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Original article

Scrambler therapy in the management of somatosensory signs and symptoms related to neuropathic pain: an exploratory and prospective analysis

Domenico Russo[1, 2], *Federica Zoratto*[1], *Gastone Tirocchi*[2], *Michela Guarda*[1]

[1] Hospice, Casa di Cura "San Marco", Latina, Italy; [2] Algology Unit, Studio Polispecialiastico "Albamedica", Albano Laziale, Italy

Summary. *Objectives:* Neuropathic pain is a severe and disabling health problem, often difficult to treat and characterized by specific somatosensory signs and symptoms. The goal of this study is to detect the effect of Scrambler therapy (ST) on the reset of Neuropathic Pain Diagnostic Questionnaire (DN4), in a cohort of patients affected by intense drug-resistant neuropathic pain. *Methods:* Patients with chronic neuropathic pain were consecutively enrolled to receive 45-minute daily ST for an average of 10 consecutive days. Evaluation of pain intensity by Numerical Rating Scale (NRS) score and DN4 questionnaire was performed at the beginning and at the end of the treatment. Primary endpoint was to achieve a significant negativization of DN4 (DN4 <4) in the study population after 10 ST sessions. Secondary endpoints were to detect a correlation between DN4 negativization and pain intensity reduction ≥50% (patient responders), finally to analyse the impact of ST on each item of DN4 survey. *Results:* We prospectively treated 45 patients. Mean baseline DN4 score was 5.67 [±1.43] and fell by 50.3%, with a mean DN4 score of 2.82 [±2.18] at the end of treatment (OR 2.84; 95%CI: 2.07-3.62; p<0.0001). In 28 out of 45 (62.2%) patients we reported a negativisation of DN4 (p<0.0001). Correlation between the percentage of patient responders and patients with negativization of DN4 was statistically significant (p<0.0062). Analysing each DN4 item pre- and post-ST, we reported a significant negativization in 6 out of 10 DN4 items. *Discussion:* Our prospective exploratory analysis met the primary endpoint and ST seems to resolve relevant somatosensory signs and symptoms related to neuropathic pain. Based on these encouraging results, the next step will be to evaluate these neuropathic pain features with dedicated tools. (www.actabiomedica.it)

Key words: crambler therapy, neuropathic pain, Neuropathic Pain Diagnostic Questionnaire, somatosensory signs and symptoms

Introduction

In 2011, the International Association for the Study of Pain (IASP) published a new definition of neuropathic pain according to which neuropathic pain is defined as *"pain caused by a lesion or disease of the somatosensory system*" (1). Neuropathic pain is not a single disease, but a syndrome caused by a range of different diseases and lesions, which manifests with somatosensory signs and symptoms such as hyperalgesia, allodynia, dysesthesia and sensitivity deficit (1). Despite increased knowledge about neuropathic pain pathophysiology, the current therapy for neuropathic pain is not satisfactory: more than two-thirds of patients obtain insufficient pain relief (1, 2). Recent scientific evidence supports the hypothesis that persis-

tent neuropathic pain develops as a consequence of enhanced pain sensitivity. Physiological changes, which cause these alterations, include sensitization of nociceptors, neuronal circuits and modifications of genes expression that encode for pain signalling molecules or receptors involved in these pathways (3-5).

Therefore, there is a need to integrate non-pharmacological strategies for neuropathic pain management (6, 7). ST is an electrostimulation technique whose action mechanism is largely unknown. It differs from transcutaneous electrical nerve stimulation (TENS) although both provide stimulation via peripheral nerves (8). The theoretical approach interprets the nociceptive system in terms of cybernetics, referring to the information theory. Biophysical and chemical changes are deliberately confined in a "black box". The hypothesis of the inventor focuses on restoring homeostasis after treatment, which means focusing on the clinical effects of the treatment. In clinical practice ST seems to produce a remodulation of the pain system's response and someone suggested the reduction of central sensitization and an increase in pain threshold. The increase of pain threshold after ST cycle, measured by quantitative sensory testing (QST), seems to confirm this hypothesis (8-12).

Marineo et al. (10, 12) investigated safety and efficacy of ST, highlighting how it appeared to relieve chronic neuropathic pain better than guideline-based drug management. Coyne and Smith (13, 14) have reported similar encouraging results in patients with chemotherapy neuropathic pain and post-herpetic pain respectively. Moreover, recently the Scrambler Therapy Group has published results from a multicenter retrospective analysis, confirming the efficacy and safety of ST in the management of several different types of refractory chronic neuropathic pain (15).

Despite these interesting results, to date few investigators have examined the influence of ST on somatosensory signs and symptoms related to neuropathic pain.

All these considerations constituted the background for our prospective, exploratory analysis conducted with the aim to detect, in a cohort of patients affected by intense drug-resistant chronic neuropathic pain, the efficacy of ST in resolving somatosensory signs and symptoms of neuropathic pain.

Methods

Patients were included in this study if their pain intensity was ≥4, on the Numerical Rating Scale (NRS), at least four days a week in the previous three months. Moreover, patients were eligible if they had reported a positive Neuropathic Pain Diagnostic Questionnaire (DN4). DN4 is developed to screen components of neuropathic pain in yes/no answers consists of 10 items: Burning, Painful Cold, Electric Shocks, Tingling, Pins and Needles, Numbness, Itching, Hypoesthesia to touch, Hypoesthesia to prick, Pain caused or increased by Brushing. Examination of sensitivity to touch and tactile allodynia were performed with the use of a soft brush, while examination of sensitivity to pricking was performed with the use of a Von Frey hair. The cut-off score, for the diagnosis of neuropathic pain, was determined as 4 times a "yes" answer out of 10 DN4 items (score 0-10) (16).

The work was based on a consecutive case series of selected patients who satisfied inclusion criteria. The inclusion and exclusion criteria are reported in Table 1.

Patients were treated at the Pain Therapy Unit of Casa di Cura "San Marco", Latina. ST was planned for 45-minutes daily, for ten consecutive days (from Monday to Friday). Treatment was discontinued if symptoms disappeared before the tenth session, but if pain intensity was still decreasing at the tenth session, ST was continued until complete resolution or until stable condition.

An expert physician or nurse administered treatment. As ST is considered an operator-dependent treatment (8), a physician or nurse, who has administered therapy, must have been trained through theoretical and practical courses for the use of this method, achieving a clinical practice of ST over at least four years (8, 17). The same therapist took care of each patient for the entire duration of treatment.

The operator chose the best treatment areas before each session. Electrodes were not applied over the painful area but immediately beside the pain-affected area or in the dermatomes above and below. The stimulus was slowly increased to the maximum intensity tolerated by the patient. During this stimulation complete pain relief was expected; otherwise the operator had to add or move channels to increase the cover-

Table 1. Inclusion and exclusion criteria

Inclusion	Exclusion
NRS pain intensity ≥4 in the preceding three months	Presence of dermatological conditions that preclude application of skin electrodes
Presence of pain for at least six months	Presence of serious psychiatric disorder
Frequency of pain more than four days per week	Uncontrolled seizures
Clinical diagnosis of neuropatic pain DN4 posive (score ≥4) Age >18 years Consent to Scrambler therapy treatment	Any form of implanted medical device
Pregabalin and gabapentin had to be suspended at least three day before the start of treatment	

age (8). *"Pain intensity 0"*, during stimulation, is an extremely critical parameter and it was pursued with particular attention (8, 17).

The same physician recorded pain intensity by NRS and DN4 questionnaire at the beginning and at the end of each treatment.

During the first day of treatment patients were examined and interviewed, they also gave written informed consent. Patients have not changed their current drug pain treatment for the duration of the neuromodulation, in order to highlight the real pain relief provided by the ST. For the conduct of this study, the approval of the relevant ethics committee has been requested and obtained.

The primary endpoint of this analysis was to achieve a significant negativization of DN4 (DN4 <4) in the study population after ST. Secondary endpoints were to detect a correlation between DN4 negativization and pain intensity reduction ≥50% (patient responders), to analyse the impact of Scrambler therapy on each item of DN4 survey, finally to observe a variation between the assumed pain therapy before and after Scrambler therapy. Fisher's exact test and Student's t–test have been used where appropriate. Statistic significance was set for p-*value* <0.05.

Results

45 patients with neuropathic pain were recruited for the study. The characteristics of these 45 assessed patients are reported in Table 2. Median age was 65 years (range 29-96), 30 patients (66.7%) were female and 15 (33.3%) male. All patients had suffered from neuropathic pain for more than 3 months and in a continuous manner with intense episodes, despite therapy (Table 3). Some of previous studies about ST focused on neuropathic pain caused by single pathologies, some others were about multiple neuropathic pain syndromes. Our work is part of this second category of studies: we included several kind of neuropathic

Table 2. Characteristics of study population

Characteristics	Patients (n=45) n (%)
Sex	
Male	15 (33.3)
Female	30 (66.7)
Age (years)	
Mean	65
Range	29-96
Diagnosis	
Lumbar radiculopathy	13 (28.9)
Post herpetic neuralgia	12 (26.7)
Peripheral neuropathy	8 (17.8)
Cervical radiculopathy	4 (8.9)
Trigeminal neuralgia	3 (6.7)
LBP	2 (4.4)
Post surgical pain	1 (2.2)
FBSS	1 (2.2)
Multiple Sclerosis	1 (22)

FBSS: failed back surgery syndrome; LPB: low back pain

Table 3. Pain therapy taken before Scrambler Therapy

Drugs	Previous therapy N. patients (%)
FANS	17 (37.7)
Steroids	4 (8.8)
Anticonvulsants	30 (66.6)
Antidepressants	4 (8.8)
Weak opioids	4 (8.8)
Strong opioids	11 (24.4)
Other	2 (4.4)
No therapy	0 (0)
Monotherapy	20 (44.4)
Polytherapy	25 (55.6)

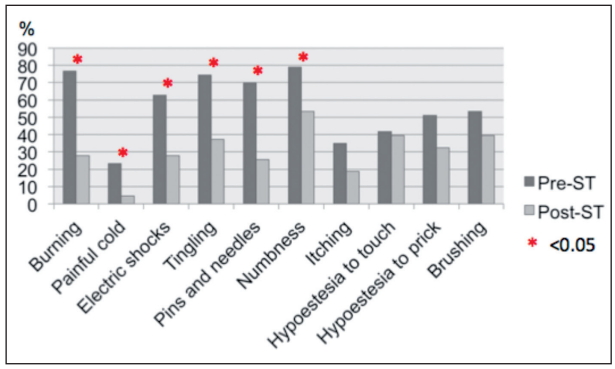

Figure 1. DN4 items pre- and post- Scrambler therapy

pain, most of them were post herpetic neuralgia (12 patients; 26.7%) and lumbosciatalgia due to radicular compression (13 patients; 28.9%) (Table 2).

All patients underwent a median 10.5 ST sessions (range 5-20); 4 out of 45 patients (8.8%) discontinued treatment, before completing 10 sessions, due to complete resolution of pain.

Mean baseline NRS value before treatment was 7.56 [±1.39 Standard Deviation (SD)]; value decreased significantly at the end of ST to 2.04 [±2.50 SD] (73% of reduction from baseline) [Odds Ratio (OR) 5.51; 95% Confidence Interval (CI): 4.66-6.36; p<0.0001] (Table 4). In 40 out of 45 (88.8%) patients there was a pain intensity reduction ≥50% (*patient responders*). Mean baseline DN4 score was 5.67 [±1.43] and fell by 50.3%, with a mean DN4 score of 2.82 [±2.18] at the end of treatment (OR 2.84; 95%CI: 2.07-3.62; p<0.0001) (Table 4). In 28 out of 45 (62.2%) patients there was a negativisation of DN4 (p<0.0001) (Table 4).

Correlation between the percentage of *patient responders* and patients with negativization of DN4 was statistically significant (p<0.0062). Analysing each DN4 item pre- and post- ST, we reported a significant negativization for burning, painful cold, electric shocks, tingling, pins and needles and numbness. No significant negativization was observed for itching, hypoesthesia to touch, pricking hypoesthesia and tactile allodynia (Figure 1).

Table 4. NRS and DN4 scores pre- and post- Scrambler Therapy

	pre-ST	post-ST	p-value
NRS*	7.56	2.04	<0.0001
DN4*	5.67	2.82	<0.0001
Negative DN4	0/45 PTS; 0%	28/45 PTS; 62.2%	<0.0001

* average value; pts: patients; ST: Scrambler Therapy

Discussion

Neuropathic pain is a heterogeneous pain category, that includes several independent dimensions such as somatosensory signs and symptoms, some of them positive others negative. Positive somatosensory symptoms are expression of hyperexcitability (hyperalgesia, allodynia), while negative somatosensory signs and symptoms are due to nerve damage (touch hypoesthesia and pricking hypoesthesia); finally we find paraesthesia and dysesthesia (18).

All this suggests the need for a multimodality approach. Electrical neurostimulation would seem to contribute to improving neuropathic pain treatment. As previously reported, efficacy of ST was investigated in relieving neuropathic pain (10, 12). The first study was conducted by Sabato et al. on 226 patients, all suffering from intense drug resistant neuropathic pain and enrolled to receive ST (10). After treatment, 80% of patients obtained pain relief ≥50%, 10% of patients responded with pain relief from 25% to 49% and the remaining 10% had no response. In a subsequent pilot, randomized, controlled study, Marineo et al. enrolled 52 patients with chronic neuropathic pain and randomized them to receive ST *versus* standard pharmacological treatment (12). After one month from

treatment, the mean Visual Analogue Scale (VAS) pain score was reduced from 8.1 to 5.8 in the control group and from 8.0 to 0.7 points in the Scrambler group (p<0.0001). Recently, the Scrambler Therapy Group published results from a multicenter retrospective analysis. In this study, 201 patients affected with chronic neuropathic pain were treated with ST, according to the same pattern shown in our study. This experience has confirmed efficacy of ST in the management of several different types of refractory chronic neuropathic pain (15). To date, 20 reports, of varying scientific quality, have been published regarding this device and the positive findings from these preliminary studies support that ST provides benefit for patients with refractory pain syndromes (8).

Studies on the treatment of neuropathic pain are often limited to verifying the variations in pain intensity. However, it has been revealed that the global rating of pain intensity is correlated only to simultaneous improvement in more neuropathic pain features (8, 18, 19).

Therefore, it is important to understand whether different neuropathic pain symptoms respond differently to the treatments.

ST through neuromodulation would act on somatosensory system, but how it acts on different symptoms remains unknown. Marineo et al, reported a positive effect of ST on allodynia. Specifically, the presence of allodynia was reduced at one and three months in the ST group and changes were statistically significant, comparing ST group *versus* control group, at one month (p=0.0017), two months (p=0.0094) and three months (p=0.0644) (12).

Recently, in a pilot study, Pachman et al. have investigated the effect of ST for treatment of established chemotherapy-induced peripheral neuropathy (CIPN). 37 patients were enrolled reporting at the end of ST a 53% reduction in pain score, a 44% reduction in tingling and 37% reduction in numbness (20).

Our prospective exploratory analysis confirms the efficacy data of ST to relieve neuropathic pain (73% of pain intensity reduction from baseline; p<0.0001). This study met the primary endpoint, achieving a negativization of DN4 in 62.2% of study population (p<0.0001) with a significant correlation between reduction of pain intensity ≥50% and DN4 negativization after ST treatment (p=0.0062). We reported a significant disappearance of 6 out of 10 items of DN4 questionnaire. These data suggest that ST could act on multiple somatosensory signs and symptoms of neuropathic pain and may be able to induce an overall improvement on neuropathic pain syndrome.

The symptoms significantly disappeared after Scrambler therapy were burning, painful cold, electric shocks, tingling, pins and needles and numbness; unlike we observed that touch hypoesthesia and pricking hypoesthesia did not disappear after ST: this result was predictable because of hypoesthesia's anatomical nature (21).

Also itching did not disappear after ST treatment. Some neurological illnesses cause neuropathic pain and itching, but it is the least understood among somatosensory sensations (22).

Finally, allodynia did not disappear significantly after ST; in our work this result is in contrast with Marineo et al. previous observations (12). Our result could be attributed to the small sample size. Really, same patients in our study have experienced a significant reduction of allodynia intensity or in the concerned area, but DN4 questionnaire is not suitable to detect these variations. DN4 has been developed to discriminate between neuropathic and non-neuropathic pain, not for monitoring improvements after treatment; it reported only the presence or absence of somatosensory signs and symptoms related to neuropathic pain, but not their intensity. In this study the negativization of DN4, combining with pain intensity reduction at the end of ST, is an important indication of neuropathic pain resolution; at the same time the failure of a specific symptom to disappear is not sufficient to exclude its clinically relevant improvement.

Conclusion

This prospective exploratory analysis, compared to the previous evidence, suggests a role of ST not only reducing pain intensity but also somatosensory signs and symptoms related to neuropathic pain, resulting in significant negativizzation of DN4 diagnostic tool for neuropathic pain. Based on these data, the next step will be to evaluate quantitatively the various soma-

tosensory signs and symptoms related to neuropathic pain, with specific tools, such as Neuropathic Pain Symptom Inventory, in a context of randomized clinical trials involving an experimental group treated with ST *versus* a control group undergoing active sham.

Disclosure and Conflicts of Interest

Dr Domenico Russo claims to have received payments by the Life Episteme Italy to support training courses for new medical users of Calmare MC5 device. Other authors claim they have no conflicts of interest.

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Correspondence:
Federica Zoratto, MD
Viale XXI Aprile 2 - 04100 Latina, Italy
Tel. +39-366-3704175
Fax +39-773-487394
E-mail: federica.zoratto@gmail.com