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Effects of neuro-adaptive electrostimulation therapy on pain and disability in fibromyalgia

A prospective, randomized, double-blind study

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Abstract

Background: To evaluate the effectiveness of non-invasive neuro-adaptive electrostimulation (NAE) therapy for treating chronic pain and disability in patients with fibromyalgia.

Method/design: A prospective, randomized, sham-controlled study was conducted in 37 women with fibromyalgia. Participants were randomly assigned to receive either active NAE (n = 20) or stimulation with a sham device (n = 17). Participants in the experimental arm received eight 30-minute sessions over 4 weeks (2 sessions per week). The sham group received eight 30-minute sessions of sham stimulation. Therapeutic effects on pain relief, disability, and quality of life were evaluated using outcome measures at baseline, at 4 weeks, and after 3 months' follow-up.

Results: The findings indicated a significant reduction of pain in the active NAE group compared with the sham group immediately post-intervention, with a difference on the Visual Analog Scale (VAS) of 3 points ($P = .001$), and at 3 months' follow-up ($P = .02$). There were significant intragroup differences between the groups ($P < .05$) at post-intervention. After the intervention, both groups presented significant reductions on the Fibromyalgia Impact Questionnaire (FIQ) with respect to baseline ($P = .004$), but not at the 3-month follow-up. In the conditioned pain modulation (CPM) in thumb variable we found significant differences between the groups at the 3-month follow-up ($P = .02$). No additional benefits for conditioned pain modulation and disability were observed between groups at the 3-month follow-up. Furthermore, anxiety/depression and catastrophizing improved in both groups, but no differences between groups were found.

Conclusions: In this fibromyalgia cohort, NAE therapy significantly improved pain and quality of life at 4 weeks, but not at 3-month follow-up, compared with the sham stimulation group. Future investigations are needed in larger populations to confirm these findings.

Abbreviations: ACR = American College of Rheumatology, BDI = Beck Depression Inventory, CPM = conditioned pain modulation, FIQ = Fibromyalgia Impact Questionnaire, FM = fibromyalgia, IMMPACT = Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials, JSS = Jenkins Sleep Scale, NAE = neuro-adaptive electrostimulation, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold, SCENAR = self-controlled energo neuroadaptive regulator, SF-36 = the 36-item Short-Form Health Survey, STAI = State Trait Anxiety Inventory, tDCS = transcranial direct current stimulation, TENS = transcutaneous electrical nerve stimulation, TS = temporal summation, TSK = Tampa Scale of Kinesiophobia, VAS = Visual Analog Scale.

Keywords: electrostimulation, fibromyalgia, pain, rehabilitation

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1. Introduction

Fibromyalgia (FM) is a chronic complex syndrome characterized above all by generalized musculoskeletal pain, and by other frequent symptoms such as fatigue, sleep disorders, anxiety/depression, and cognitive impairments.[1] FM directly affects performance of daily life activities and reduces health-related quality of life in these patients.[2] It affects approximately 2% of the general population in both sexes, with rates of 3.4% among women and 0.5% among men.[3] Despite the high prevalence, its diagnosis and management remains a challenge for patients and healthcare professionals. The pathophysiology of pain in FM is not yet clear, but the latest research points to an alteration in pain processing and transmission, produced by neuroplasticity changes and dysfunction in the pain nociceptive pathways of the central nervous system.[4] This translates into phenomena such as hyperalgesia, allodynia, increased temporal summation due to hyper-excitability in the posterior horn of the cord, and a decrease in the activation of descending inhibitory pain pathways.[5]

The current treatment of FM patients is aimed at improving their symptoms and thus raising their quality of life. Non-pharmacological treatments using physical therapies have been applied for decades for the treatment of cardinal symptoms in FM such as pain, joint stiffness, and muscle fatigue.[6] Electrotherapy is one of the techniques used in FM patients, since transcutaneous electrical nerve stimulation (TENS) is able to modulate pain by activating descending central inhibitory mechanisms and reducing the excitatory signals of the posterior horn of the cord.[7] A recent systematic review of the efficacy of this technique in FM patients found it to be effective in pain relief in 7 of the 8 studies included; however, the sample sizes were small and the power of the studies was low.[8] Transcranial direct current stimulation (tDCS) is another electrotherapy technique that is being studied for the treatment of FM, due to its direct effect on the CNS, although the current evidence is limited. Anodic tDCS in the left primary motor cortex has demonstrated its efficacy in improving pain and sleep quality in people with FM.[9]

In our study, we use neuro-adaptive electrostimulation (NAE), a relatively new form of electrotherapy which has not been widely studied to date. The NAE device is able to administer doses of impulses according to the electrical impedance responses it receives from the skin. The device used is capable of detecting areas of altered sympathetic response such as activation zones or passage zones of nerve branches, which in many cases are subjected to electrostimulation. In addition, the beneficial effects of NAE also seem to be related to its ability to stimulate nerve fibers which are not commonly activated by other types of electrotherapy, and to generate afferent information and subsequently promote efferent reactions.

