Systematic Review

Electric Stimulation for Pain Relief in Patients with Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Fibromyalgia (FM) is a syndrome whose primary symptoms include chronic widespread muscle pain and fatigue. The treatment of patients with FM aims to provide symptomatic relief and improvement in physical capacities to perform daily tasks and quality of life. Invasive or non-invasive electric stimulation (ES) is used for pain relief in patients with FM.

Objective: This systematic review aimed to assess the effects of treatment with ES, combined or not combined with other types of therapy, for pain relief in patients with FM.

Study Design: Systematic review and meta-analysis.

Setting: Electronic search was conducted on databases (from the inception to April 2016): MEDLINE (accessed by PubMed), EMBASE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), and Physiotherapy Evidence Database (PEDro).

Methods: Two independent reviewers assessed the eligibility of studies based on the inclusion criteria: randomized controlled trials (RCTs) examining the effects of ES combined or not with other types of treatment for pain relief in patients with FM (according to the American College of Rheumatology), regardless of the ES dosages. The primary outcome was pain, assessed by the visual analogue scale (VAS). The secondary outcomes extracted were quality of life, assessed by short form-36 health survey (SF- 36), and fatigue, assessed by VAS.

Results: Nine studies were included, with 301 patients. The meta-analysis for pain showed positive effect of ES treatment versus control [-1.24 (95% CI: -2.39 to -0.08; I^2: 87%, $P = 0.04$) n = 8 RCTs]. The sensitivity analysis for pain showed significant results for invasive ES, combined or not with other types of therapy [-0.94 (95% CI, -1.50 to -0.38; I^2 0%, $P = 0.001$) n = 3 RCTs]. No significant improvement was found regarding quality of life [-3.48 (95% CI: -12.58 to 5.62; I^2: 0%, $P = 0.45$), n = 2 RCTs] or fatigue [-0.57 (95% CI, -1.25 to 0.11; I^2 34%, $P = 0.100$; n = 4 RCTs].

Limitations: This systematic review included a small number of studies and reduced number of participants in each study. Furthermore, most of the studies showed some biases and lack of methodological quality.

Conclusion: This meta-analysis indicates that there is low-quality evidence for the effectiveness of ES for pain relief in patients with FM. However, moderate-quality evidence for the effectiveness of electroacupuncture (EA), combined or not combined with other types of treatment, was found for pain relief.

Clinical Trial Registration Information: PROSPERO under the identification CRD42015025323

Key words: Electric stimulation, electroacupuncture, transcutaneous electric nerve stimulation, pain, fibromyalgia, review, physical therapy, rehabilitation

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Fibromyalgia (FM) is defined as a clinical syndrome whose primary symptoms include chronic widespread muscle pain, fatigue, sleep disturbances, and tenderness with hyperalgesia to pressure on tender points (1-5). The pain in patients with FM interferes in daily life activities (ADL) and results in a decreased quality of life (5). This disorder affects approximately 2% – 8% of the general population (6), and presents a higher incidence among women (7). The pathophysiology of chronic pain in patients with FM is still not completely understood (8). Generally, data suggest that ineffective descending inhibition of the central nervous system (CNS) may cause an abnormal modulation of sensory inputs (such as mechanoreceptor inputs), resulting in pain (9).

The treatment of patients with FM aims to provide symptomatic relief and improvement of physical capacities to perform daily tasks and quality of life (5,10). Both non-pharmacological and pharmacological interventions have been used for FM treatment (5). Electric stimulation (ES) is a non-pharmacological option used to enhance the function of endogenous pain inhibition systems and may be beneficial to people with FM (11,12).

There are 2 modalities of ES: invasive ES and non-invasive ES. Transcutaneous electrical nerve stimulation (TENS) is a non-invasive type of ES, which is frequently used for acute and chronic pain in several clinical conditions (10). It works by means of the activation of descending inhibitory pathways, from the midbrain and brain stem, to inhibit excitability of nociceptive neurons in the spinal cord (11). When the electrical current is combined with the traditional Chinese acupuncture, it is called electroacupuncture (EA). EA is considered a type of invasive ES and has long been used to alleviate pain and stiffness in people with FM (12).

Even though several placebo-controlled trials assessing the effects of TENS and EA on pain in patients with FM have been published in recent years (3-5,10,13-16), further understanding of the efficacy of these electrical-based stimulation techniques is still needed. Furthermore, some studies were conducted with small sample sizes (17) and have presented controversial results. Therefore, the aim of this study was to systematically review the effects of treatment with ES, combined or not combined with other types of therapy, for pain relief in patients with FM.

