TREATMENT WITH A NEW NUTRACEUTICAL COMPOUND ON PATIENTS SUFFERING FROM BALANCE DISORDERS: DIZZINESS HANDICAP INVENTORY SCORES

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ABSTRACT

Objective: *Purpose: To investigate whether treatment with citicoline, in association with vitamin B6, ginger, melissa and ViNitrox, could improve Dizziness Handicap Inventory (DHI) scores in patients affected by dizziness and vertigo.*

Materials and methods: *Fifty-five consecutive subjects (ranging from 49 to 71 years of age) who complained of dizziness and vertigo of unknown origins were treated with citicoline (500 mg) along with ginger (200 mg), vitamin B6 (2.1 mg), melissa (300 mg) and ViNitrox (150 mg) twice per day for a two-month period.*

Patients underwent pure tone audiometry (PTA) and a neurotological visit including spontaneous nystagmus testing, bedside examination and the Romberg Test. To evaluate the perceived severity of dizziness and vertigo, its impact on life and the efficacy of treatment, patients were assessed using the DHI before and after treatment.

Results*: The majority of patients did not report any family history of hearing impairment (94.54%), and 67.27% did not report any kind of hearing loss at the moment of the first examination; mean PTA0.5-4 kHz resulted in 32.5 dB HL and 31.9 dB HL for the left and right ear, respectively. DHI mean value before treatment was 55.85 ± 11.69, while it decreased to 19.85 ± 10.56 after completing therapy (p=0.0001); no significant association between the variables examined and post-treatment DHI values was found (p>0.05).*

Conclusion*: Our results suggest that the use of citicoline should be taken into consideration when managing patients suffering from balance disorders.*

Keywords: *Citicoline, balance disorder, dizziness, vertigo.*

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Introduction

It is well-known that, in developed countries, the elderly population (>65 years old) is growing much faster than the total population; in Italy, the old age index (number of elderly people per 100 people under the age of 14 years) has been estimated to be 157.7 and is projected to increase to 257.9 in the year 2065. The growth of the elderly population determines a greater percentage of age-dependent diseases, including pathologies causing static and dynamic postural control dysfunctions and associated symptoms (e.g., vertigo and dizziness).

Since about one-third of the population over 60 years old experiences a balance disorder at least once, vertigo and dizziness are unanimously recognized as among the most common complaints reported by patients of all ages[(1)].

Balance disorders have a considerable impact on patient quality of life: the interruption of daily activities, use of sick leave, avoiding leaving the house and increasing fall-related injuries constitute the majority of complaints reported[(2)]. One of the first challenges in assessing and managing a dizzy patient is to identify the exact origin of the symptoms; this may be challenging because the maintenance of balance in humans is based on the brain processing of sensory inputs provided by the vestibular, visual, and proprioceptive systems as well as the cognitive system; 3 for this reason, an impairment of any of the aforementioned systems could be responsible for dizziness and vertigo symptoms.

Differential diagnosis of dizziness and/or vertigo should be done between peripheral causes (e.g., BPPV, vestibular neuritis, labyrinthitis, Meniere's disease), central causes (e.g., vestibular migraine, stroke, vertebrobasilar insufficiency, neurodegenerative disorders) and other causes such as psychiatric diseases, medication-induced dizziness and cardiovascular and/or metabolic diseases[4].Additionally, a consistent number of patients complain of dizziness and vertigo without a clear detectable cause. Balance disorders in these patients may be associated with so-called presbystasis, the aging of the vestibular system[4]. Previous research has demonstrated that age-related changes affecting the vestibular system include: reduced numbers of hair cells in the vestibular organ, fragmentation of otoconia, loss of afferent fibres in the superior and inferior vestibular nerves, reduced numbers of cells in the vestibular nuclei.5 In addition, loss of visual acuity, slowing of motor response, progressive loss of muscle strength, osteoarthritis, cardiovascular disease and mild cognitive impairment may contribute to the onset of symptoms[3].