The effectiveness of NAE therapy has been studied in acute conditions such as lateral ankle sprain, post-operative treatment of femur and ankle fracture, total knee replacement surgery, and chronic diseases such as knee osteoarthritis, neck pain, and chronic plantar fasciitis.[10,11] In a study performed in patients with whiplash comparing the efficacy of NAE and TENS, NAE showed better outcomes in both neck pain and disability compared with the TENS group.[26] However, the evidence regarding this type of therapy is extremely scarce and its effectiveness in patients with FM has not been evaluated to date.

Therefore, we considered that NAE may be an effective add-on treatment for pain in FM due to its ability to influence nociceptive pain processing pathways. The aim of this study is to evaluate the effectiveness of NAE therapy in reducing pain and in improving disability in individuals with FM.

2. Materials and methods

2.1. Study design

A unicenter, prospective, randomized sham-controlled trial study was conducted in a cohort of FM patients. All participants read and signed an informed consent form prior to enrollment. The study protocol was approved by the local Ethical Committee (University Rey Juan Carlos, Madrid, Spain; reference number: 03/2019) and conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study is registered at clinicaltrails.gov (NCT# 03882567).

2.2. Participants

Forty-four potentially eligible patients were recruited from local FM associations from June 2018 through October 2019. All participants were of Caucasian descent and from the same geographical area. Inclusion criteria for this study were: female sex, age between 18 and 65 years, previous diagnosis of FM by a rheumatologist following the 2010 American College of Rheumatology (ACR) case criteria.[1] The exclusion criteria were: inflammatory rheumatic condition; planned elective surgery during the study period; ongoing unresolved disability claims; and symptoms of bipolar disorder, major depressive disorder, panic disorder, and/or psychosis.

2.3. Randomization and blinding

The sample size was calculated using *G*Power software* v3.1. A blinded researcher performed the randomization of subjects, using the statistical program GraphPad version 8.0 (GraphPad software, Inc. La Jolla, CA). The sample was divided into 2 groups (NAE group and sham-controlled group). Only the therapist had access to the allocation schedule, and patients and evaluators were blinded to the treatment allocation.

2.4. Procedures and interventions

To apply NAE, we used the self-controlled energo neuroadaptive regulator (SCENAR) 1NT-02.2C device, marketed under the commercial name SCENAR Physio (Ritm OKB ZAO, Taganrog, Russia; http://www.scenar.com.ru) (Fig. 1). SCENAR is a transdermal neuro-stimulator destined for non-invasive treatment of physiological systems of the body related to pain. External electrodes for paravertebral and facial localizations optimize access and application with a max supply current not greater than 650 mA. SCENAR provides two-phase stimuli without a DC-component with a waveform depending on the skin impedance under the electrode, generated at a fixed frequency that can be controlled within 15 to 350 Hz. The duration of the first phase ranges 4 ± 2 to 500 ± 50 μseconds, and the amplitude of the first pulse of the second stimulus phase varies from 1.7–2.5 V to 100–150 V. The protocol, specifically oriented to anatomical areas involved in sensitization and impairment of nociceptive pathways, is applied for 30 min in 8 twice-weekly sessions. During the procedure, soft, comfortable transdermal stimulation is applied while the patient is in prone or supine position (depending on the pathways to be treated). The placebo

Figure 1. NAE device.

group underwent the same procedure for readings of conductivity skin reaction (time-impedance-type values) and the therapy stimulation phase with the sham device. Treatments were always carried out at the same times by a therapist with experience in handling the SCENAR device (Transdermal Electrostimulator SCENAR class IIa, CE-2265 Operating Manual. Version 7.2–02, May 2018).

2.5. Measures

All eligible participants were asked to fill out validated self-reported outcome measures to serve as symptom assessment tools under the supervision of a trained investigator (CU-C) who oversaw participant compliance. The measures used are listed here:

2.5.1. Pain intensity. Pain intensity was assessed on a visual analog scale ranging from 0 to 10 (Visual Analog Scale (VAS) = 0; no pain, and VAS = 10; maximum pain).[12]

2.5.2. Pressure pain threshold. Pressure pain threshold (PPT) is a quantitative sensory test of tissue sensitivity and it is defined as the minimal amount of pressure at which a sense of pressure changes to pain.[13] PPTs near the pathological site are thought to represent the degree of peripheral nociception, whereas low PPTs distal to the pathology are markers of central nervous system hyper-excitability.[14] Recordings were collected over the thumb and the midpoint of the trapezius muscle between the acromioclavicular joint and spinal procesus of the C7.[15] A pressure algometer (Force Dial FDK/FDN 100 model, Wagner Instruments, Greenwich CT) was used (kg/cm^2). A mean score of 3 measurements was calculated. Temporal summation (TS) quantifies the state of neuronal excitability in the dorsal horn. It was measured using the protocol of 2009 Cathcart et al, causing 10 noxious mechanical stimuli in the PPT in the distal phalanx of the third finger and in the upper trapezius.[16] Conditioned pain modulation (CPM) measures the disturbance of the descending pain inhibitory system, which was also assessed by Cathcart et al's protocol.[16] To this end, the occlusion cuff was used as a conditioning stimulus and the pressure algometry as a test stimulus. Test stimuli were applied over distal phalanx of the third finger and in the upper trapezius.