Methods

Protocol and Registration

This systematic review was performed in accordance with the Cochrane Collaboration (18) and is presented as suggested the Preferred Reporting Items for Systematic Review and Meta-Analyses: The PRISMA Statement (19). The protocol of the study was registered at the International Prospective Register of Systematic Reviews, PROSPERO, under the identification CRD42015025323 and can be integrally accessed online (www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015025323).

Eligibility Criteria

To be included in this review, the studies had to be randomized clinical trials (RCTs) focused on determining the effects of TENS and EA combined or not combined with other treatment techniques for pain relief in patients with FM. Studies should follow the American College of Rheumatology (ACR) recommendations for FM diagnosis (20). In addition, studies had to have at least one intervention group and one control group. In all studies, the control group received no electric current transmission. Studies that applied TENS and EA in painful body areas were included, regardless of the dosages.

The exclusion criteria were studies without a comparator and studies with an unreliable description of FM. Clinical trials that did not provide information regarding the magnitude of the intervention's effect, either in the experimental or in the control groups, were excluded from the meta-analysis. If a trial had multiple publications, only the most recent one was included and the others were used only for supplemental information.

Search Strategy

Literature searches were conducted in the following electronic databases (from the inception to April 2016): MEDLINE (accessed by PubMed), EMBASE, Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), and Physiotherapy Evidence Database (PEDro). The search terms, used individually or combined, included: "fibromyalgia," "electrical stimulation," "transcutaneous electrical nerve stimulation," "electroacupuncture," and a string of words previously proposed, which yielded a high sensibility in the search for RCTs (21). To enhance the sensitivity of the search, words related to the outcomes of interest were not included. No language restrictions were set. References used in the published articles were identified and used as an additional source

to identify other clinical trials. The detailed strategies for PubMed are shown in Table 1. The strategies for other databases are available upon request.

Study Selection and Data Extraction

Two investigators (APS and CS), in duplicate, have independently evaluated titles and abstracts of all articles identified by the search strategy. All abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated these full-text articles and made their selection in accordance with the eligibility criteria. Disagreements between reviewers were solved by consensus, and if the disagreement persisted, a third reviewer (RM) resolved it. To avoid possible double counting of patients who could have been included in more than one report from the same authors/working groups, the patient recruitment periods and areas were evaluated, and authors were contacted for clarification. The same 2 reviewers (APS and CS) independently conducted data extraction with regard to the methodological characteristics of the studies, interventions, and outcomes using standardized forms. Disagreements were resolved by consensus or by a third reviewer (RM). Interventions were detailed with regard to length, intensity, type of activity, and frequency. The primary outcome extracted was pain, assessed by the visual analogue scale (VAS). The secondary outcomes extracted were quality of life, assessed by Short Form-36 Health Survey (SF- 36), and fatigue, assessed by VAS.

Risk of Bias Assessment

Study quality assessment included adequate sequence generation; allocation concealment; blinding of investigators, participants, assessors, and outcomes assessors; intention-to-treat analysis; and description of losses and exclusions. Studies had to have a clear description of adequate sequence generation to be considered as fulfilling these criteria. The description of how the allocation list was concealed could include terms like "central," "web-based," or "telephone randomization," or a clear statement that the allocation list was concealed. Intention-to-treat analysis was

