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Original article

Topical Fisionerv® is effective in treatment of peripheral neuropathic pain

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Summary. *Background:* Management of neuropathic pain (Neu P) is complex and difficult. Although there are several therapeutic options, treatment with Neu P is often inadequate, which led to undertreated patients. Thus, it would be desirable, for Neu P treatment, further multimechanistics approaches. *Objective:* The aim of the present study was to evaluate, in Neu P management, the effectiveness of "FISIONERV, a gel for topical use. *Setting:* This study was conducted in the "Rehabilitation Unit of N. Melli's Hospital, Brindisi, Italy". *Patients and intervention:* In this study a double- blind randomized controlled clinical trial was conducted over 8-week treatment on 58 outpatients affected by Neu P caused by lumbar sciatica or lumbar disk herniation and/or lumbar canal stenosis (31 subjects), or with carpal tunnel syndrome (27 subjects), randomly assigned to the following two groups: Group A; n=29, received (*fisionerv*® gel, 3 times/day) added to physiotherapy (forty minutes-daily session). Group B; n=29 received a vehicle gel (placebo, 3 times/day) added to physiotherapy (forty minutes-daily session). *Measurements:* Pain was assessed by a visual analogue scale (VAS). Neuropathic symptoms frequency (pain, burning, paraesthesiae and numbness) were scored at baseline and at the end of the treatment. Treatment compliance and safety were also evaluated. *Results:* Both groups experienced a significant reduction in VAS and neuropathic symptoms after 8-treatment weeks. However, a significant ($p<0.05$) improvement was observed in group A (VAS mean 5.3 (1.10) with respect to group B (VAS mean=6.17 (0.80), already after 4 weeks of treatment. A further VAS reduction was recorded at 8 treatment weeks, with significant difference between the treatments (group A: VAS mean=1.89 (0.77); group B: VAS mean=3.79 (1.20) ($p<0.001$). In addition, more patients of the group A, than in group B, reported an improvement of their neurophatc pain ($p<0.01$). No adverse drug reaction was observed. Conclusion: Use of *fisionerv*®, in combination with physiotherapy, resulted a useful approach to NP treatment. *Clinical rehabilitation impact:* These preliminary observations suggest that some interesting goals (better pain control and physical wellbeing) could be achieved by a multimodal therapy in NP patients. (www.actabiomedica.it)

Key words: peripheral neuropathies, *fisionerv*® emulgel, physiatric treatment, neuropatic pain

Introduction

Aim of the study

Neuropathic pain (NeuP) is a symptom which occurs as a result of injury or dysfunction of the nervous system caused by a lot of conditions affecting the peripheral or central nervous system. Compared to other types of pain, it is debilitating, both physically and psychologically. It could be constant or intermittent, spontaneous or induced by a trigger stimulus and could give allodynia or hyperalgesia. The cause could be due to the pathological changes or damages in neurons which can disrupt the normal pain signaling process causing sensitization or stimulation of spontaneous neuronal activity which is perceived as pain. Because of the complex nature of Neu P and, since the treatment of the underlying pathophysiogy causing neurophaties may not be always possible, a multidisciplinary and integrated approach is often used to manage the pain mainly improving the patient's quality of life. Valid drugs today available for Neu P treatment result often inadequate, considering that only 40-60% of treated patients may report an adequate pain relief and comorbidities whereby polidrugs intake could appear an unbearable situation (1). Furthermore, several guidelines have been published for the pharmacological management of Neu P which underline the importance of drugs efficacy, patient comorbidities, potential side effects and drug interactions, as well as abuse potential and costs (2-5). Other additional drugs like *capsaicin or lidocaine* could be used topically to relieve pain in a specific area of the body or to relieve particularly severe pain for shorts period of time, primarily in patients which cannot or don't prefer to intake drugs due to their interference with the ongoing treatment. Capsaicin preparations (cream or ointment) have shown some effectiveness on pain. Derivated from "*capsicum chili pepper*", capsaicin has been used for centuries as a topical analgesic. It is a selective agonist of TRPV1 receptors (transient receptor potential vanilloid receptor 1) expressed in afferent neuronal "c" fibers. Local activation of TPRV1 by heat, ph changes or endogenous lipids, normally leads to nerve depolarization propagated to spinal cord and brain thus causing local heat stinging and itching sensation. Prolonged activation of TPRV1 by capsaicin results in loss of receptor functionality, causing impaired local nocyneception for extended period. The therapy also involves the use of neuroprotective drugs, such as alpha-lipoic or tioctic acid, which have antioxidant action, in order to improve nerve conduction speed and endoneural blood flow and thereby reducing pain. *Fisionerv* ® is an ozolipoil gel containing stabilized ozonized oil together with a dynamic pool of functional molecules to release bioperoxides and ozonides, in synergic action with tioctic acid plus Vitamin E, capsaicin, panthenol, arginine, valine, isoleucine, leucine and glutamine. Generally, although the neuropathic pain poorly responds to treatment with NSAIDs or pure analgesics, such classes of drugs are however equally and widely used in these diseases. Our aim is to demonstrate the validity of *fisionerv*® to ameliorate the painful state of the treated patients and to significantly improve the suffering pain with respect to the control group. The important aspect put on evidence in this procedure is the lack of needing other concomitant pharmacologic therapies during the treatment with *fisionerv*®. Their quality of life obtained a significative improvement with a long-lasting pain reduction during the walk, the upright posture and during sleep, especially in supine position.

Formulation: *fisionerv*® emulgel is packed in 100 ml aluminum tube. The emulgel is constituted of Carbopol 990 Polymer which produces the gelling water and Carbopol Ultrez 20 which emulsifies the ozonized olive oil, previously stabilized with alpha lipoic acid and Vitamin E acetate.

Materials and methods

Study design

Consecutive outpatients (Department of Physical and Rehabilitative Medicine, N. Melli's Hospital, Brindisi, Italy) with clinical features of Neu P from November 2015 to June 2016 were invited to participate in this 8-week, randomized, controlled, clinical trials. A total of 76 consecutive outpatients affected by low back pain with leg pain (24 women and 22 men) or carpal tunnel syndrome (16 women and 14 men) were screened for eligibility. This study, conducted in com-

pliance with the "*ethical principles for medical research involving human subjects*" of the Declaration of Helsinki and *in accordance with Italian laws and regulations*. The informed consent of all the patients was obtained prior the begin of the study.

Inclusion criteria: The enrolled patients were suffering neuropathies for more than six months, with chronic pain from moderate to severe (VAS>4) and with little or absent response to systemic or local analgesic therapy.

Exclusion Criteria: Were excluded from the study pregnant or breastfeeding patients, spinal tumor, major organ transplantation, uncontrolled major depression or psychiatric disorder, acute or uncontrolled medical illness (malignancy or active infection), chronic severe condition that could interfere with interpretation of the outcome assessments. Also allergy to study drugs and placebo were taken into consideration as exclusion criteria. On the total number of admitted outpatients, only 58 patients were enrolled in the present study: (low back pain=31; 17 women and 14 men; carpal tunnel syndrome=27; 14 women and 13 men; mean age=63,5 years , SD=7.1) (Table 1).

Enrolled patients, all over 18 years old, were informed about the reasons and objectives of the present study, releasing an informed consent as spontaneous adhesion to the study.

Study protocol and treatments

All the enrolled patients (58) were randomized by an independent investigator, using a computer generated-random-number table to the following treatment groups:

Group A (treated group); n=29, received *fisionerv®* gel, three times/day) added to physiotherapy (forty minutes-daily session);

Group B (control group); n=29 received a vehicle gel (placebo, three times /day) added to physiotherapy (forty minutes-daily session).

Dosage: *fisionerv®* for topical use was administered 3 times a day.

Assessment: Before starting the study, all the patients underwent a screening included medical history and physically examination gender, age and occupation were documented, as well as other clinical characteristics such as the diagnosis, time since first diagnosis, diagnostic tests performed and concomitant treatments.

All the patients were asked, by a blinded interviewer, for neuropathic pain according to the original Scott- Huskisson scale with score from 0 ('no pain') to 10 (unbearable pain) (6).

Table 1. Baseline demographic and clinical characteristics of participants with neuropathic pain in groups. A and B

Characteristics	Group A (n= 29)	Group B (n= 29)	*p*
Age	57.09 [(16.40) 50.00-64.18]	51.65 [(12.23) 46.36-56.94]	*0.21*[a]
Range	27-78	31-78	
Time since onset of pain (mo)	6.95 [(1.06) 6.49-7.41]	7.22 [(1.20) 6.69-7.74]	*0.44*[a]
Range	6-9	6-10	
Sex (female/male) No (%)	16/13	15/14	*1.00*[b]
Type of neuropathic pain (NeuP) No (%)			
Low back pain with leg pain (female/male) No (%)	9/7	8/7	*1.00*[b]
Tunnel Carpal Syndrome (female/male) No (%)	7/6	7/7	*1.00*[b]
***VAS** score* Low back pain	8.26 [(0.70) 7.87-6.78]	8.00 [(1.00) 7.44-8.55]	*0.40*[a]
***VAS** score* Tunnel Carpal Syndrome	7.66 [(1.17) 7.01-8.31]	7.36 [(1.04) 6.77-7.94]	*0.45*[a]

Values are means [(SD: standard deviation) 95% CI: 95% confidence interval unless otherwise specified;
VAS: Visual Analogic Scale (0-10 point);
[a] As determined by an independent 2-sample t;
[b] As determined by Fisher's exact test.

All outcomes before treatment (T0) and at the scheduled follow-ups (T1=4-treatment-weeks and T2 =8-treatment-weeks were assessed by a third blinded independent observer.

Neuropathic symptoms frequency (pain, burning, paraesthesiae and numbness) were also scored at baseline and at the end of the treatment.

The compliance of the patients with the study was assessed by checking whether the patients followed the physiotherapy sessions that were prescribed at the start of the study and recording adverse reactions, intolerance, or "lack of efficacy" as perceived by the patients.

Both experimental groups were composed by 29 patients: treated group: (**Group A**)=16 women and 13 men, control group (**Group B)=**15 women and 14 men (table 1).

On these two groups of patients we have studied the effectiveness of our galenic topic preparation "*fisionerv*"®, compared to a similar gel but without ozonides used in placebo group.

Patients were not allowed to take any other analgesic compound for the entire duration of the study.

Statistical evaluation: The results are reported as descriptive statistics: quantitative parameters are reported as median, minimum, maximum and standard deviation; qualitative parameters are reported as absolute and relative frequencies. Comparisons were made with a chi-squared test for qualitative parameters and with an unpaired Student's t test for quantitative ones.

Two-way analyses of variance (ANOVAs) for repeated measures of VAS scores were performed with group (treatments) as the between-subjects factor and time and group interactions × time as the within-subjects factors. Post hoc comparisons were made by Bonferroni multiple comparisons test. Statistical analysis was performed according to the principle of intention to treat, with missing data imputed with the "last observation carried forward" technique. All analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina). Computed *P* values were 2-sided and $p<0.05$ was used to determine statistical significance.

Results

As shown in table 1, the participants' baseline characteristics did'nt show statistically significant differences between the experimental groups.), Of the 58 patients with Neu P, 38 (65.5%) had numbness and 20 (35%) had tingling and touch hypoesthesia at baseline. Repetead measure Two way Anova for VAS scores showed a significant effect of Treatment: F=3.01 df=1/56; p<0.0001 and a significant treatment-time interaction: F=3.67; df= 2/112, p<0.0001. A significant change in VAS score over time also was observed in both groups: F=75.88; df=2/112. The effect on pain relief was perceptible-at 4-treatment-weeks (T1) versus baseline (T0) in both groups although it was more evident in group A than in group B with a statistically difference between treatment groups (p<0.05). Comparing VAS scores at 8 weeks of treatment (T2 versus T1), the difference between the treatments resulted more significant (p<0.001) Table 2.

In addition, more patients of the group A reported that their neurophatic pain was significantly improved with respect to the patients of the group B ($p<0.01$; *Chi square test).* No drug reaction was observed.

Table 2. Time course of VAS scores in Treatments groups at the baseline and follow-ups: T1 (4 treatment- weeks); T2 (8 -Treatment weeks);Tukey Multiple comparisons test between treatment groups

	Group A (n= 29)	Group B (n= 29)	p
T0	8.26 [(0.70) 7.62-8.38]	7.69 [(1.03) 7.29-8.08]	n.s.
T1	5.31 [(1.10)4.89-5.73]°	6.17 [(0.80) 5.86-6.47]#	<0.05*
T2	1.89 [(0.77) 1.60-2.19]°	3.79 [(1.21) 3.33-4.25]#	<0.001**

* p<0.05 T1 group B vs T1 Group A
** p<0.001 T2 group B vs T1 Group A
° p<0.001 vs baseline and T1
# p<0.001 vs vs baseline and T1

Conclusions

Previous studies with ozolipoil were made in 2015 by Inchingolo et al (11) in order to test, on actinic ulcers of patients receiving radiation therapies, a mixture with a formulation containing, other than ozolipoile, several natural active ingredients. Although there are several therapeutic options, Neu P treatment results often inadequate leaving patients undertreated thus, a better use of available options and multimechanistics approaches to Neu P management, based on the patient's characteristics, may result beneficial. Multiple factors are involved in the pathophysiology of peripheral neuropathies and it is very difficult to pinpoint the right treatment. For this reason new treatments are desired. In this context, *fisionerv*® represents a topical gel which encloses, in its formulation, a wide range of active ingredients related with different mechanisms involved in peripheral neuropaties. Results clearly demonstrate a significant pain improvement in the group treated with *fisionerv*® with respect to placebo group. The important aspect put on evidence in this procedure is the lack of needing other concomitant pharmacologic therapies during the treatment with *fisionerv*®. Their quality of life obtained a significative improvement with a long-lasting pain reduction during the walk, the upright posture and during sleep, especially in supine position. However, further studies and larger groups of patients are needed to validate these preliminar data in order to confirm our encouraging results.

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Conflict of interest: None to declare

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