2.5.3. Fibromyalgia Impact Questionnaire. The validated Spanish version of the Fibromyalgia Impact Questionnaire (FIQ) was used to assess functional disability and the physical impact of the disease in FM patients. The FIQ comprises 10 items that measure physical disability and the degree of specific symptoms such as pain, rigidity, fatigue, depression and anxiety, disability, and general well-being during the last week. Each symptom is measured on a response scale of 0 (absence of symptoms) to 10 (very severe symptoms) using visual analogue scales. The overall FIQ score ranges from 0 to 100, where higher scores indicate a greater negative impact of FM on functioning, classified into the following 3 categories: low impact (<50 points), moderate (50–75 points), and severe (>75 points). The FIQ has demonstrated good psychometric properties and an internal consistency of 0.93 in the Spanish FM population.[17]

2.5.4. Short form 36-item health-related quality of life. The Spanish version of the Short Form 36-item Health Survey (SF-36) is one of the most widely used scales to evaluate generic health-related quality of life, measuring physical and mental functioning within the context of an individual's health status.[18] It comprises 36 questions which explore 8 dimensions of the state of health: physical functioning (limitation of physical activities of daily life), physical role functioning (interference at work), bodily pain, general health perception, vitality, social functioning (interference in habitual social life), emotional role (interference in work due to emotional problems), and mental health (depression, anxiety, self-control, and general well-being). The SF-36 produces 2 summary components, 1 physical and 1 mental, each one generated by combining the scores of each dimension. SF-36 scores range from 0 to 100, with scores below 50 indicating a more disabling effect of the individual's health on his/her functioning.

2.5.5. Jenkins sleep scale. The Jenkins Sleep Scale (JSS) is a brief questionnaire which has demonstrated good psychometric properties in FM and in improving pain symptoms.[19] It contains 4 items that evaluate the frequency and intensity of sleep problems, with values ranging from 1 to 5. Higher scores indicate more acute sleep difficulties.

2.5.6. Pain catastrophizing scale. Catastrophizing about pain was assessed with the Pain Catastrophizing Scale (PCS) in its

validated Spanish version. The PCS comprises 13 self-administered items divided into 3 subscales that assess rumination (4 items), magnification (3), and helplessness (6). Items are rated in relation to the frequency of respondents' feelings and thoughts related to pain, and are valued on a 5-point Likert scale from 0 (never) to 4 (all the time). The 3 subscales are added together and the total score ranges from 0 to 52, with higher scores corresponding to a greater frequency and intensity of negative thoughts and feelings regarding pain. The Spanish version of the PCS has demonstrated good psychometric properties in patients with FM, with a Cronbach's alpha of 0.87.[20]

2.5.7. State trait anxiety inventory. The Spanish version of the State Trait Anxiety Inventory (STAI) was used to measure trait and state anxiety in the study population. It has 20 items for assessing trait anxiety and 20 for state anxiety. All items are rated on a 4-point scale (e.g., from "almost never" to "almost always"). The STAI assesses trait anxiety (STAI-T), which refers to relatively stable individual differences in anxiety proneness: that is, to interpersonal differences in the tendency to perceive stressful situations as dangerous or threatening, and to respond to such situations with more intense state anxiety (STAI-S) reactions. Higher scores indicate greater anxiety.[21]

2.5.8. Beck depression inventory. The Spanish version of the Beck Depression Inventory (BDI) contains a 21-item self-report rating inventory that measures symptom intensity in depression. The cut-off point for defining depressed and non-depressed individuals is set at a value of 18. The BDI has demonstrated high internal consistency, with alpha coefficients of 0.88 and 0.81 for fibromyalgia populations.[22]

2.5.9. Tampa scale of kinesiophobia. The original 17-item version of the Tampa Scale of Kinesiophobia (TSK) was used. The TSK is a self-completed questionnaire used to assess the subjective rating of Kinesiophobia, or fear of movement. The total score ranges from 17 to 68 with higher scores indicating a higher degree of Kinesiophobia. Several studies have demonstrated the validity and reliability of the scale as a psychometric measure.[23] Outcomes were collected pre-, post-intervention, and after 3 months' follow-up by an evaluator blinded to treatment allocation.

2.6. Statistical analysis

For the statistical analysis, the program R (version 5.3.1, Austria) was used. The Shapiro–Wilk test was then applied to detect significant deviations from normality ($P < .05$) for the FIQ, JSS, SF-36, PPT, TS, and CPM questionnaires. The Shapiro–Wilk test was applied to the baseline quantitative variables of both groups. All were normal, with the exception of the variable "duration of illness" in the intervention group. Qualitative variables were described in absolute values and frequencies, and quantitative variables with mean and standard deviation or with medians and interquartile range (IQR) depending on whether they were normally distributed. For the variables other than "duration of illness" (VAS, PCS, and TSK) the distribution was normal, and so parametric tests were applied. Quantitative variables were analyzed using a two-factor repeated measures ANOVA (between–within) or its robust equivalent using pseudostatistics such as Wald and ANOVA, bootstrap, and averages truncated to 20% depending on the fulfilment of the assumption of normality. Qualitative variables were analyzed using the Cochran–Mantel–Haenszel test. The effect size on quantitative variables was defined with η^2 as 0.01 to 0.06 (small), 0.06 to 0.14 (medium), and >0.14 (large), or with the Kendall W, being defined as <0.1 (small), 0.1 to 0.3 (medium), and >0.3 (large). In the qualitative variables, the effect size was defined between pairs with significant differences using Cramer's V, defined as 0.071 to 0.212 (small), 0.212 to 0.354 (medium), and >0.354 (large). The level of significance was set at $P < .05$.