Table 1. *Literature search strategy used for the PubMed database.*

#1 Patient	"Fibromyalgia" [MESH] OR "Fibromyalgias" OR "Fibromyalgia-Fibromyositis Syndrome" OR "Fibromyalgia Fibromyositis Syndrome" OR "Fibromyalgia-Fibromyositis Syndromes" OR "Syndrome, Fibromyalgia-Fibromyositis" OR "Syndromes, Fibromyalgia-Fibromyositis" OR "Rheumatism, Muscular" OR "Muscular Rheumatism" OR "Fibrositis" OR "Fibrositides" OR "Myofascial Pain Syndrome, Diffuse" OR "Diffuse Myofascial Pain Syndrome" OR "Fibromyositis-Fibromyalgia Syndrome" OR "Fibromyositis Fibromyalgia Syndrome" OR "Fibromyositis-Fibromyalgia Syndromes" OR "Syndrome, Fibromyositis-Fibromyalgia" OR "Syndromes, Fibromyositis-Fibromyalgia" OR "Fibromyalgia, Secondary" OR "Fibromyalgias, Secondary" OR "Secondary Fibromyalgia" OR "Secondary Fibromyalgias" OR "Fibromyalgia, Primary" OR "Fibromyalgias, Primary" OR "Primary Fibromyalgia" OR "Primary Fibromyalgias"
#2 Intervention	"Transcutaneous Electric Nerve Stimulation" [MESH] OR "Transcutaneous Electric Nerve Stimulation" OR "Electrical Stimulation, Transcutaneous" OR "Stimulation, Transcutaneous Electrical" OR "Transcutaneous Electrical Stimulation" OR "Percutaneous Electric Nerve Stimulation" OR "Percutaneous Electrical Nerve Stimulation" OR "Transdermal Electrostimulation" OR "Electrostimulation, Transdermal" OR "Transcutaneous Electrical Nerve Stimulation" OR "Transcutaneous Nerve Stimulation" OR "Nerve Stimulation, Transcutaneous" OR "Stimulation, Transcutaneous Nerve" OR "Electric Stimulation, Transcutaneous" OR "Stimulation, Transcutaneous Electric" OR "Transcutaneous Electric Stimulation" OR "TENS" OR "Analgesic Cutaneous Electrostimulation" OR "Cutaneous Electrostimulation, Analgesic" OR "Electrostimulation, Analgesic Cutaneous" OR "Electroanalgesia" OR "Electric Stimulation"[Mesh] OR "eletric stimulation" OR "Electrical Stimulation" OR "Electrical Stimulations" OR "Stimulation, Electrical" OR "Stimulations, Electrical" OR "Stimulation, Electric" OR "Electric Stimulations" OR "Stimulations, Electric" OR "Electric Stimulation Therapy"[Mesh] OR "Electric Stimulation Therapy" OR "Stimulation Therapy, Electric" OR "Therapeutic Electrical Stimulation" OR "Electrical Stimulation, Therapeutic" OR "Stimulation, Therapeutic Electrical" OR "Therapy, Electric Stimulation" OR "Electrotherapy" OR "Therapeutic Electric Stimulation" OR "Electric Stimulation, Therapeutic" OR "Stimulation, Therapeutic Electric" OR "Electrical Stimulation Therapy" OR "Stimulation Therapy, Electrical" OR "Therapy, Electrical Stimulation" OR "Electroacupuncture" [Mesh] OR "Electro-acupuncture"
#3 Type of study	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos [mh] OR placebo*[tw] OR random*[tw] OR research design [mh: noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR crossover studies [mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal [mh] NOT human [mh]).
Search	#1 and #2 and #3

considered as confirmed when the number of randomized participants and the number of analyzed patients were identical, except for patients lost to follow-up or who withdrew consent for study participation. Two reviewers (APS and CS) independently performed the quality assessment. We used the grading system of recommendation, assessment, development, and evaluation (GRADE) to evaluate the quality of evidence (22).

Data Analysis

Pooled-effect estimates were obtained comparing the change from the baseline to the end of the study in each group. Regarding the continuous outcomes, if the unit of measurement was consistent across trials, the results were presented as the weighted mean difference with 95% confidence intervals (95% CIs). If the unit of measurement was inconsistent, the results were expressed as the standard mean difference with 95% CI. Calculations were performed using the random effects method, given the heterogeneity of outcome measurements ($I^2 > 0$). A P value ≤ 0.05 was considered statistically significant. The statistical heterogeneity of the treatment effects among studies was assessed using Cochran's Q test and the inconsistency I^2 test, in which values above 25% and 50% were considered as indicative of moderate and high heterogeneity, respectively. All analyses were conducted using Review Manager, version 5.3 (Cochrane Collaboration).

Results

Description of Studies

The initial search identified 594 abstracts, 13 of which were considered potentially relevant. Due to the very strict inclusion criteria set in this study, only 9 studies (4,5,10,13,14,16,17,23,24) met the eligibility criteria and were included in this systematic review, providing data from 301 patients. Two additional studies were found in the reference list of published articles. The 9 included studies reported data on pain, but 8 (4,10,13,14,16,17,23,24) were included in the meta-analysis. One study (5) was not included in the meta-analysis of pain because it did not use the VAS scale. Figure 1 shows the flow diagram of the studies

