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Research Paper

Use of an α-lipoic acid, *Boswellia serrata*, methylsulfonylmethane, and bromelain dietary supplement (OPERA®) for polyneuropathic pain management

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ABSTRACT: *Polyneuropathy is a very incapacitating disease of the peripheral nerves but there are few effective treatments often associated with side effects such as dizziness and drowsiness that can worsen the quality of life of patients. The study aims at demonstrating the benefits, safety, and tolerability of OPERA®, a nutritional supplement, containing α-lipoic, Boswellia serrata, methylsulfonylmethane, and bromelain with anti-inflammatory, analgesic, and anti-edema activity. Between November 2018 and April 2019, thirty consecutive adult patients attending Neurological Institute Casimiro Mondino with longer polyneuropathy were treated with OPERA®, once a day, for 2 months. Patients were evaluated at baseline and after 2 months using the Visual Analogue Scale (VAS) and Douleur Neuropathique en 4 Questions (DN4). At the baseline, on the average, the number of pain attacks was 5,2 (range 4-7), medium VAS 6,7(range 5-8), and medium DN4 6,1 (range 4-8) while at the end of treatment all parameters analyzed have significantly improved (p<0.0001): on the average, the number of pain attacks was 1,2 (range 0-2), median VAS 1,7 (range 0-4) and median DN4 1,4 (range 0-3). Improvements were observed in all patients regardless of disease. OPERA® has well tolerated: on a numerical scale from 1 to 10 the average score was 8 (range 7-10). The compliance of patients was optimal, no side effects related to the product were reported and no weight gain in patients occurred. This study showed the benefits, safety, and good tolerability of OPERA® in polyneuropathy treatment, and data are encouraged to be confirmed by further investigations.*

KEYWORDS: *α-lipoic acid; Boswellia serrata; Methylsulfonylmethane; Polyneuropathic pain.*

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I. INTRODUCTION

Symptoms related to polyneuropathies, such as numbness or tingling, burning pain (especially at night), muscle weakness, and pricking sensations (paresthesia) often harm a patient's quality of life [1]. Polyneuropathies are generalized disorders of the peripheral nervous system. They affect individually or in combination the motor, sensory and vegetative nerves, the sheath-like structures of their connective tissue, and the blood vessels, which supply them. Polyneuropathies are differentiated according to the rapidity of onset: acute within 4 weeks, subacute between 4-8 weeks, and chronic for more than 8 weeks. A further differentiating feature is the type of distribution: the most frequent type is distal-symmetrical polyneuropathy (i.e. affecting the hands and feet), proximal (proximal regions), and cranial (cerebral nerves). The overall prevalence of polyneuropathy in the general population seems around 1 % and rises to up to 7 % in the elderly. Polyneuropathy seemed more common in Western countries than in developing countries; there are indications

that females are more often affected than males. Diabetes, alcohol overconsumption, cytostatic drugs, and cardiovascular disease are more commonly associated with polyneuropathy [2]. The reported prevalence of painful diabetic polyneuropathy typically ranges from 10% to 26%, based on different diagnostic criteria for neuropathic pain (DPN). In a European multicenter study on 1171 diabetic patients, the prevalence of painful DPN in subjects with type 1 and type 2 diabetes was 11.6% *vs* 32.1%, respectively in the lower limbs and 7.1% *vs* 16.6% in the upper limbs [3]. Other neuropathy causes include physical nerve injury, tumors, exposure to toxins, alcoholism, kidney failure, autoimmune responses, nutritional deficiencies, shingles, HIV infection, and vascular or metabolic disorders [4]. Early diagnosis and treatment of peripheral neuropathy are so important because the peripheral nerves have a limited capacity to regenerate and treatment may only stop the progression but not reverse the damage. Diagnostic testing may include blood and urine analysis, electromyography, nerve conduction studies, and skin, nerve, and muscle biopsies. Imaging tests may include a CT scan, X-rays, or magnetic resonance imaging [5]. Several scales can be used to detect neuropathic pain such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Neuropathic Pain Questionnaire (NPQ), and the neuropathic pain diagnostic questionnaire (DN4) [6-8]. The DN4 is a simple questionnaire that also attempts to distinguish neuropathic pain from no neuropathic pain: the 10-item questionnaire consists of sensory descriptors and signs related to bedside sensory examination. The investigators compared patients with neuropathic pain (i.e. traumatic nerve injury, postherpetic neuralgia, and post-stroke pain) with no neuropathic pain patients (i.e. osteoarthritis, inflammatory arthropathies, and mechanical low back pain). They noted that several symptoms (pain descriptors and paresthesia/ dysesthesia) and signs (evoked pain and sensory deficits) were significantly more frequent in the neuropathic pain group. A cutoff score of 4 has a predictive value of 86%, a sensitivity of 82.9%, and a specificity of 89.9%. The pain VAS is a continuous scale, usually, 10 centimeters in length, that measure the pain intensity from none (score of 0) to an extreme intensity of the pain (score of 100) [9]. Several medications are employed to relieve peripheral neuropathy signs and symptoms including pain relievers such as nonsteroidal anti-inflammatory drugs, opioids, antiepileptic drugs such as gabapentin and pregabalin (associated with side effects as drowsiness and dizziness), tricyclic antidepressants such as amitriptyline, doxepin, and nortriptyline, and topical treatments with capsaicin ointment. Concerning complementary treatments acupuncture, herbal supplements, acetyl-L-carnitine, and α-Lipoic acid might help reduce neuropathy pain. OPERA® (Gam FarmaS.r.l. -Milan Italy) is a new dietary supplement where α-lipoic acid (ALA) (240 mg), *Boswellia serrata* (40 mg), methylsulfonylmethane (200 mg), and bromelain (20 mg) are combined in a single hard-gelatin capsule. ALA is a strong lipophilic antioxidant that is effective in the treatment of diabetic neuropathy [10]: *Boswellia serrata*, methylsulfonylmethane, and bromelain exhibit anti-inflammatory, and anti-edema activity [11-13]. OPERA® is a dietary supplement, developed with innovative technology Actisystemboxes® for controlled and diversified absorption. This device allows the release of active ingredients targeted in inflammatory sites, increasing efficiency, and lowering the minimum effective dose up to 1/10. A clinical study concerning chemotherapy-induced peripheral neuropathy (CIPN) demonstrated that after 12 weeks of treatment with OPERA® showed an improvement in both pain and CIPN symptoms. Moreover, treatment with OPERA® supplement was well tolerated by patients and no significant toxicity was reported. [14]. Our study aims at demonstrating the benefits, safety, and tolerability of OPERA® in reducing polyneuropathic pain symptoms.

