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RESEARCH ARTICLE

TOPICAL FISIONERV® IS EFFECTIVE IN TREATMENT OF PERIPHERAL NEUROPATHIC PAIN

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ABSTRACT

The aim of the present study was to evaluate, in Neu P management, the effectiveness of "fisionerv®", a gel for topical use. This study, conducted in the "Rehabilitation Unit of N. Melli 's Hospital, Brindisi, Italy". was a double- blind randomized controlled clinical trial, 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). Patients were 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). Pain, burning, paraesthesiae and numbness were assessed by a visual analogue scale (VAS) at baseline and at the end of the treatment. Groups A showed a significant reduction in VAS and neuropathic symptoms after 8-treatment weeks with a significant difference between the treatments (group A: VAS mean=1.89 (0.77); group B: VAS mean= 3.79 (1.20) ($p < 0.001$).

INTRODUCTION

Aim of Thhe 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, 3, 4, 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. Derived 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

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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 receptors by capsaicin results in loss of receptor functionality, causing impaired local nociception for extended period. The therapy also involves 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. F*isionerv*® 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, these classes of drugs are however equally and widely used in these diseases. In this manuscript 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 CarbopolUltrez20 which emulsifies the ozonized olive oil, previously stabilized with alpha lipoic acid and Vitamin E acetate.

MATERIALS AND METHODS

Study Design: A total of 76 outpatients (*Department of Physical and Rehabilitative Medicine, N. Melli 's Hospital , Brindisi, Italy*) with clinical features of Neu P,affected by low back pain with leg pain (24 women and 22 men) or carpal tunnel syndrome (16 women and 14 men) from November 2015 to June 2016 were screened for eligibility and invited to participate in this 8-week, randomized, controlled, clinical trials This study was conducted in compliance with the "*ethical principles for medical research involving human subjects*" of the Declaration of Helsinki and *in accordance with Italian laws and regulations.*

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 patients, major organ transplanted, affected by uncontrolled major depression or psychiatric disorder, by acute or uncontrolled medical illness (malignancy or active infection), by chronic severe condition which could interfere with the interpretation of the outcome assessments. Allergy to study drugs and placebo were also taken into consideration as exclusion criteria. On the total number of 76 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) (See 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 58 enrolled patients 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 patients underwent a screening including medical history, physically examination gender, age, occupation.It was further documented any clinical characteristics such as the diagnosis, time since first diagnosis, diagnostic tests performed and concomitant treatments. All patients were asked, by a blinded interviewer, about neuropathic pain, according to the original Scott-Huskisson scale with score from 0 ('no pain') to 10 (unbearable pain)(6). 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 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 physiotherapic sessions prescribed at the start of the study and when recording adverse reactions, intolerance, or ''lack of efficacy''.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.

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 (months)	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)			
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 (8.87-6.78]	8.00 (8.55-7.44]	*0.40*[a]
***VAS** score* Tunnel Carpal Syndrome	7.66 (8.31- 7.01)	7.36 (7.94- 6.,77]	*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.

Repeated 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 statistical 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*
T0Baseline	**8.26 [(0.70) (8.38-7.62]**	**7.69 (1.03) (8.08- 7.29]**	**n.s.**
T1After 4 treatment weeks	5.31 [(1.10) (5.73-4.89]°	6.17 (0.80) (6.47-5.86]#	<0.05*
T2After 8 treatment weeks	1.89[(0.77) (2.19- 1.60]°	3.79 (1.21) (4.25- 3.33]#	<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 baseline and T1

DISCUSSION

This study assesses the effectiveness of our galenic topic preparation *"fisionerv"* ®, compared to a similar gel but without ozonides used in placebo group together with the degree of pain sensitivity of intra-articular analgesia induced in patients. There were immediate effects of the intra-articular treatment leading to higher PPTs (reduced pain sensitivity) at the knee and surrounding muscles and this effect up to two weeks after the beginning of treatment.Also the reduced pain sensitivity was not confined to the lower extremity due a reduced pain sensitivity observed at the control site on the contralateral arm. There are no definitive models explaining the transition from localized to widespread musculoskeletal pain conditions, but it has been suggested that initial excitation and sensitisation of peripheral nociceptors (e.g., due to joint inflammation) may cause sufficient input to the central pain systems to cause central sensitisation of dorsal horns neurons and/or higher brain centres [12, 13] where, at the beginning of the study, it was shown hyperalgesia in the leg and arm muscles. Further, our results may support the proposed action of *fisionerv*® emulgel on inflammation with a slow but progressive action. Widespread hypersensitivity in mechanical pressure pain was detectable in treated patients. Pain is the principal clinical detectable sign in the nociceptive system. Our treatment may have a potential role in preventing and reducing spreading algesia in patients, well defined into our controlled trials.The lack of association between pain sensitivity (PPT), pain sensitivity changes and improvements in current articular and muscular pain, could be explained by the difference in the constructs of the two pain assessment types where clinical pain improvement could be influenced by a wide range of parameters, including nociception, psychosocial factors and affections [14]. In contrast, the PPTs are based on an instant painful stimulation, thus presumably reflecting the nociceptive mechanisms. On the other hand, the sample size may preclude detection of statistically significant associations. [15]; In addition, it is interesting that different results at different sites were obtained with the computer-controlled and manual pressure algometers. The reason might be that the manual algometry is both operator and patient dependent with the inherent variability related to manual pressure application, whereas the computer-controlled is purely patient dependent. Manual algometry is readily available to the broad audience, whereas the computer-controlled algometer is custom made for research purposes only. Besides the small sample size, an important aspect of the present study is the presence of a control group. Thus, placebo effects could be ruled out, and placebo might explain the immediate increase in PPT at the control site after injection. Furthermore, it has been shown that intra-articular anesthesia can have analgesic effects for up to 7 days [16], which may confound our findings somewhat. However, these data are the first of their kind and provide important stepping stones for future investigations.

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 several natural active ingredients, other than ozolipoile. 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 could desired in different pain mechanisms evaluation in knee osteoarthritis and knee replacement (12, 13, 14, 15, 16). 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* ®. The treated patients obtained a significative improvement in their quality of life with a long-lasting pain reduction during the walk, the upright posture and sleep, especially in supine position. However, further studies and larger groups of patients are needed to validate these preliminary data in order to confirm our encouraging results

"The authors have declared that no competing interests exist."

References

1. Attal *et al*., 2006 Handbook of Clinical NeurologyVol. 81, PAIN, pages 705-713).
2. Burke D[1], Fullen BM[1,2], Stokes D[3]*et al*.Neuropathic pain prevalence following spinal cord injury: A systematic review and meta-analysis.Eur J Pain.2017 Jun 21, 1: 29-44.
3. Cruccu G, Sommer C, Anand P. *et al*., EFNS guidelines on neuropathic pain assessment: (revised 2009) *Eur J Neurol.* 2010; 17 (8), 1010-1018
4. Deng Y, Luo L, Hu Y, *et al*. Clinical practice guidelines for the management of neuropathic pain: a systematic review.*BMC Anesthesiol*. 2016 18;16:12
5. Dworkin RH, Turk DC, Wyrwich KW, *et al*., Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: *J Pain*. 2008; 9(2):105-121.
6. Filipetto FA[1], Zipp CP, Coren JS Potential for pregabalin abuse or diversion after past drug-seeking behavior, *J Am Osteopath Assoc*.2010 Oct;110(10):605-607
7. Inchingolo F[1], Tarullo A[2], Cagiano R[2] *et al*.Successful use of a topicalmixture with ozolipoile in the treatment of actinic ulcers, *ClinCosmetInvestigDermatol.* 2015; 8: 147-150.
8. Anna K Clark, Elizabeth A Old, and MarziaMalcangio Neuropathic pain and cytokines: current perspectives *J Pain Res.* 2013; 6: 803-814.
9. Price DD, Bush FM, Long S. *et al*, A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain.* 1994*;* 56*:* 217-226.
10. Tashjian RZ, Deloach J, Porucznik CA. *et al*, Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. *J Shoulder Elbow Surg.* 2009*;* 18*:* 927-932.
11. Williamson A, Hoggart B, Pain: a review of three commonly used pain rating scales. *J ClinNurs.* 2005*;* 14*:* 798-804.
12. Graven-Nielsen T. Fundamentals of muscle pain, referred pain, and deep tissue hyperalgesia. *Scandinavian Journal of Rheumatology*. 2006;35 (supplement 122):1-43.
13. Suri P, Morgenroth DC, Kwoh CK *et al*. Low back pain and other musculoskeletal pain comorbidities in individuals with symptomatic osteoarthritis of the knee: data from the osteoarthritis initiative. *Arthritis Care & Research*. 2010;62(12):1715-1723.
14. Wolff BB. Methods of testing pain mechanisms in normal man. In: Wall PD, Melzack R, editors. *Textbook of Pain*. Edinburgh, UK: Churchill Livingstone; 1984. pp. 186-206.

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