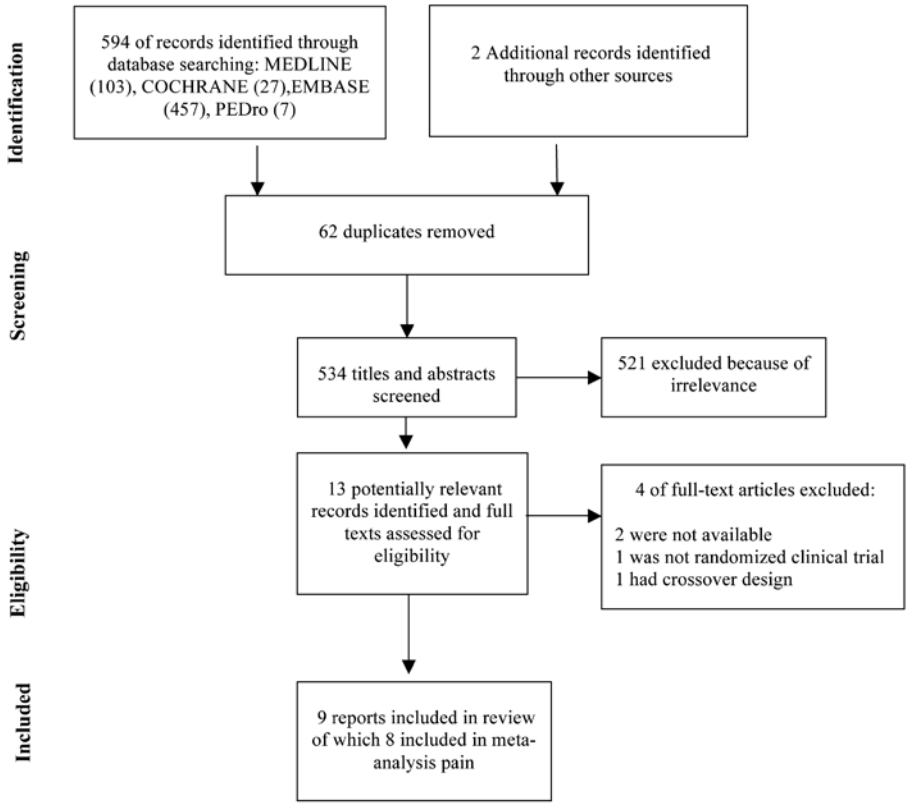

Fig. 1. *Flow diagram of studies included in the review.*

included in this review, and Table 2 summarizes the characteristics of these studies.

Six trials (4,5,10,17,23,24) compared TENS with control (total n = 180, TENS group n = 93). Three trials compared EA with control (total n = 121, EA group n = 61) (13,14,16). In 4 studies (4,5,10,23) TENS stimulation frequencies ranged from 80 to 150 Hz and the pulse duration from 0.7 to 1.5 μs. In one study (17) TENS stimulation frequency was 15 Hz and the pulse duration was 1.5 μs. Moreover, in one study (24) the stimulation frequencies were 2 and 100 Hz and the pulse duration was 2.0 μs. The time of intervention

Table 2. *Characteristics of the included studies in the systematic review.*

Author, Year	Intervention	Participants	Comparator	N (IG/CG)	Age ± SD (IG/CG)	Female gender (IG/CG)	Protocol
TENS							
Carbonario et al, 2013 (4)	TENS + Education + Exercise	Women with FM	Education + exercises	14/14	52.9 ± 5.9/51.9 ± 9	14/14	IG: 1 education session; 16 sessions, 2x/week in pairs. 30 min of ergometric bicycle, without load and free rhythm. Stretching with gradual increase of repetitions and 30 min of TENS (150 Hz, 150 μs) in trapezium and supraspinatus tender points. CG: 1 education session; 16 sessions, 2x/week in pairs. 30 min of ergometric bicycle, without load and free rhythm. Stretching with gradual increase of repetitions. Outcomes: Pain (VAS), quality of life (FIQ), and fatigue (VAS).
Da Silva et al, 2008 (17)	TENS	Patients with FM	Hydrotherapy	5/5	50.6 ± 13.4/47.0 ± 5.6	4/5	IG: 10 sessions, 3x/week, 40 min on trapezium, supraspinatus, gluteus and behind of knees tender points (15 Hz, 150 μs). CG: 10 sessions, 3x/week, 40 min Hydrotherapy Outcomes: Pain (VAS) and quality of life (SF-36 and NHP).
Di Benedetto et al, 1993 (23)	TENS	Patients with primary FM	SAMe	15/15	51 ± 9.5*	15/14	IG: 6 weeks, 5 x/week, 20 min TENS (80-100 Hz, 70 μs) on 4 tender points. CG: 6 weeks, 200 mg via intramuscular at 8 AM and 200 mg tablets, one at 12 noon and one at 6 PM. Outcomes: Pain (VAS) and Fatigue (VAS).
Lauretti et al, 2013 (24)	Double active TENS device	Patients with FM	Placebo TENS	13/10	30 ± 12/35 ± 8	13/9	IG: 7 consecutive days, 20 min. Applied both active TENS (2 and 100 Hz, 200 μs) devices at the low back and cervical areas (C7 and T1). CG: 7 consecutive days 20 min. Two devices did not transmit electrical stimulus. Outcomes: Pain (VAS) and fatigue (tool not described).
Löfgren and Norrbrink, 2009 (10)	TENS	Patients with FM	Superficial warmth stimulation	16/13	41.5 ± 23.58*	16/13	IG: 3 weeks, daily, at home, at least 30 min/ TENS session (80 Hz) on painful body areas. CG: 3 weeks, daily, at home, at least 45 min to 2h thermal stimulation (40º). Electrodes on painful sites. Outcomes: Pain intensity: NRS (0 – 100), quality of life (FIQ), and fatigue (VAS).