II. MATERIALS AND METHODS

This clinical study consisted of a consecutive of 30 adult Caucasian patients (17 male, 13 female) with polyneuropathy attending the Neurological Institute Casimiro Mondino, Pavia (Italy). Inclusion criteria: patients over 18 years of age with polyneuropathy, not undergoing pharmacological treatment for polyneuropathy. Patients' clinical characteristics are summarized in table 1. Patient heterogeneity is determined by 2 reasons: a) recruit patients with different pathologies that cause polyneuropathy; b) evaluate the pharmacological response with OPERA® in different forms of polyneuropathy, especially in the diabetic and post-chemotherapy form. All patients are treated with OPERA® once a day for 2 months. Study design and study procedures were reviewed and approved by our ethics committee and informed consent was obtained from all individual participants included in the study. Patients were evaluated at baseline and after 60 days using the Visual Analogue Scale (VAS) and Douleur Neuropathique en 4 Questions (DN4): data relative to efficacy and tolerability were collected. At the baseline, the average number of pain attacks was 5,2 (range 4-7), medium VAS 6,7 (range 5-8), and medium DN4 6,1 (range 4-8).

Variable	N (%) *Total N= 30*
Sex	
Male	17 (56 %)
Female	13 (44 %)
Age (mean-range)	53 (38 -72)
Diagnosis	
Diabetes	11 (37 %)
Compressive radiculophaty	7 (23 %)
Cancer	6 (20 %)
Post-herpes neurophaty	4 (13 %)
Hepatitis C	2 (7 %)

Table 1: Characteristics of the study patients.

III. RESULTS AND DISCUSSION

All patients started with OPERA® supplementation at enrollment and completed consumption of OPERA® in the eighth week. Treatment was well tolerated (on a numerical scale from 1 to 10 the average score was 8, range 7-10) and no acute toxicity directly related to the intake of OPERA® were reported during the study period. The compliance of patients was optimal, no side effect was reported and no weight gain occurred. At the end of treatment, all analyzed parameters were significantly improved ($p<0.0001$): average number of pain attacks was 1,2 (range 0-2), median VAS 1,7 (range 0-4), and median DN4 1,4 (range 0-3). DN4 highlights neuropathic pain and therefore influences the correct diagnosis of polyneuropathy, while the NRS scale (VAS) determines the overall reduction of pain intensity (e.g. headaches, and chronic pain). Improvements were observed in all patients regardless of disease (figure 2). Polyneuropathy is a very incapacitating disease of the peripheral nerves: the morbidity associated with it can lead to pronounced alterations in quality of life, thus impairing the independent performance of activities of daily living [15]. Polyneuropathies (peripheral neuropathies) are the most common type of disorder of the peripheral nervous system in adults, and specifically in the elderly, with an estimated prevalence of 5–8%, depending on age. Approximately 50% of all polyneuropathies are associated with pain [16].

