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Research Article

Effectiveness of Bacopa Monnieri in the Therapy of Vertigo in association with Citicoline, Ginger, Vitamin B6 and Passionflower

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Abstract

A new drug is now available for the neuro-otologists; it is classified in the category of supplements, which has proved effectiveness in control of the symptoms caused by uncompensated labyrinthine pathology. The association of citicoline (already in commerce in other formulations and combinations) with ginger, vitamin B6, passionflower and bacopa has been useful in the symptomatic improvement of treated patients. In fact, of the fifty patients subjected to the study, as many as 49 benefited from the preparation, as demonstrated both by the anamnestic evaluation and by the comparison between the instrumental results at the day of the beginning (0-time, T0) and sixty days later, the day of the end of the study (60-time, T60). A great number of patients - almost half of those studied - had a complete remission of the symptoms, while many others had a very important recovery, with an improvement in the quality of life. We have not experienced any side effects; moreover, no patient stopped the treatment. The clinical use of this new preparation is therefore indicated in the pharmacological treatment of dizzying symptoms, and we see a main utility in the treatment of long-lasting, subacute, persistent or even chronic pathologies. However, we do not exclude the use of the preparation also in acute cases, as there are also chemical substances in the package with a symptomatic effect, in particular on autonomic phenomena. This finding could be the subject of future studies, and we find a very interesting use for a further improvement in the quality of life of patients suffering from balance pathology

Keywords: Vertigo; Bacopa; Citicholin; therapy

Background

For the pharmacological therapy of now vertiginous pathology we have Manu products, which allow the clinician to act effectively both on the symptoms and, above all, on the mechanisms underlying the various and numerous equilibrium pathologies. Since the late seventies, betahistine has marked a milestone in the treatment of vertigo, with mechanisms of action that, at first only hypothesized, have gradually become clear over the decades. And, if betahistine still remains a clear and strong cornerstone today in the therapy, nonetheless, in recent years, multifunction preparations with therapeutic efficacy that are anything but negligible have appeared. This allows the specialist who deals with vertigo to have numerous pharmacological weapons, with the advantage of being able to carry out symptomatic and even pathogenetic therapy in a single time. The idea was of combining different chemicals in order to produce pluripotentials drugs. This new preparation fits into this perspective, which the pharmacopoeia classifies as a supplement, and which was conceived with a set of five chemical substances, each of which plays a role in the overall therapeutic strategy.

Thus we have citicoline, a substance already in use for decades and whose neuroleptic properties are now well known; citicoline is present in various preparations proposed by the pharmacopoeia for the treatment of both vertiginous pathology and various neurological diseases, since its therapeutic efficacy in many deficiencies, especially neuronal, is well known. This new citicoline preparation is accompanied by ginger, whose properties in the treatment of gastrointestinal pathology have been known for many decades. Vitamin B6, pyridoxal phosphate, so known for its effectiveness in the treatment of vegetative phenomena that often accompany dizzying symptoms, is also present to strengthen the symptomatic efficacy of ginger. Coming to the peculiarities of the latter preparation that we are going to examine, we have bacopa and passionflower. But, while passionflower is a chemical substance well known for its delicate and well-tolerated sedative activities, bacopa makes only recently its entry into the world of the official pharmacopoeia, thanks to the knowledge that Ayurvedic doctrine recognizes. We therefore decided to test the therapeutic impact of this new therapeutic proposal in the clinic, with the hope of having an effective weapon in hand - which is already on the market, having passed the AIFA approval - and with the intention of evaluating its real impact in everyday clinical life

a) Citicoline: chemical substance included in the pharmacological category of psychostimulants and nootropics, acts on the alterations of neuronal metabolism; it has an anti-edema effect; reduces the threshold values of the alert reaction and of the muscular response with a facilitating effect on the pyramidal system and inhibiting on the extrapyramidal system

b) Ginger: aromatic plant, whose use is not limited in the kitchen. Ginger has long been known as a natural remedy, well known in popular medicine, for its astringent, expectorant and carminative functions, therefore used against problems such as diarrhea, stomach pain and swelling and disorders of the upper airways. In traditional Chinese medicine, however, being considered a "hot" plant, ginger is used to solve all those typical diseases of the cold season, such as colds, sore throats and coughs.