Table 2 (cont). *Characteristics of the included studies in the systematic review.*

Author, Year	Intervention	Participants	Comparator	N (IG/ CG)	Age ± SD (IG/CG)	Female gender (IG/CG)	Protocol
Mutlu et al, 2013 (5)	TENS + Exercise	Patients with FM	Exercise	30/30	43.30 ± 10.8/45.63 ± 9.1	30/30	IG: 12 weeks, 3 days a week, 40-min exercises. TENS (80Hz) once a day in the weekdays for the first 3 weeks. Was applied to the most painful areas (neck, shoulder, back and hip regions) for 30 min. CG: 12 weeks, 3 days a week, 40-min exercise. Outcomes: Pain (VAS) and quality of life (SF-36 and FIQ).
EA							
Deluze et al, 1992 (13)	EA	Patients with FM	Control	28/27	49.0 (2-0)/46.8 (2-3)**	33/21	IG: 3 weeks, 6 days a week. Electroacupuncture (1 – 99Hz) was applied four common acupuncture points (dorsal interosseous muscle of the hand and the anterior tibial muscle on both sides. At most 6 other sites were chosen depending on the patient's symptoms and pain patern. CG: 3 weeks, 6 days a week. The current used was similar to but weaker than that used in the real procedure. No increase was made after the threshold of perception had been reached. Outcomes: Pain (VAS).
Itoh and Kitakoji, 2010 (16)	EA	Patients with FM	Control	8/8	47.3 ± 13.3/45.7 ± 15.2	***	IG: 5 weeks, once at week, at least 30 min/ Electroacupuncture session (4 Hz) on painful body areas. CG: 5 weeks, 2 or 3 days a week received clinical examinations. Outcomes: Pain (VAS) and quality of life (FIQ).
Martin et al., 2006(14)	EA	Patients with FM	Control	25/25	51.7 ± 14.1/47.9 ± 11.2	25/24	IG: 6 treatment sessions during a 2-3 week, at least 20 min/ Electroacupuncture session (2 and 10Hz) on large intestine and stomach, bilaterally, and over the axil circuit's areas. CG: 6 treatment sessions during a 2-3 week, at least 20 min. The device did not transmit electrical stimulus. Outcomes: Pain (VAS), quality of life (FIQ), and fatigue (VAS).

FM, Fibromyalgia; IG, intervention group; CG, control group; TENS, transcutaneous electrical nerve stimulation; VAS, visual analogue scale; FIQ, Fibromyalgia Impact Questionnaire; SAMe, S-adenosyl-L-methionine; NHP, Nottingham Health Profile; SF- 36, short form-36 health survey; NRS, numerical rating scale; MPS, myalgic pain score. *Trials did not report the ages separately. ** Median and range *** Trials did not report the gender separately.

ranged from 20 to 40 minutes. Additionally, the EA stimulation frequencies ranged from 2 to 10 Hz in 2 studies (14,16), and from 1 – 99 Hz in one study (13). The time of intervention ranged from 20 to 30 minutes.

Risk of Bias

Among the included studies, 55% presented adequate sequence generation and 77% described losses to follow-up and exclusions, showing a low risk of bias for these analyses. On the other hand, when consider-

ing the assessment of the outcomes, 11% reported adequate allocation concealment, 22% performed intention-to-treat analyses, 0% reported blinding of patients and investigators, and 33% reported blinding of outcome assessors. These scores represent a high risk of bias (Table 3).

The quality of evidence, assessed by the GRADE, found low to moderate-quality evidence for the included studies. Considering each outcome, the ES (EA+TENS) showed low-quality evidence for pain relief and moderate-quality evidence for fatigue. Regarding EA, we found moderate-quality evidence for pain relief. Concerning TENS, low-quality evidence for pain relief and fatigue, and a moderate-quality evidence for quality of life was detected.