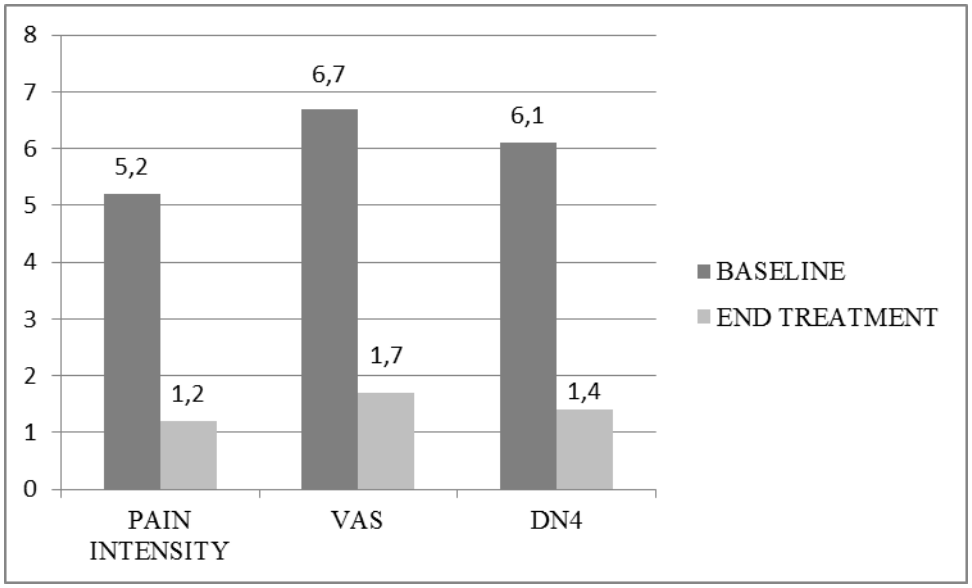

Figure 2: Efficacy data.

The neuropathic pain is caused by spontaneous activity and the sensitization of damaged axons, mediated by overactive sodium channels, as well as the effect of inflammatory mediators and growth factors. Since, therefore, the mechanisms of neuropathic pain differ fundamentally from those of nociceptive pain, special treatment approaches are needed. The options for treatment depend on the cause, which should therefore be identified as precisely as possible by an appropriate diagnostic evaluation. Pharmacological treatment of neuropathic pain included gabapentin, pregabalin, duloxetine, and tricyclic antidepressants as drugs of the first choice, whereby attention needs to be paid to side effects such as dizziness and drowsiness that can worsen the quality of life of patients [17]. New safe and effective treatments are warranted. A rising interest has developed over the past few years for the use of natural products or complementary medicine [18]. A widening body of research indicates alternative medicine may offer significant benefit to this patient population: particularly, several studies have been carried out in this setting with vitamin E, glutathione, acetyl-L-carnitine, vitamin B12, and especially ALA [19]. ALA among the well-researched nutrients for peripheral neuropathy has been used as a treatment for peripheral neuropathy in Europe for decades. Three large scales, double-blind, placebo-controlled trials – ALA in Diabetic Neuropathy (ALADIN) studies have examined various routes of administration, dosages, and neurological effects of ALA [20-22]. A meta-analysis of four placebo-controlled trials (n=1,258) – ALADIN I and III, SYDNEY, and a fourth unpublished trial (Neurological Assessment of Thioctic Acid; NATHAN II), all with the same protocol of 600 mg ALA administered I.V. for three weeks, found a continuous daily improvement in symptom scores beginning on the eighth day of treatment [23]. A recent systematic review of the literature confirmed the efficacy and safety of ALA in the treatment of diabetic polyneuropathy by significant improvements in neuropathy symptoms (pain, burning sensation, tingling, numbness) and clinical signs (reflected Achilles tendon, vibration perception, perception of pain and temperature, muscle strength) [24]. In our study, OPERA® demonstrated efficacy with lower doses of ALA in reducing neuropathic pain in all patients treated, regardless of the disease. Moreover, the presence of effective substances on inflammation, pain, and edema allows having a faster effect on the symptoms of the treating patients, considerably improving the quality of life in carrying out daily activities.

IV. CONCLUSION

Our study showed the benefits, safety, and good tolerability of OPERA® in polyneuropathic pain treatment regardless of the underlying disease. The use of this dietary supplement should be taken into consideration as a good practice in this setting of patients. Data from our experience are encouraging to be confirmed by further investigations. Furthermore, supplementation with Opera® could be useful in the treatment of polyneuropathic disorders resulting from COVID-19 infection. Further studies on this type of patient could be of great interest.

Conflict of interest statement: The authors stated that there are no conflicts of interest regarding the publication of this article.

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