c) Vitamin B6, a water-soluble vitamin (that is able to dissolve in water) which is naturally present in many foods; six different molecules are defined (pyridoxine, pyridoxal, pyridoxamine and the corresponding 5 'phosphate esters), but the biologically active form is represented by pyridoxal phosphate alone. It performs multiple functions in the body and is involved in more than 100 enzymatic reactions, largely related to protein metabolism; it is also necessary for the synthesis of the neurotransmitters serotonin and nor-adrenaline and for the formation of myelin, a structure capable of protecting the central nervous system. It plays an important role in brain development during pregnancy and is involved in important functions of the immune system. For all these reasons, pyridoxine is frequently used in the formulation of supplements containing the vitamin B complex [1,2].

d) Many properties are recognized in Bacopa, in the Bacopa Monnier variety, well known in Ayurvedic doctrine. Contains powerful antioxidants, substances that help protect against cell damage caused by potentially harmful molecules (called "free radicals"). When fat molecules react with free radicals, they undergo a process called "lipid peroxidation", involved in several conditions, such as Alzheimer's, Parkinson's, and other neurodegenerative disorders. Bacopa Monnier is recognized as having a preventive effect on the damage caused by this process. Furthermore, Bacopa can reduce inflammation: test-tube studies have shown the suppression of the release of pro-inflammatory cytokines, the inhibition of enzymes, such as cyclooxygenase, caspase and lipoxygenase, which play a key role in inflammation and pain; there is still no demonstration of these effects in humans, but there are scientific demonstrations in vitro. Other studies show that Bacopa can increase brain function by improving spatial learning and the ability to retain

information. The study that we report (2) also discovered the increase in the length and branching of the dendrites. Another recognized advantage of Bacopa is its action on ADHD, the neurological development disorder characterized by symptoms such as hyperactivity, impulsivity and inattention. However, on the ability of this herb to prevent anxiety and stress, being considered an adaptogenic herb that elevates mood and reduces cortisol levels, there are still no concordant data, as alongside studies that would seem to confirm this action there are others that have not found significant effects. Instead, the action that has been well demonstrated is antihypertensive, releasing nitric oxide, which helps to dilate blood vessels, resulting in improved blood flow and lowering blood pressure. As for the possible anticancer properties, test-tube studies have shown that bacosides, the active class of compounds in Bacopa monnieri, are able to kill aggressive brain tumor cells and inhibit the growth of breast and colon cancer cells. and to the skin; however, certainties of this effect in vivo are still lacking.

Finally, Passiflora, in its caerulea, incarnata and edulis varieties. The green parts are used, rich in flavonoids and indole alkaloids, maltol and fatty acids. The medicinal properties of Passionflower were already known to the Aztecs, who used passionflower as a relaxant. The infusion, the syrup and the fluid extract have sedative properties of the nervous system, tranquilizers, anxiolytics, antispasmodics, curative of insomnia, tachycardia and hysteria; induce physiological sleep and non- dull daytime activity [3]. Already at the time of the First World War, passionflower was used in the treatment of "war anxieties". The infusion was also used for psychoasthenia. The pharmacological characteristics of Passiflora incarnata make it useful for facilitating, with medical supervision, weaning from psychotropic drugs [4].

Objective

To evaluate clinical effectiveness of a new drug, a supplement containing Citicoline, vitamin B6, Ginger, Bacopa and Passionflower

Methods

50 subjects were involved in the study, belonging to the Otoneurology Laboratory of the University of Turin between November 2021 and March 2022. These are patients suffering from vertiginous pathology in its various manifestations, both rotary vertigo and dizziness, a set of symptoms ranging from instability to insecurity, imbalance without a real rounding sensation but which can equally be ascribed to pathology of the vestibular system. All patients with a defined diagnosis of the most common labyrinthine pathologies, such as paroxysmal vertigo, vestibular neuritis and endolymphatic hydrops, were excluded from the study; the reason for this choice is double: first of all, these diseases are treated with well validated therapeutic protocols, in which the approach with pharmacological remedies does not play a leading role; furthermore, it seems to us that the main indication of a multipurpose supplement such as the one we wanted to evaluate is overall the compensation in a post-acute or even late stage of the disease; and the symptomatic effect is welcome, but it did not seem appropriate to include vestibular neuritis and endolymphatic hydrops in the study, diseases for which the symptomatic approach is now well defined and plays a limited part in the therapeutic strategy; the same goes for paroxysmal vertigo, which makes use of liberating maneuvers and for which the prescription of drugs has a completely marginal role. The study was therefore carried out on patients with instrumentally demonstrated labyrinthine dysfunction. The sample of individuals being analyzed includes 31 female and 19 male subjects, for a total of 50. The following pathologies were found:

a) A vestibular alteration was detected in 20 patients (40%) during the nystagmus study with bedside examination and / or with evoked nystagmus; we have united in this group all patients suffering from joint pathology (whether vertebral or limb), thirteen of which with concomitant headaches, without the characteristics of migraine; common to all these patients is that they have already undergone physiotherapy treatments without significant improvement in symptoms.

b) 14 patients (28%) suffer from Perceptive Postural Persistent Disease, in its known forms, namely phobic postural vertigo, visual vertigo, motion sickness and chronic subjective disease; an item common to 8 patients in this group is a positive history of uncompensated vestibular neuritis.

c) 8 patients have nuanced symptoms with positivity on the Fazekas scale for Small Vessel Disease; 5 of these patients have radiological signs classifiable as grade 1 on the Fazekas scale, 2 of them alterations of grade two and one of grade three.

d) 5 patients were diagnosed with residual dizziness, i.e. results of instability after one or more liberating maneuvers for labyrinth lithiasis.

e) 3 patients instead have a picture of labyrinthine hypofunction following the intake of ototoxic antibiotics (Figure 1). As we can see in Figure 2, the population examined is mainly female, as widely noted in the literature for the use of specialist care for balance disorders at all ages. The following Figure 3 shows the age distribution of the subjects examined; almost all decades of adult life are represented, with a clear prevalence of subjects over 50 years.

BPPV	no
Vestibular neuritis	no
Menière disease	no
Visual vertigo	4
Phobic postural vertigo	1
Motion sickness	5
Toxic labyrinthosis	3
Small vessel disease	8
Residual dizziness	5
Headache and joint pathology	20

Figure 1: diagnosis of admission for patients included in the study.

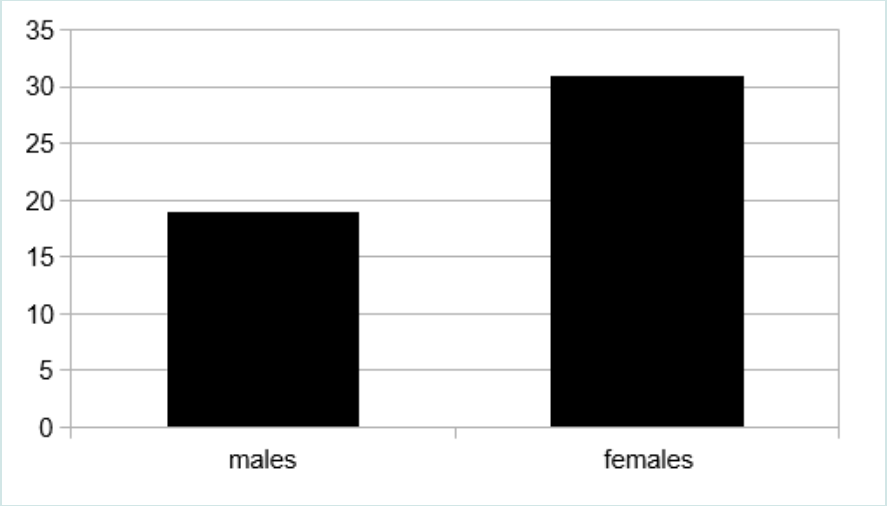

Figure 2: distribution of patients by gender.

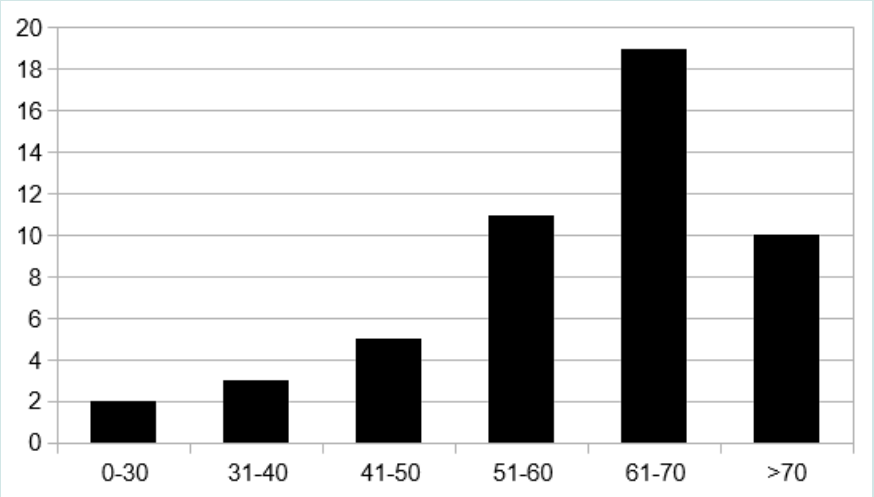

Figure 3: distribution of patients by age groups.

At the start of the study, all subjects underwent otoscopy and a complete ENT examination, then the DHI questionnaire was administered; then, we performed the instrumental evaluations with tonal audiometric examination and bedside examination; finally, we proceeded with the stimulation through the video impulsive test and / or the caloric balance with bithermic test according to the Fitzgeradl-Hallpike method

Questionnaire DHI (Dizziness Handicap Inventory)

It is the standardized and validated anamnestic questionnaire for the quantification of the malaise in the subjects with imbalance or vertigo; it consists of twenty-five multiple choice questions and classifies the answers according to three different aspects (functional, emotional and physical) that the symptom causes. In particular, it shows the impact of the dizzying symptom on daily life activities, objectifying the perceived disability. This test also seemed essential for our research, as it allowed us to quantify the effect of the pathology in the daily routine of the patient examined. For the purpose of our study, the quiz questions were asked in advance of the impulsive instrumental tests.

Otoscopy

The clinical physical examination of the ear was essential in order to diagnose and therefore exclude any pathologies of the external ear as regards the vestibular and auditory functions. It can identify the presence of abnormalities or malformations of the portions examined, inflammation or infections of the external and middle ear, earwax plugs or foreign bodies, also evaluating translucency, mobility and any endothympanic effusions. Any inflammatory, infectious or neoplastic auricular pathology could interfere with the functions we assessed, causing a selection bias. In fact, even a trivial plug of earwax can be accompanied by imbalance, albeit rarely, or at least cause a feeling of discomfort to the patient that would invalidate a correct experimental approach.

Liminal tonal audiometry

Complementary examination, but with a significant clinical impact also with regard to balance disorders. The objective of the test is to evaluate auditory sensitivity by searching for the weakest sound impulse that the subject is able to recognize for each frequency of the tonal field; it uses an audiometer, which generates pure tones. This test mainly explores the anterior labyrinth, however it is very useful for the clinician especially in dropsy diseases, where it is considered essential to reach the diagnosis.

Bedside examination

Vestibular evaluation that investigates, without the use of sophisticated tools, the function of static and dynamic balance. The patient is observed in different positions while performing maneuvers aimed at shows any positioning phenomena: eye movements, response to provocation maneuvers and vestibulo-spinal tests are investigated. It is now a validated and consolidated method for achieving a diagnosis of vestibular disorder in a very high percentage of cases and does not require the availability of complex or technological tools

vHIT and caloric balance

Finally, after having extensively explored vestibular and auditory functionality, we carried out the search for evoked nystagmus, both with the impulsive test (video Head Impulse Test) and with the caloric balance (Fitzgerald-Hallpike test).

Drug therapy

The therapy with the drug in study in question was recommended to all patients: the supplement based on citicoline, ginger, vitamin B6, bacopa and passionflower, in oral formulation, at a dose of two tablets per day for sixty days

Timing

At the first evaluation (T0) the entire protocol was performed for the patients; assigned the therapy, they were asked to fill out the DHI questionnaire at T15, T30 and T45 at home. Then the check-up was carried out at T60, i.e. on the sixtieth day after the start of therapy, with the repetition of the oto neurological visit, i.e. otoscopy, bedside examination and search for the evoked nystagmus [3-8].