Effects of Interventions

Pain

Eight studies (4,10,13,14,16,17,23,24) (n = 241) evaluated pain by means of the VAS and were included in the meta-analyses. TENS and EA, combined or not with other types of therapy, were associated with reduction of pain when compared with the control group (–1.24 [95% CI, –2.39 to –0.08; I^2 87%, *P* = 0.04]; Fig. 2A).

One study (n = 60) (5) was not included in the meta-analysis for pain because another scale was used (myalgic pain score). This study showed significant pain relief when physical exercise was combined with TENS after 3 weeks of treatment (*P* = 0.01). However, no significant difference was observed between groups after 12 weeks of treatment (*P* = 0.87).

A sensitivity analysis, related to the type of intervention, was performed to investigate possible differences between studies. Five studies (4,10,17,23,24) that applied TENS, with or without another type of therapy, showed no significant pain relief when compared with control group (–1.34 [95% CI, –3.27 to 0.59; I^2 93%, *P* = 0.17]; Fig. 2B). Three studies (13,14,16) that applied EA, with or without another type of therapy, showed significant pain relief (-0.94 [95% CI, –1.50 to -0.38; I^2 0%, *P* = 0.001]; Fig. 2B).

Quality of Life

Quality of life was evaluated by means of the Short-Form 36 Health Survey (SF-36) in 2 trials (5,17) (n =70) and they were included in the meta-analysis. TENS or TENS combined with other types of treatment showed no significant improvement in quality of life when compared with the control group (-3.48 [95% CI: -12.58 to 5.62; I^2: 0%, *P* = 0.45)]; Fig. 2C).

Five studies assessed quality of life by means of the Fibromyalgia Impact Questionnaire (FIQ) (4,5,10,14,16) (n = 183). A meta-analysis could not be performed because the studies evaluated different items of the FIQ.

Fatigue

Fatigue was evaluated by means of VAS in 4 studies (4,10,14,23) (n = 137), and they were included in the meta-analysis. ES with or without other types of therapy did not reduce fatigue when compared with the control group (–0.57 [95% CI, –1.25 to 0.11; I^2 34%, *P* = 0.10]; Fig. 2D). Sensitivity analysis was performed

Table 3. *Risk of bias of the included studies.*

Author, Year	Adequate sequence generation	Allocation Concealment	Blinding of patients and investigators	Blinding of outcome assessors	Description of losses and exclusions	Intention-to-treat analysis
TENS						
Carbonario et al, 2013 (4)	No	No	No	No	Yes	No
Da Silva et al, 2008 (17)	No	No	No	No	No	No
Di Benedetto et al, 1993 (23)	No	No	No	No	No	No
Lauretti et al, 2012 (24)	Yes	No	No	No	Yes	No
Löfgren & Norrbrink, 2009 (10)	No	No	No	No	Yes	Yes
Mutlu et al, 2013 (5)	Yes	No	No	Yes	Yes	No
EA						
Deluze et al, 1992 (13)	Yes	Yes	No	No	Yes	No
Itoh and Kitakoji, 2010 (16)	Yes	No	No	Yes	Yes	Yes
Martin et al, 2006 (14)	Yes	No	No	Yes	Yes	Yes