3. Results

3.1. Participants' demographic and clinical data

Forty-four consecutive patients were screened, and 37 patients with FM (mean age ± SD: 52 ± 8 years) were potentially eligible to participate. Figure 2 shows the recruitment and retention of the study patients through the trial. Baseline demographic and clinical characteristics of the patients in each group are presented in Table 1.

3.2. Response to treatment

3.2.1. Pain intensity. There was a significant time factor ($F = 11.161$; $P = .001$) but no significant group × time interaction ($F = 2.728$; $P = .07$) for pain intensity assessed by the VAS. Post-hoc analysis indicated that patients with FM receiving NAE had significant reductions in pain post-intervention (experimental group mean, 3.4; 95% CI: 2.6–4.3; control group mean, 5.3; 95% CI: 4.4–6.3, $P < .001$; significant difference between groups −1.9; 95% CI: −3.2 to 0.6, $P = .005$), as well as at the 3-month follow-up (experimental group mean, 4.7; 95% CI: 3.5–5.8, $P = .005$; control group mean, 5.6; 95% CI: 4.3–6.9; difference between groups −0.9; 95% CI: −2.6 to 0.8, $P > .05$) period (Table 2). Between-groups effect sizes were large ($d = 1.95$) after the intervention and small ($d = 0.35$) at the 3-month follow-up period. TS in the thumb and trapezius muscle presented a non-significant time factor ($F = 0.115$–1.457, all $P > .3$) and a non-significant group × time interaction ($F = 0.779$; 1.853, $P = .2$). The CPM in the thumb variable presented significant differences in the group factor ($F = 6.328$, $P = .02$). The post-hoc test showed significant differences between the groups at 3 months ($P = .02$) with a medium effect size ($r = 0.43$, 95% CI: − 0.3 to 0.4) in favor of the intervention group. No differences in CPM over the trapezius were found between the 2 groups during treatment sessions or in the time and group factor ($P > .05$).

3.2.2. Disability. The ANOVA indicated a significant time factor ($F = 16.489$; $P = .001$) but no significant group × time interaction ($F = 2.343$; $P = .10$) for FIQ. The post-hoc analysis revealed significant decreases in FIQ in both groups at post-intervention compared with baseline data (all, $P < .004$), but not at 3-month follow-up. There was also a statistically significant difference between the active versus sham groups ($P = .04$) post-intervention (Table 3).

3.2.3. Quality of life. For the physical, mental, and total scores on the SF-36, the ANOVA did not reveal a significant time factor ($F = 0.312$–1.958, all $P > .20$) or a significant group × time interaction ($F = 0.198$–0.374, all $P > .60$) (Table 3). JSS presented a significant time factor ($F = 6.858$; $P = .002$) but not a significant group × time interaction ($F = 1.576$; $P = .20$). We found significant differences in the experimental group ($P = .001$), but not in the control group at post-intervention. There was a significant difference between the 2 groups ($P = .01$) post-intervention.