Results

We show below the results of the assessments carried out using the tests above. At the otoscopic examination, as for the previous tests, no value of pathological significance emerged in the patients under study. All the subjects examined, in fact, show to have a normal ear canal, with good visibility in the exploration of the tympanic membrane. This parameter was considered essential to eliminate any item of pathology from the history. The liminal tonal audiometry highlights the spectrum of different results of the population, emphasizing how the phenomenon of presbycusis is mainly represented in the age group of patients. The average audiometric threshold fluctuates from normal values (less than 25 audiometric decibels) to high values (more than 60 dB HL) in a small percentage of patients and aged no less than sixty years. In the following table we graphically report the average of the cut off or audiometric threshold, detected through the liminal tonal audiometric examination (Figure 4). The Figure 5 below, on the other hand, illustrates the results of the evaluation of patients with bedside examination, carried out before the instrumental surveys; this test allowed us to detect changes in labyrinthine reflectivity and signs of pathology of the central vestibular system, useful correlation with the anamnestic data collected in the first instance.

0- 25 dB HL	17
26-40 dB HL	15
41-60 dB HL	10
More than 60 dB HL	8

Figure 4: Average threshold values detected with the tonal audiometric examination.

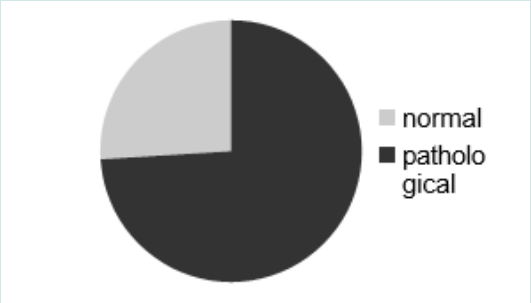

Figure 5: detection of pathological signs on bedside examination at the beginning of the study.

Finally, we show the results on DHI at the beginning and at the end of therapy. The Dizziness Handicap Inventory (DHI) questionnaire was completed in time 0 by all subjects with the specialist's interface for any doubts that might arise in the interpretation of the questions. The scores found in the Figure 6.1. As shown in the graph, 49 out of 50 patients (98%) benefited from the therapy, while only one patient (2%) did not experience any benefit. Among these, the group that has achieved the best symptomatic remission is that of PPPD in its various components. The Figure 6.2 below shows the DHI value at time 0 and at time 60 in patients suffering from labyrinthine dysmetria and joint disease. The Figure 6.3 below shows the DHI value at time 0 and at time 60 in patients with Persistent Postural Perceptual Disease. The Figure 6.4 below shows the DHI value at time 0 and at time 60 in patients with Small Vessel Disease. In the Figure 6.5 below, the trend of DHI in patients suffering from Residual Dizziness, non-acute instability following one or more liberating maneuvers for paroxysmal vertigo. In the Figure 6.6 below, the trend of DHI in patients suffering from labyrinthine toxicosis. At last, the comparison of the bedside examination findings at the beginning and at the end of therapy, where it is highlighted that there is a significant improvement in the clinical picture after treatment (Figure 6.7).

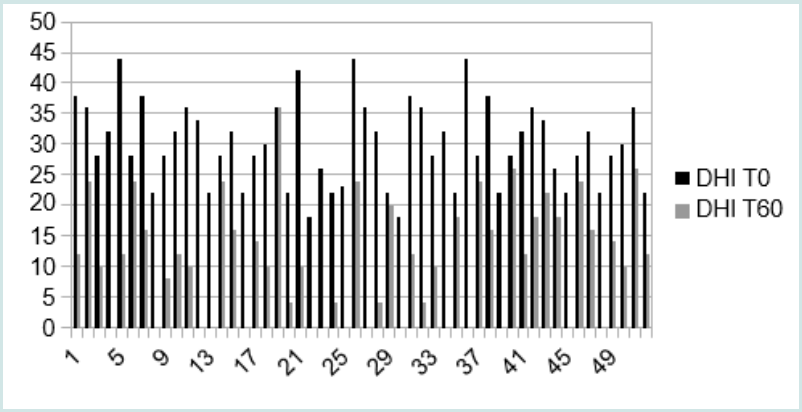

Figure 6.1: comparison between T0 and T60 on the entire sample of treated patients.

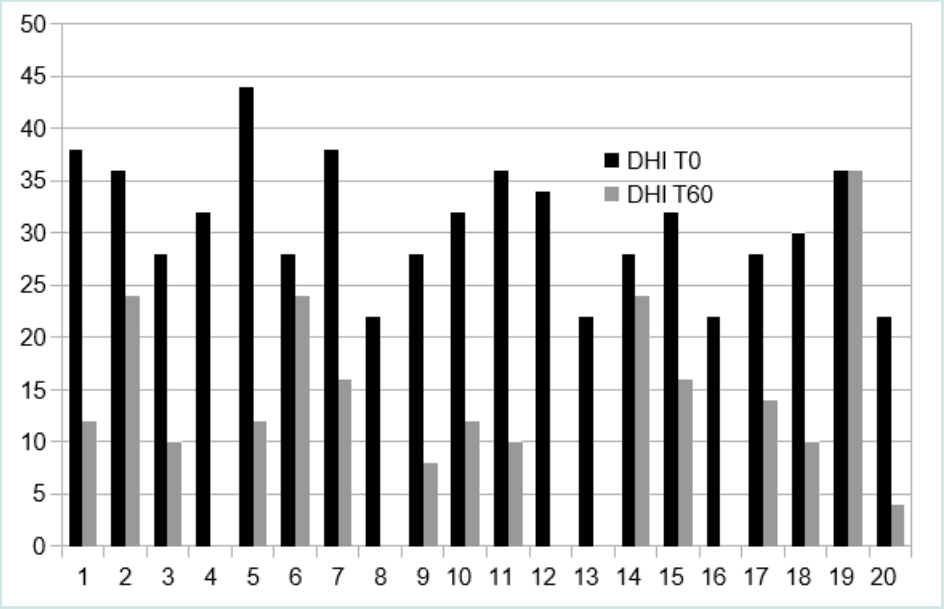

Figure 6.2: Trend of DHI in patients affected by labyrinthine dysmetria with joint pathology.

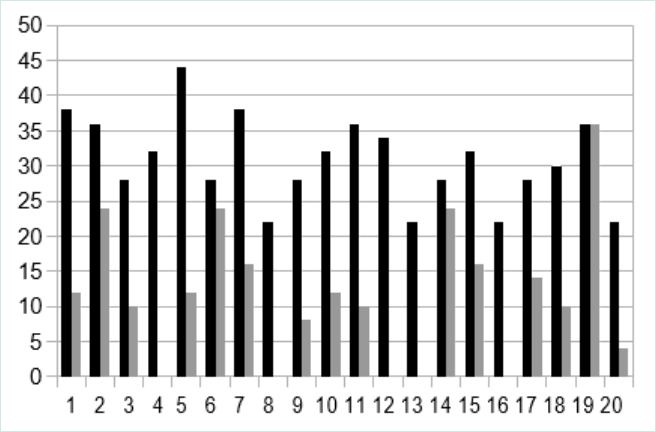

Figure 6.3: Trend of DHI values respectively at T0 and at T60 in patients with PPPD.

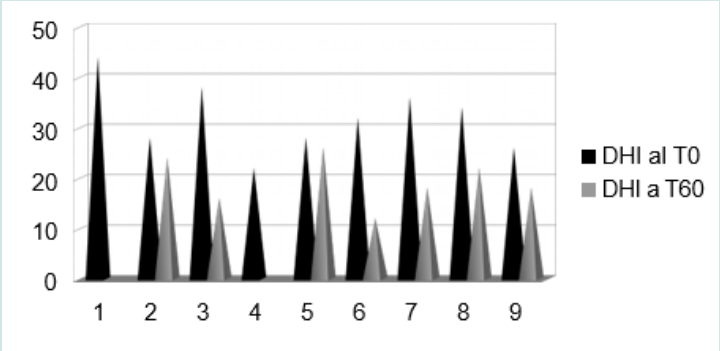

Figure 6.4: Trend of DHI in patients with Small Vessel Disease.

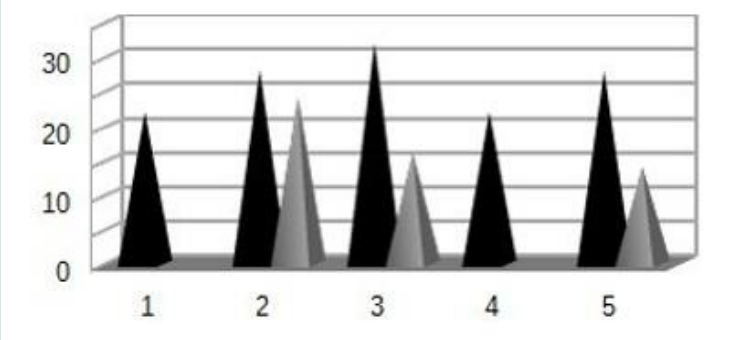

Figure 6.5: Trend of DHI in patients affected by Residual Dizziness.

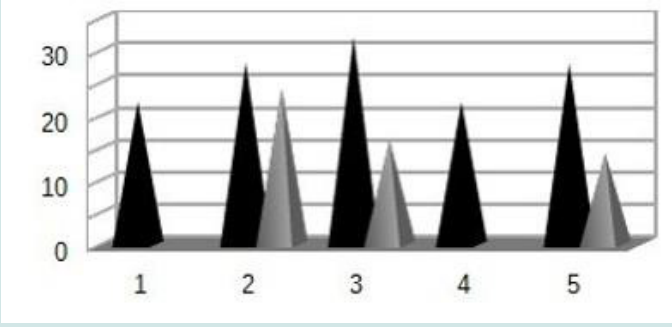

Figure 6.6: Trend of DHI in patients with toxic labyrinthosis.

Figure 6.7: Comparison between T0 (left) and T60 (right) on pathological findings at bedside examination on patients undergoing treatment with the supplement.

Conclusions

The possibility of a symptomatic effect together with a pathogenetic and, when possible, causal effect allows us today to have greater efficacy in the therapeutic approach to vertiginous pathology. With this study we wanted to evaluate a preparation already on the market, containing five different active ingredients, especially of the plant world origin, with which we have obtained satisfactory results in controlling the symptoms of treated patients. We have deliberately excluded from the study the common and defined most frequent labyrinthine pathologies in order not to add bias in pathologies that have a more acute course: in order to be able to fully evaluate the preparation in question, it seemed appropriate to choose clinical situations with stable symptoms, subacute or even chronic, excluding the variable of an acute pathology that could spontaneously have a favorable course. In this way we can confirm that the results, evaluated both subjectively and instrumentally, are more convincing than a clinical improvement caused by the drug under study, and not by the natural history of the disease: it is known in fact that the three diseases in question have a course characteristic temporal, paroxysmal by definition in labyrintholithiasis, episodic in hydrop disease and spontaneous remission in vestibular neuritis.

Instead, by choosing patients with stable, subacute or chronic suffering, the result of the therapy seems to us much more convincing. Despite these brilliant results, an evaluation of the patient by means of exploratory tests of the labyrinthine function and also evocative response tests seemed indispensable to us, in order to add an objective parameter to the global evaluation, to integrate the subjective feedback of the DHI questionnaire: so we evaluated all patients, both at time 0 and at the end of therapy, at time 60, with the bedside examination and with the caloric balance and / or with the video impulse test, in order to gather as much information as possible to corroborate the clinical results of the therapy carried out. We have given preference to the impulse test, both because it is less annoying for the patient, and because it is more complete and faster. Since the end of the first decade of this century, technological innovation in the vestibular field has made great strides in instrumental diagnostics of vertiginous pathology, obfuscating conventional examinations, especially evocative tests for which it is necessary to create a nystagmus, therefore a discomfort. for the patient. Nonetheless, it seemed more appropriate to evaluate the subjects by also examining the labyrinthine responses at low frequency, therefore with the caloric balance, to enrich a functional picture as complete as possible. We therefore collected from various sources the information that seemed necessary for an evaluation as complete as possible on the effectiveness of this new preparation. And we can say that all the data examined, from the anamnestic to the clinical approach, to the bedside examination and finally to the evoked tests, agree to define the picture of a preparation that has shown good efficacy in the treatment of vertiginous pathology.

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