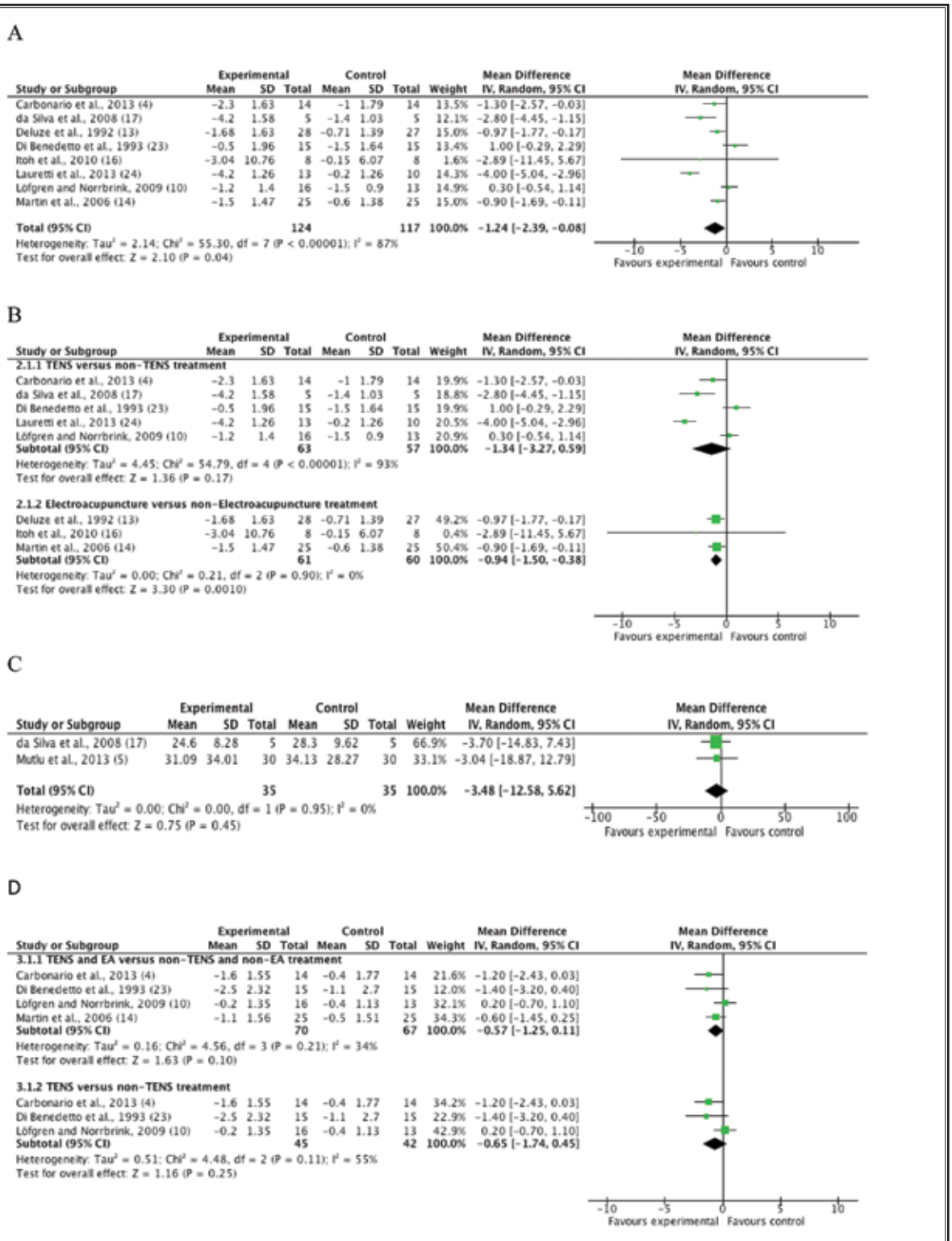

Fig. 2. *The standard mean difference and 95% confidence interval (CI) for interventions (A) for pain relief (B) for intervention types. The standard mean difference and 95% confidence interval (CI) for intervention with TENS: (C) quality of life; (D) fatigue - TENS and EA or TENS.*

to investigate possible differences between studies toward the type of intervention. Three studies that applied TENS, combined with other types of treatment, also showed no reduction of fatigue when compared with control (–0.65 [95% CI, –1.74 to 0.45; I^2 55%, P = 0.25]; Fig. 2D).

Discussion

This systematic review with meta-analysis showed that ES is an adjunct treatment option providing improvement in pain relief for patients with FM. However, ES showed no effect either on the quality of life or fatigue. To the best of our knowledge, this is the first systematic review with meta-analysis evaluating ES effectiveness on pain relief in patients with FM compared with a placebo or other type of treatment.

In most cases, the treatment of patients with FM aims to relieve symptomatic pain, reduce fatigue, and recover physical capabilities to improve daily tasks and quality of life (5,10). Non-pharmacological and pharmacological interventions may be used, combined or not, for the FM treatment (5). Fitness and strengthening exercises, as well as the warm-water therapy and ES, are among the non-pharmacological therapies recommended in recently published evidence-based guidelines (7,12). ES is able to induce pain relief and improvements in quality of life and fatigue (3,12).

ES can be divided into invasive (EA, auricular EA, and electrical heat acupuncture) and non-invasive (transcutaneous electrical acupoint stimulation, auricular transcutaneous electrical acupoint stimulation, and TENS) (25). It is very well established that ES therapy may be used as a non-pharmacological treatment and is able to adequately reduce pain in different health conditions (25).

Our meta-analyses showed that ES (EA+TENS) in comparison with a control group seems be effective for pain relief in patients with FM. Additionally, when we performed sensitivity analysis of the type of intervention, EA presented favorable results toward the experimental group regarding pain relief, while TENS showed no effect. This result can be explained by the summation effect between the electrical current and the acupuncture needle, which ends up creating a more powerful stimulus in the membrane of type 2 muscle fibers. Based on this agile depolarization, the stimulus is more quickly conducted to the CNS (26). Moreover, concerning EA, there are 3 neural centers involved in releasing chemical mediators that block pain messages. The spinal cord uses encephalin and dynorphin, and other transmitters, such as the gamma amino butyric acid (GABA), to block the afferent stimulation; the midbrain uses encephalin to activate the raphe descendant system that inhibits the transmission of pain along the spinal cord through a synergistic effect of monoamines; and the hypothalamic-pituitary axis releases β endorphin into the blood by stimulating the pituitary gland (26).