MRI findings of increased white matter hyperintensity (WMH) lesions in patients with unexplained dizziness have suggested that these abnormalities might contribute to the development of dizziness[6]. In general, WMHs are common in healthy brains of individuals in their 40s, and their volumes start to increase to more than 2000 mm^3 after the fifth decade of life, becoming larger among subjects ≥65 years[7]. Furthermore, evidence has suggested that patients with more WMHs showed less grey matter compared to low WMH subjects in middle and old age[8]. The origin of these lesions may be associated with chronic hypoperfusion secondary to small vessel disease, venous pathologies and blood-brain barrier impairment[9]. The management of risk factors, such as hypertension, hypercholesterolaemia, smoking, diabetes mellitus and lack of exercise, has been recommended for the prevention of cerebral small vessel disease. In contrast, antihypertensive treatment has led to contradictory results, while lipid-lowering treatment has been shown to have potential anti-inflammatory and pro-endothelial activities[10,11].

Because of its neuro-protective, neuro-modulatory, and neuro-regenerative properties, citicoline is often prescribed to manage acute cerebrovascular disease and its sequelae, cognitive disorders and brain atrophy, in which chronic cerebrovascular disease may represent the main risk factor in the elderly[12].

In particular, citicoline acts by increasing the synthesis of phosphatidylcholine (the primary neuronal membrane phospholipid), restoring structural phospholipids of the neuronal membrane, decreasing lipid peroxidation, reducing the accumulation of free fatty acids at the site of the lesion, enhancing the production of acetylcholine, reducing cerebral oedema, increasing cerebral blood flow, improving the permeability of the blood-brain barrier and increasing superoxide dismutase activity[13]. Moreover, from a clinical perspective, citicoline may play a role in the improvement of patients suffering from Parkinson's disease, alcoholism and drug addiction, amblyopia and glaucoma, facial neuritis, epilepsy, and vertigo[12,14-20].

The aim of this study was to investigate whether treatment with citicoline, in association with vitamin B6, ginger, melissa and ViNitrox, could improve Dizziness Handicap Inventory (DHI) scores in patients affected by dizziness and vertigo.

Materials and methods

The study was conducted by the Audiology section of the University of Palermo on 55 consecutive subjects (ranging from 49 to 71 years of age) who complained of dizziness and vertigo of unknown origins.

Exclusion criteria were: middle and/or inner ear pathologies (such as BPPV, vestibular neuritis, Meniere's disease, chronic otitis media), neurodegenerative disorders, psychiatric diseases, medication-induced dizziness, history of hypertension, diabetes, cardiovascular disorders and stroke, assumption of anti-vertiginous drugs in the two weeks before the first examination.

The study protocol was explained to patients, and written informed consent was obtained from each subject. The study design was approved by the University of Palermo Human Research Ethics Committee.

The following variables were considered: age, sex, family history of hearing impairment, history of head trauma, history of vertigo, headache and tinnitus.

A careful anamnesis was collected, followed by an ear examination through micro-otoscopy; pure tone audiometry (PTA) was performed with an Amplaid A321 audiometer in a soundproof audiometric chamber. Air conduction was measured using on-ear headphones for 500-4000 Hz; bone conduction was measured using a calibrated bone transducer for 500-4000 Hz. A complete neurotological visit, including spontaneous nystagmus, bedside examination and Romberg Test, was performed.

Each subject was treated with citicoline (500 mg) together with ginger (200 mg), vitamin B6 (2.1 mg), melissa (300 mg) and ViNitrox (150 mg) twice per day for a two-month period.

To evaluate the perceived severity of dizziness and vertigo, its impact on life, and treatment efficacy, patients were invited to compile the DHI before and after completing treatment. This tool is a 25-item survey that is composed of three subscales: a functional subscale (12 items), an emotional subscale (8 items) and a somatic response subscale (5 items), which address role and physical functioning, psychological distress, desperation and loss of control, respectively. Each item has 3 potential answers, with "yes" assigned 4 points, "sometimes" 2 points, and "no" 0 points. This leads to a total score ranging from 0, indicating no dizziness handicap, to 100, indicating the most severe patient impairment. Classically, it grades five categories of dizziness severity: slight, corresponding to a score of 0-20, mild (21-40), moderate (41-60), severe (61-80) catastrophic (81-100)[21].

Statistical analysis was conducted using the Matlab® computer programme; χ^2 test, odds ratio, and/or Fisher Exact test were used, following standard application conditions. Significance was set at 0.05.

Results

Fifty-five subjects, 28 male and 27 female, ranging from 49 to 71 years of age (mean age = 60.1± 5.36) were recruited.

Table 1 depicts the main characteristics of the total cohort. The majority of patients did not report any family history of hearing impairment (94.54%), and 67.27% did not complain of any kind of hearing loss at the moment of the first examination; as shown in Figure 1, mean PTA0.5-4 kHz was 32.5 dB HL and 31.9 dB HL for the left and the right ear, respectively.

Only 9 out of 55 patients suffered from tinnitus, while less than one-fourth of the total sample had experienced an episode of vertigo at least once in their lives. With a percentage of 9.09%, headache was an uncommon finding, while a history of head trauma was reported only by 2 patients.

Figure 2 shows the distribution of the severity of dizziness according to the DHI, pre- and post-treatment. At the moment of the first examination, 67.27% of patients presented mild to moderate disability on the DHI, while, after 60 days of treatment, 63.63% presented only a slight dizziness score. DHI mean value before treatment was 55.85 ± 11.69, while it decreased to 19.85 ± 10.56 after completing therapy (p=0.0001); no significant association between the variables examined and post-treatment DHI values was found (p>0.05).

	N (%)	DHI pre	SD	p	C.I.	DHI post	SD	p	C.I.
Sex									
F	27 (49.09)	55.85	11.78	0.9987	(-6.39-6.38)	19.56	9.96	0.8389	(-6.35-5.18)
M	28 (50.91)	55.86	11.83			20.14	11.29		
History of head trauma									
yes	2 (3.64)	43.00	7.07	0.1140	(-29.99-3.31)	19.00	7.07	0.9085	(-16.29-14.51)
no	53 (96.36)	56.34	11.59			19.89	10.72		
Familiarity for hearing impairment									
yes	3 (5.45)	58.67	11.37	0.6725	(-11.06-17.01)	13.33	8.08	0.2754	(-19.45-5.66)
no	52 (94.54)	55.69	11.80			20.23	10.62		
Hearing impairment									
yes	18 (32.72)	58.11	10.68	0.9109	(-6.42-7.18)	17.56	7.87	0.2640	(-9.49-2.65)
no	37 (67.27)	55.73	12.29			20.97	11.58		
History of vertigo									
yes	10 (18.18)	50.60	6.60	0.1170	(-14.51-1.66)	18.20	5.61	0.5886	(-9.48-5.43)
no	45 (81.89)	57.02	12.30			20.22	11.39		
Tinnitus									
yes	9 (19.56)	59.11	12.21	0.3658	(-4.67-12.46)	23.78	9.97	0.2263	(-2.99-12.38)
no	46 (83.64)	55.22	11.62			19.09	10.61		
Headache									
yes	5 (9.09)	52.80	15.01	0.5451	(-14.42-7.70)	16.40	3.29	0.4482	(-13.77-6.17)
no	50 (90.91)	56.16	11.46			20.20	10.99		
Total patients	55	55.85	11.69			19.85	10.56	0.0001	(31.79-40.21)

Tab. 1: Characteristics of the total cohort.

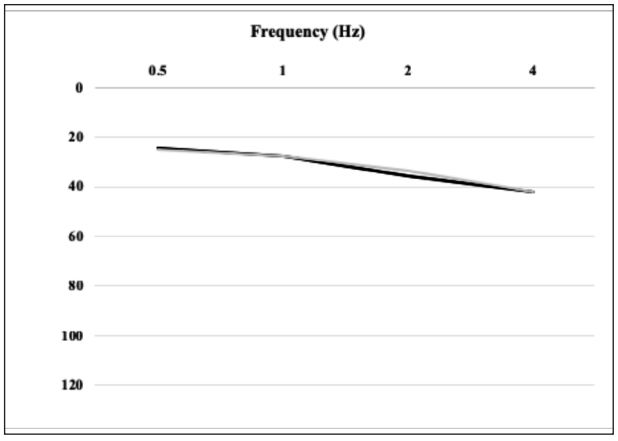

Fig. 1: Mean PTA of the total cohort for the left (black) and right (grey) ear.

Discussion

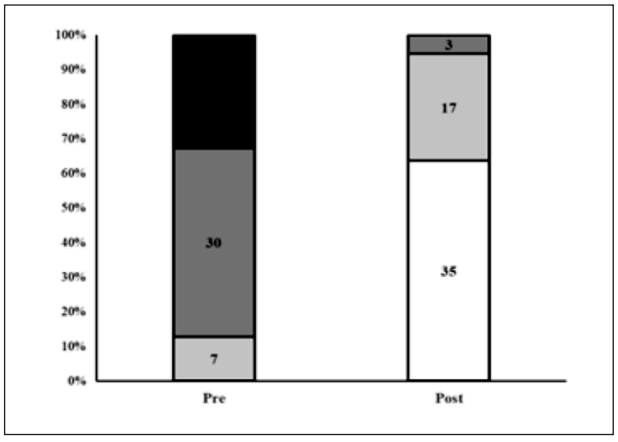

Fig. 2: DHI scores pre- and post-treatment.

The treatment of dizziness can be challenging. Over the years, different drug treatments have been proposed, such as antihistamines, calcium antagonists, histamine analogues, diuretics, neuroleptics, corticosteroids and hemorheologic agents, with extremely variable outcomes according to the studies considered[22,23].

Citicoline is the generic name of cytidine-5'-diphosphocoline (CDP-choline) which is an intracellular precursor of the phospholipids composing cell membranes. The pharmacological actions of citicoline can be explained by its capacity to reconstruct the nervous membrane lipids, improve cerebral small vessel blood flow and regulate blood–brain barrier permeability, leading to the restoration of cerebral homeostasis in patients affected by alterations due to aging. Because of these effects, citicoline has been used in the treatment of cerebral hypoxia and ischemia, intracerebral haemorrhages, cognitive disorders, Parkinson's disease, facial neuritis, epilepsy and vertigo[12,14-17].

It is possible that the association of citicoline with vitamin B6, ginger, melissa and ViNitrox may increase clinical benefits in the treatment of dizziness and vertigo. B-vitamin supplementation may slow the progression of WMHs, as evidenced by a post hoc subgroup analysis in patients with MRI evidence of severe cerebral small vessel disease at baseline[24]. Ginger exerts a marked activity against neurovegetative symptoms like nausea and vomiting. It acts by antagonizing the serotonin type 3 (5ht3) receptor expressed by gastric mucosa, favouring gastric emptying and stimulating antral contractions[25]. *Melissa officinalis* is used in traditional medicine for its tranquilizing, neuroprotective, antioxidant and anti-inflammatory activities[26]. Finally, ViNitrox, a mixture of polyphenols derived from apples and grapes, may contribute to the reduction of oxidative stress.

A meta-analysis of citicoline administration for acute and sub-acute stroke has suggested a beneficial and substantial effect of the drug, with absolute reductions of 10-12% in long-term disability and mortality rates[27]. A multicentre, randomized, double-blind study versus placebo has assessed the efficacy of citicoline for the treatment of patients with chronic vascular disease[28]. In this study, 33 patients received treatment with citicoline 1 g/d or saline as an intravenous infusion for 28 days. At the end of the treatment period, significant improvements were noted in the citicoline-treated group in the Bender-Gestalt test, Hamilton scale for depression, Parkside scale, neurological assessment scale, and attention test. In a systematic review of 14 studies published by the Cochrane Library, Fioravanti et al. examined the effects of citicoline in the treatment of cognitive, emotional, and behavioural deficits associated with chronic brain disorders in the elderly. The results demonstrated little effect of citicoline on attention, memory improvement, or positive behavioural changes[29]. Álvarez-Sabín et al. performed a randomized study on 347 patients to assess the safety of long-term citicoline administration and its possible efficacy versus typical treatments in preventing post-stroke cognitive decline in patients with first-ever ischemic stroke[30]. At 6 and 12 months, citicoline-treated patients showed better outcomes in attention-executive functions and temporal orientation. In addition, a gradual improvement of cognitive status was noted after 2 years of follow-up[31].

Petrova et al., evaluating the therapeutic efficacy of citicoline on 40 patients affected by vertigo of central origin, found an improvement of symptoms among patients who had been treated with citicoline 2000 mg IV for 5 days, followed by a daily dose of

citicoline 500 mg for at least 30 days[15].

With a DHI mean value of 55.85 ± 11.69 before treatment and of 19.85 ± 10.56 after completing therapy (p=0.0001), our results suggest that using citicoline in association with vitamin B6, ginger, melissa and ViNitrox should be taken into consideration when managing patients suffering from balance disorders. However, further investigation through randomized controlled trials are required to validate our findings.

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