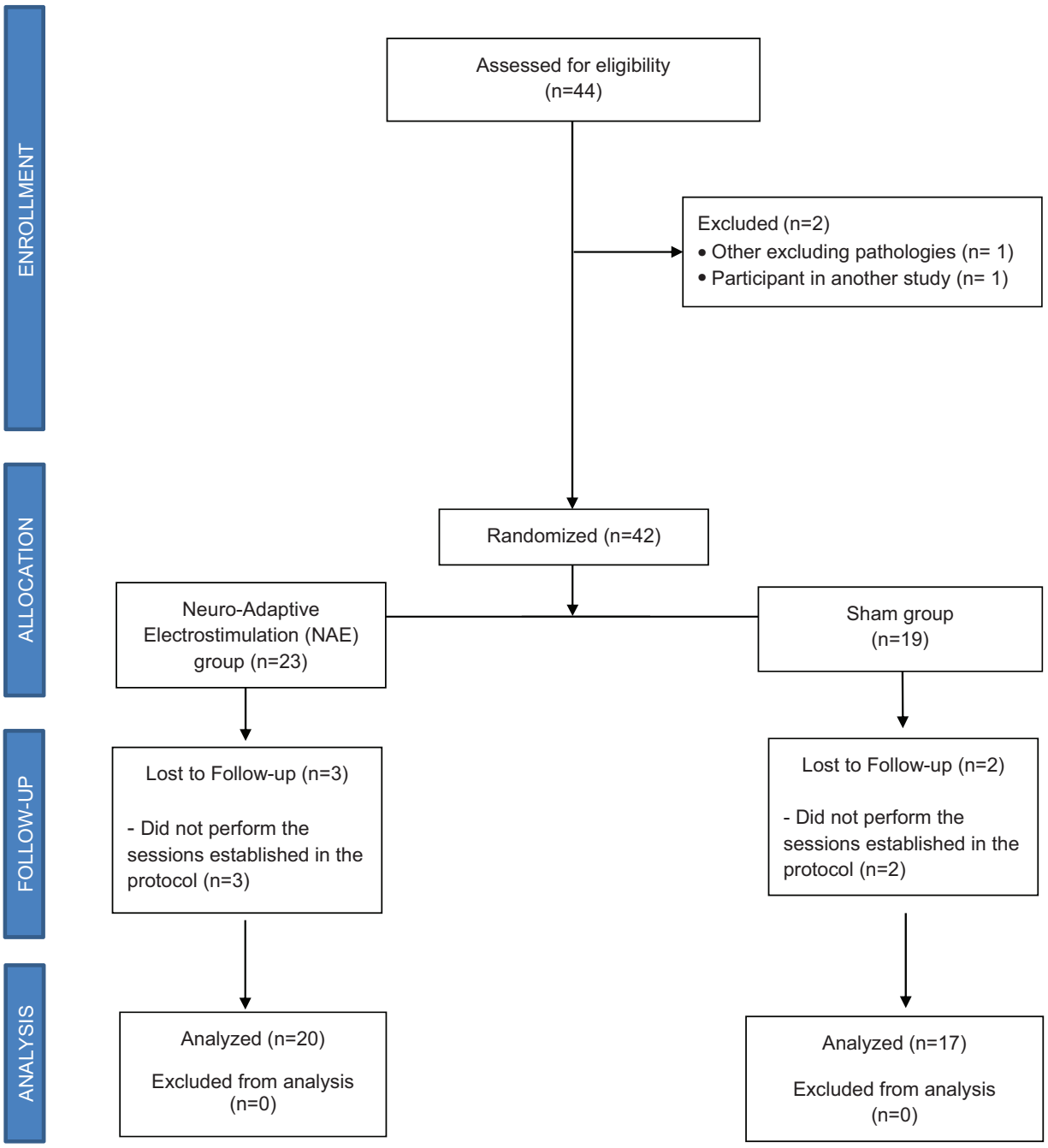

Figure 2. Consort flow chart of the study population.

Between-groups effect sizes were large ($d=6.8$) after the intervention and small ($d=0.1$) after 3 months' follow-up (Table 3).

3.2.4. Psychological parameters. The ANOVA revealed a significant effect of time ($F=13.984$; $P=.001$) but not for the group × time interaction ($F=1.242$; $P=.30$) on the PCS. The post-hoc analysis revealed significant differences at post-intervention in both groups (all, $P<.04$) as well as at 3 months' follow-up ($P=.005$) for the control group. Between-groups effect sizes were small ($d=0.4$) after the intervention and ($d=0.4$) at 3 months' follow-up period (Table 4). Kinesiophobia, as measured by the TSK, did not present significant differences for time ($F=0.216$; $P=.8$, partial eta $=.051$), or the group × time interaction ($F=1.158$, all $P=.30$). For catastrophizing, significant differences were found in the main time factor ($F=13.983$, $P<.001$, Mauchly's test $=.219$); the post-hoc test showed significant differences between the pre–post treatment and pre-treatment sessions – 3 months ($P<.001$) with a medium and significant effect size ($\eta^2=0.096$, 95% CI: 0.074–0.326) (Table 4). The variables STAI-S ($F=0.742$, $P=.009$, Mauchly's test $<.001$), STAI-T ($F=0.841$, $P=.027$, Mauchly's test $=.013$), PCS ($F=13.983$, $P<.001$, Mauchly's test $=.219$), and BDI ($F=8.136$, $P<.001$, Mauchly's test $=.057$) presented significant differences in the time factor.

Table 1

Demographic and clinical characteristics among study participants at baseline.

	Active (n = 20)	Sham (n = 17)	P[a]
Age (yr)	52 (9)	52 (8)	.92
Time from diagnosis (yr)	1.6 (0.1)	2.0 (1.7)	.83
VAS	6.4 (1.7)	6.3 (1.0)	.91
PPT thumb	3.9 (2.1)	3.9 (2.6)	.89
PPT trapezius	2.3 (1.2)	1.9 (1.3)	.82
TS thumb	2.0 (1.7)	1.9 (1.6)	.96
TS trapezius	1.6 (1.8)	1.7 (1.3)	.88
CPM thumb	−0.38 (1.6)	−0.15 (1.4)	.49
CPM trapezius	−0.63 (1.7)	−0.41 (1.1)	.62
FIQ	57.3 (14.6)	55.4 (13.2)	.81
Global SF-36	66.0 (4.0)	66.9 (2.6)	.84
JSS	14.0 (4.2)	15.9 (4.1)	.75
PCS	22.2 (12.8)	18.7 (8.1)	.68
STAI	26.2 (9.9)	27.8 (10.9)	.93
BDI	17.5 (8.2)	15.9 (9.3)	.87
TSK	29.3 (5.7)	32.8 (4.6)	.79

Values are shown as mean (standard deviation). BDI = Beck Depression Inventory, CPM = conditioned pain modulation, FIQ = Fibromyalgia Impact Questionnaire, JSS = Jenkins Sleep Scale, PCS = Pain Catastrophizing Scale, PPT = pressure pain threshold; SF-36 = Medical Outcome Study 36-item Short Form Health Survey, STAI = State Trait Anxiety Inventory, TS = temporal summation, TSK = Tampa Scale of Kinesiophobia, VAS = Visual Analog Scale.

[a] Data were analyzed using Student's *t* test for independent samples, and the Mann–Whitney *U* non-parametric test when appropriate.

However, no significant differences were found in the group factor and group–time interaction in any of the variables ($P > .05$). Effect size was small in all the variables analyzed: STAI-S ($\eta^2 = 0.037$, 95% CI: 0.011–0.206), STAI-T ($\eta^2 = 0.015$, 95% CI: 0.001–0.169), PCS ($\eta^2 = 0.096$, 95% CI: 0.074–0.326), and BDI ($\eta^2 = 0.055$, 95% CI: 0.027–0.244) (Table 4).

4. Discussion

This is the first proof-of-concept study of NAE therapy in individuals with FM. Our results showed that neuro-adaptive therapy showed a significant improvement over sham placebo at 3 months in conditioned pain modulation. There was also a significant improvement in pain intensity and sleep quality, but only immediately after the end of the session. No differences between groups in terms of disability were shown.

These results challenge those of a previous study by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group investigating the effects of pain on individuals with whiplash.[24] In that study, twenty 20-minute sessions were applied over 4 weeks with follow-up at 4, 8, 12, and 16 weeks. An improvement in pain intensity was found in the intervention group, amounting to 4.2 points on the VAS: that is, an improvement of 67.7%, which the authors describe as a clinically important change.[24] In our study, we found a change of 2 points (46.7%) immediately after the intervention, representing a clinically relevant improvement; at 12 weeks; however, the score had fallen slightly to 1.7 points.

In a recent Cochrane systematic review[8] analyzing the effects of a low frequency current similar to the therapy we used, the authors found a reduction in pain after the application of TENS in FM patients but with a very low level of evidence; the improvement in pain only exceeded 30% when TENS was combined with exercise. In our study we found that patients surpassed that degree of improvement, but only immediately after the intervention; at 3-month follow-up it was no longer observed. We attribute this to the fact that we applied only 8 sessions, compared with an average of 20 sessions that were conducted in the studies included in the review. In a pilot study, Dailey et al[25] found a 30% increase in hypoalgesia in FM patients when TENS was applied in the cervical region compared with placebo. These results are at odds with ours, since we found an increase of 23.9% in the NAE group, although there were no differences with regard to the sham (placebo) group. Perhaps the discrepancies between the studies are due to the fact that Dailey et al team performed only 1 session while we performed 8 sessions. No other studies have evaluated mechanical hyperalgesia in FM.

TS did not decrease in our study. To our knowledge, there are no studies that have measured TS in FM patients when applying physical therapy. The only study which applied an interferential current at 1 or 4 kHz compared with placebo in patients with low back pain found statistically significant changes in patients who received interferential current vs the placebo group; these differences may have been due to their use of medium frequency and that fact that the patients underwent more sessions.[21] No previous studies have assessed CPM with NAE. Dailey et al[25] evaluated the effects of a single session of TENS in patients with FM and found a rate of improvement in the CPM about 30%. In our study the change at 3 months' follow-up was 97.4%, higher than in previous studies. The difference may be attributed to the differences in the number of sessions carried out in the 2 studies.[25]

Table 2

Pain intensity. Mean (SD) for outcomes at all study visits for each group, mean (SD) difference within groups, and mean (95% CI) difference between groups.

	Groups						Difference within groups				Difference between groups	
	Baseline		4-wk		Follow-up		Post minus Pre		FU minus Pre		Post	FU
Outcomes	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active minus Sham (n = 37)	Active minus Sham (n = 37)
VAS	6.4 (1.7)	6.3 (1.0)	3.4 (2.1)	5.3 (1.5)	4.7 (2.6)	5.6 (2.3)	**−3.0[*] (0.5)**	−1.0 (0.5)	**−1.8[*] (0.6)**	−0.8 (0.7)	**−1.9[#] (−3.2 to −0.6)**	−0.9 (−2.6 to 0.8)
Thumb PPT (kg/cm^2)	3.9 (2.1)	3.9 (2.6)	3.4 (1.2)	3.7 (2.5)	3.7 (1.4)	4.5 (2.3)	−0.5 (0.3)	−0.2 (0.4)	−0.2 (0.6)	0.6 (0.6)	−0.3 (−1.5 to 1.0)	−0.8 (−1.9 to 0.5)
Trapezius PPT (kg/cm^2)	2.3 (1.2)	1.9 (1.3)	1.8 (0.8)	2.0 (1.9)	1.9 (0.7)	2.1 (1.0)	−0.4 (0.2)	−0.1 (0.2)	−0.3 (0.2)	−0.2 (0.3)	−0.2 (−1.1 to 0.8)	−0.2 (−0.7 to 0.4)
Thumb TS (kg/cm^2)	2.0 (1.7)	1.9 (1.6)	2.0 (2.2)	2.2 (1.2)	2.6 (2.1)	1.7 (1.1)	0.0 (0.5)	0.3 (0.4)	−0.6 (0.5)	−0.2 (0.5)	−0.2 (−1.4 to 1.0)	0.9 (−0.2 to 2.1)
Trapezius TS (kg/cm^2)	1.6 (1.8)	1.7 (1.3)	1.9 (1.7)	1.4 (1.7)	2.7 (2.3)	1.6 (1.4)	0.3 (0.4)	−0.3 (0.5)	1.1 (0.5)	−0.1 (0.5)	0.5 (−0.6 to 1.7)	1.1 (−0.2 to 2.4)
Thumb CPM (kg/cm^2)	−0.38 (1.6)	−0.15 (1.4)	−0.03 (2.4)	−0.29 (1.2)	**0.4[*] (4.6)**	−0.56 (0.8)	0.35 (0.6)	−0.15 (0.6)	0.78 (0.4)	−0.41 (0.5)	0.27 (−1.0 to 1.6)	**0.96[#] (0.1 to 1.8)**
Trapezius CPM (kg/cm^2)	−0.63 (1.7)	−0.41 (1.1)	−0.43 (1.8)	0.09 (1.9)	−0.28 (1.2)	−0.59 (1.1)	0.20 (0.5)	0.50 (0.5)	0.35 (0.4)	−0.17 (0.4)	−0.51 (−1.7 to 0.7)	0.31 (−0.4 to 1.1)

CPM = conditioned pain modulation, FU = at 3-mo follow-up, PPT = pressure pain threshold, TS = temporal summation, VAS = Visual Analog Scale.

[*] Significant difference within group.

[#] Significant difference between group, $P < .05$ (95% confidence interval).

Table 3

Disability and quality of life. Mean (SD) for outcomes at all study visits for each group, mean (SD) difference within groups, and mean (95% CI) difference between groups.

	Groups						Difference within groups				Difference between groups	
	Baseline		4-wk		Follow-up		Post minus Pre		FU minus Pre		Post	FU
Outcomes	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active minus sham (n = 37)	Active minus sham (n = 37)
FIQ	57.3 (14.6)	55.5 (13.2)	34.9 (11.0)	44.2 (15.9)	46.3 (19.1)	44.3 (18.5)	**−22.4*(3.0)**	**−11.3*(3.2)**	−11.0 (4.8)	−11.1 (5.2)	**−9.3#(−18.3 to −0.3)**	1.9 (−10.6 to 14.6)
SF-36 (physical)	50.6 (3.6)	50.5 (2.5)	51.1 (5.4)	51.2 (4.3)	51.0 (5.8)	51.1 (5.0)	0.5 (1.1)	0.7 (1.2)	0.4 (1.3)	0.6 (1.2)	−0.2 (−3.5 to 3.1)	−0.2 (−2.8 to 4.5)
SF-36 (mental)	44.6 (3.2)	45.9 (3.2)	46.1 (6.2)	46.9 (2.5)	43.0 (6.3)	45.6 (26.5)	1.6 (1.2)	1.0 (1.3)	−1.6 (1.7)	−0.3 (1.7)	−0.7 (−4.1 to −2.5)	−2.6 (−6.9 to 1.6)
Global SF-36	66.0 (4.0)	66.9 (2.6)	67.4 (7.6)	68.1 (4.1)	65.2 (7.8)	66.5 (7.1)	1.4 (1.4)	1.2 (1.6)	−0.8 (1.7)	0.4 (1.8)	−0.7 (−4.8 to 3.9)	−1.3 (−6.3 to 3.7)
JSS	14.6 (3.8)	15.9 (4.1)	10.4 (4.5)	14.4 (4.3)	12.3 (4.4)	14.1 (4.3)	**−4.2*(1.0)**	−1.5 (1.0)	−2.3 (1.0)	−1.8 (1.3)	**−4.0#(−7.0 to −1.0)**	−1.8 (−4.9 to 1.2)

FIQ = Fibromyalgia Impact Questionnaire, FU = at 3-mo follow-up, JSS = Jenkins Sleep Scale, SF-36 = the 36-item Short Form Health Survey questionnaire.
* Significant difference within group.
# Significant difference between groups, $P < .05$ (95% confidence interval).

Table 4

Psychological outcomes. Mean (SD) for outcomes at all study visits for each group, mean (SD) difference within groups, and mean (95% CI) difference between groups.

	Groups						Difference within groups				Difference between groups	
	Baseline		4-wk		Follow-up		Post minus Pre		FU minus Pre		Post	FU
Outcomes	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active (n = 20)	Sham (n = 17)	Active minus sham (n = 37)	Active minus sham (n = 37)
PCS	22.2 (12.8)	18.7 (8.1)	14.2 (7.4)	13.2 (5.1)	17.8 (10.7)	12.6 (7.5)	**−8.0*(1.9)**	**−5.5*(2.0)**	−4.5 (2.0)	**−6.1*(2.2)**	1.0 (−3.3 to 5.3)	5.1 (−1.1 to 11.4)
TSK	29.3 (5.7)	32.9 (4.6)	30.1 (5.6)	31.4 (5.8)	29.8 (5.3)	31.2 (5.6)	0.8 (1.0)	−1.5 (1.0)	0.5 (1.2)	−1.7 (1.3)	−1.3 (−5.2 to 2.5)	−1.4 (−5.0 to 2.3)
STAI-S	26.2 (9.8)	27.7 (10.8)	19.3 (8.1)	24.5 (11.5)	21.8 (13.0)	24.2 (13.2)	*−6.8 (7.0)*	*−3.2 (7.3)*	*−4.4 (13.2)*	*−3.4 (9.3)*	*6.6 (−0.4 to 14)*	*3.8 (−5.0 to 13)*
STAI-T	30.7 (12.1)	28.5 (11.7)	25.2 (9.8)	26.7 (11.6)	27.6 (11.7)	27.6 (11.9)	*−5.7 (9.5)*	*−1.7 (4.8)*	*−3.1 (9.9)*	*0 (0)*	*2.7 (−4.4 to 9.8)*	*1.5 (−6.6 to 9.6)*
BDI	17.4 (8.2)	15.9 (9.4)	11.9 (6.5)	13.5 (6.6)	13.1 (8.6)	12.6 (6.5)	*−5.5 (9.0)*	*−2.3 (5.9)*	*−4.3 (7.8)*	*0 (0)*	*2.2 (−1.3 to 5.7)*	*0.1 (−4 to 4.2)*

BDI = Beck Depression Inventory, FU = at 3-mo follow-up, PCS = pain catastrophizing scale, STAI-S = state anxiety, STAI-T = trait anxiety, TSK = Tampa Scale of Kinesiophobia.
* Significant difference within group.

In a previous study in which SCENAR was used, disability improved by 14.3 points (60%) compared with TENS treatment in patients with whiplash-associated disorders.[26] This finding is at odds with ours, since in our NAE group disability fell by 23.9%. The difference may be due to the fact that those authors applied 20 sessions and their sample comprised patients with whiplash-associated disorders. However, our data for the FIQ score (14%) is not considered a clinically important difference.[27]

In our study, patients undergoing NAE therapy improved the quality of sleep. These results corroborate those found by Lauretti et al[28] who found an improvement in sleep quality when applying a TENS either at 2 sites or at a single site. They applied seven 20-minute sessions, a dosage similar to ours, but the results were evaluated only immediately after the end of treatment, not after follow-up. In our study there were improvements compared with placebo (a change of – 3.61 points) at the end of treatment, but not at 3-month follow-up. Studies which have applied pharmacological treatment achieved a higher improvement, reaching – 6.2 points.[29] In our study the change was only observed immediately after the end of the treatment, with a reduction of 36% (8 points) in catastrophizing in the NAE group, but not at the 3-month follow-up. Although the placebo group improved as well, with a change of 32.7% (6.1 points) at 3 months' follow-up, the results reflect a reduction in catastrophizing in the NAE group. Electrotherapy interventions like tDCS have also demonstrated positive effects for anxiety/depression in FM patients.[30] Another intervention, pain neuroscience education, showed a 22% reduction of catastrophizing (4.2 points) and a 15.8% reduction in anxiety (6.1 points) in FM patients at 3 months' follow-up.[31]

Our study has some limitations. The first one is the short follow-up; we have not been able to identify changes that occurred over a longer time period after applying NAE. Another limitation is the small sample size, which means that we are unable to extrapolate the data to the entire FM population, and may have induce type II errors. Finally, patients were not asked if they knew that they had been assigned to the placebo group, so we do not know the reliability of the placebo method. Additional studies are now needed to address these issues.

In summary, this study found that NAE therapy significantly relieved pain and improved health-related quality of life (disability) at 4 weeks compared with the sham-controlled group, but not after 3 months of follow-up.

5. Conclusions

NAE therapy demonstrated an improvement in pain intensity, disability, and sleep impairment immediately after treatment but not at 3 months; it also showed a benefit for conditioned pain modulation at 3 months' follow-up though the effect size was small. Further more rigorous studies with larger sample sizes and longer follow-up periods are urgently required to increase our knowledge about the effectiveness of NAE in pain relief and disability in fibromyalgia.

Author contributions

CU-C, JF-C, AAR, and IMA-D conceived and planned the experiments. CU-C carried out the trial. CU-C, JF-C, and IMA-D planned and carried out the simulations. CU-C, JF-C, and JNC-Z contributed to the interpretation of the results. CU-C, JF-C, JHV, and JC-M took the lead in writing the manuscript. All authors have contributed significantly to the work with critical feedback and have reviewed and approved the final version of the manuscript.

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