On the other hand, TENS therapy has presented no significant results for pain relief in this meta-analysis. It is known that TENS therapy is capable of reducing pain in conditions such as osteoarthritis, chronic musculoskeletal pain, and postoperative pains (27-29). The effects of TENS for pain relief may be explained by the "gate control theory" (30,31). This theory states that the dorsal horn of the spinal cord participates in the pain transduction. This includes the control of messages that will be sent to (or delivered from) higher levels of the brain, thus reducing pain perception. A different mechanism for pain relief by TENS therapy involves the release of endogenous opioids into the brain (32) through local vasodilation after injury (2,33).

Furthermore, some authors report that high-frequency TENS acts by stimulating large-diameter afferent fibers, inhibiting second-order neurons in the dorsal horn and preventing impulses carried by small-diameter fibers from being transmitted (34). This theory proposes that unmyelinated C fibers and thinly myelinated A-δ fibers transmit information to the spinal cord, resulting in reflex sympathetic vasoconstrictor stimulation. This effects are associated with the "gate control theory" (30). Thus, both low- and high-frequency TENS can reduce pain through the activation of opioids receptors. Low-frequency TENS activates mu-opioid receptors, and high-frequency TENS activates delta opioid receptors (35).

Regarding quality of life and fatigue, we observed that ES, combined or not with other types of therapy, has shown no effect. Also, in a sub-analysis with 3 studies examining the effects of TENS on fatigue, combined or not with other types of therapy, no significant effect was observed. The small number of studies included in the meta-analysis and the reduced sample sizes may explain this result.

Average treatment effect sizes have been used by several meta-analysis and systematic reviews (36,37) to evaluate the efficacy of interventions. It is based on thresholds defined by Cohen, which categorize effect sizes as small [standardized mean difference (SMD) of 0.2], medium (SMD of 0.5), and large (SMD of 0.8) (38)

(SMD is the difference in means between active and control groups divided by their pooled standard deviation). Our study has found a medium effect size (SMD – 0.66) when evaluating the effectiveness of treatments with ES for pain relief compared with a placebo or another intervention.

Limitations of the Review

Even though the results are favorable to ES therapy for pain relief in patients with FM, a limitation of this systematic review and meta-analysis is that most of the studies showed some biases. Four studies did not properly describe the generation of a random sequence (4,10,17,23) and none has clearly described allocation concealment or reported the patient blinding.

Furthermore, 5 studies (4,10,13,17,23,24) did not describe the blinding of the assessors. Two studies (17,23) did not report drop-outs or the patient's exclusions as well as the patient's exclusions. Three studies (10,14,16) have used the intention to treat analysis. Therefore, the sensitivity analyses were limited due to the lack of methodological quality, the small number of included studies, and the reduced number of participants in each study.

Comparison with Other Studies

A variety of complementary or alternative medicine interventions to treat and manage the symptoms of patients with FM have already been described. Deare et al (12) published a meta-analysis including 9 randomized and controlled trials evaluating any type of invasive acupuncture for FM treatment. The authors found a low- to moderate-level evidence that acupuncture improves pain and stiffness in people with FM. Also, EA is probably better than manual acupuncture for improving global well-being, sleep, and fatigue.

Terry et al (39) published an overview of systematic reviews aiming to critically evaluate single alternative medicine interventions for the treatment of FM. Five systematic reviews met the inclusion criteria, evaluating the effectiveness of homoeopathy, chiropractic, acupuncture, hydrotherapy, and massage. The systematic reviews found some evidence of beneficial effects arising from acupuncture, homoeopathy, hydrotherapy, and massage. However, they did not demonstrate any evidence of beneficial effects of chiropractic interventions.

In addition to that, a systematic review investigated the scientific evidence relating to electro-thermal and phototherapeutic methods for the treatment of FM syndrome. Seven studies were reviewed, which identified interventions using laser, TENS, and interferential current alone and combined with ultrasound. In conclusion, pain levels were significantly reduced in all of the studies (40).

Conclusion

This meta-analysis indicates that there is low-quality evidence for the effectiveness of ES on pain relief in patients with FM. However, moderate-quality evidence for the effectiveness of EA, combined or not with other types of treatment, was found for inducing pain relief. