.628 for A; 0.762 for B; 0.765 for C (P<0.001 in all cases). Improvement according to the patient (PtGA) in the three treatment groups (Table IV) was slightly different according to the initial presence of dizziness, vertigo, or both. In particular, in case of vertigo, improvement appeared to be higher when using mesoglycan or betahistine + mesoglycan compared to betahistine (93.7% and 94.1%, *vs.* 81.4%). A lower percentage of patients with dizziness reported improvement compared to those with vertigo (overall 80.1% *vs.* 89.1% respectively) also in patients with dizziness, the improvement was higher with mesoglycan (86.2%) or the combination betahistine + mesoglycan (85.1%) compared to betahistine (65.7%). Concerning risk factors, the presence of diabetes or hypertension appeared to have an effect only with betahistine, *i.e.* the percentage of clinical improvement was lower when the risk factor was present (Table V). The percentage of improvement according to the risk factor score showed

TABLE IV.—*Percentage of improvement according to the patient (PtGA) in the three treatment groups depending on the inclusion criterion "dizziness/vertigo."*

Clinical improvement (PtGA)				
Criteria		Betahistine	Betahistine + mesoglycan	Mesoglycan
Dizziness	N. (%)	44 (65.7)	75 (86.2)	74 (85.1)
Vertigo	N. (%)	57 (81.4)	48 (94.1)	59 (93.7)
Dizziness and vertigo	N. (%)	46 (74.2)	61 (88.4)	64 (94.1)

TABLE III.—*Evaluation of clinical changes at the end of the study by the physician (PGA) and the patient (PtGA) concordance between PGA and PtGA Cohen's κ: 0.628 for A; 0.762 for B; 0.765 for C (P<0.001 in all cases).*

Clinical changes	A. Betahistine		B. Betahistine+mesoglycan		C. Mesoglycan	
	PGA N. (%)	PtGA N. (%)	PGA N. (%)	PtGA N. (%)	PGA N. (%)	PtGA N. (%)
Improved	173 (80.5)	160 (74.8)	197 (90.0)	194 (89.4)	206 (90.4)	207 (90.4)
Unchanged	40 (18.6)	45 (21.0)	21 (9.6)	22 (10.1)	21 (9.2)	19 (8.3)
Worsened	2 (0.9)	9 (4.2)	1 (0.5)	1 (0.5)	1 (0.4)	3 (1.3)

TABLE V.—*Percentage of improvement according to the patient (PtGA) in the three treatment groups depending on the presence of diabetes or hypertension.*

Variables		Clinical improvement (PtGA)		
		Betahistine	Betahistine + mesoglycan	Mesoglycan
		N. (%)	N. (%)	N. (%)
Diabetes	Yes	36 (60.0)	65 (86.7)	58 (93.5)
	No	109 (79.6)	116 (90.6)	135 (88.8)
Hypertension	Yes	92 (69.7)	133 (91.7)	135 (89.4)
	No	57 (81.4)	52 (83.9)	61 (92.4)

a negative trend in the group treated with betahistine: 80.0% of improvement for no risk factors, 81.0% for 1, 74.2% for 2, 68.0% for 3, and 45.5% when 4 risk factors were present.

Discussion

In the present clinical trial, we compared the effect of betahistine, mesoglycan, alone or in combination, on vertigo and dizziness in elderly patients. The results were very similar in all the treatment groups. In all groups, all clinical parameter (*i.e.* nystagmus, HIT, HST) significantly improved from baseline to follow-up. No worsening of hearing threshold was observed in all groups. In addition, a significant improvement in quality of life was reported in all groups for the three scales of the DHI. However, the improvement in all the parameters was much the same for all treatments. It is interesting to observe that the group with a higher level of reported improvement was that of patients treated with mesoglycan (90.0%), followed by betahistine and mesoglycan (89.4%) and lastly betahistine (74.8%). In particular, patients with vertigo appeared to benefit from the treatment with mesoglycan. Regarding the effect of mesoglycan in our recent study (2018) on treatment of audio vestibular disorders of vascular origin, 100% of the patients with vertigo reported an improvement at the final visit, while the percentage was lower in patients with tinnitus both alone and in combination with vertigo (67.7% and 70%, respectively). Dizziness and vertigo occur frequently in elderly people.[19] Dizziness, vertigo, and imbalance are likely the most common presenting complaints among patients 75 years and older in clinical practice.[20] These disorders may be due to inner ear or nervous system pathology (central or peripheral), cardiovascular disease, medication, leg pathology, or psycho-pathologic processes (psychogenic dizziness). One of the most common causes of vertigo in older adults is benign positional vertigo, due to a combination of the aging otolith membrane, alterations in calcium metabolism, and microvascular ischemia. It is important to treat vestibular disorders in the older patient, since vertigo, and thus imbalance, are associated with a diminished level of independent activities, an increased incidence of falls, and as a consequence also clinical depression.

The origin of vertigo is often difficult to recognize, and this makes the choice of the right treatment difficult. Classes of medications useful in the treatment of vertigo include anticholinergics, antihistamines, benzodiazepines, calcium channel antagonists, and dopamine receptor antagonists.[21] A specific regiment of drug therapy should be tailored to the cause of vertigo. For example, in both Menière's disease and vestibular neuritis, vestibular suppressants such as anticholinergics and benzodiazepines are used, while drug treatments are not recommended for BPPV and bilateral vestibular paresis, where physical therapy treatment is preferred.

Betahistine has been used for more than 40 years for the management of vertigo and vestibular pathologies with different etiologies, showing an excellent safety profile with the usual dose range from 8-48 mg daily. Different clinical studies and meta-analyses have demonstrated that betahistine is effective and safe in the treatment of Menière's disease, BPPV, vestibular neuritis, and other types of peripheral vertigo.[22] Betahistine has been shown to be useful in reducing or eliminating tinnitus in patients with vestibular disorders.[23] However, a Cochrane review[24] on the use of betahistine in patients suffering from vertigo from different causes concluded that there is low quality evidence that there may be a positive effect of betahistine in terms of reduction in vertigo symptoms. Anyway, they concluded that betahistine is generally well tolerated with a low risk of adverse events. The efficacy of betahistine appeared higher when used in conjunction with Epley's maneuver than alone in patients with BPPV.[25] On the contrary, when used alone it provided short term relief for acute symptoms by improving the microcirculation in the labyrinth and reducing the symptoms of vertigo.

Very few studies are available on the efficacy of mesoglycan in the treatment of vertigo. Mesoglycan acts improving the microcirculatory hemodynamic and oxygen diffusion with direct effect on vestibular receptor producing improvement of the vertigo and instability.[26] A recent study[11] conducted on 873 patients with cardiovascular risk factors suffering from tinnitus, instability or peripheral vertigo alone or in combination, showed that the treatment with mesoglycan significantly and objec-

tively improved the cochleovestibular symptoms and the quality of life of patients, and it was well tolerated.

In this study mesoglycan showed a very similar efficacy compared to betahistine, and even a higher improvement according to the patient. The presence of risk factors had an influence on improvement only for betahistine, with a lower improvement for more risk factors.

Conclusions

In conclusion, both betahistine and mesoglycan, as well as their combination, appear effective in the improvement of vertigo and dizziness in elderly patients. The clinician should choose the best treatment for the patient, depending on symptoms, risk factors, and the general clinical condition. It is possible that the improvement of stability due to mesoglycan action is due to the improvement of microcirculation not only in the vestibular system but also in all central nervous system. The mesoglycan could so contribute to reactivate the neural connections re-establishing the vestibular network better than the bethaistine that instead reduce the vestibular function improving the symptom but is not useful for the healing of disease. An important aspect of this study is the use of subjective measures, such as the DHI and the PtGA. These are measures that report the clinical improvement from the patient's point of view, which is a very important outcome in clinical research and practice together with the "objective" clinical improvement.

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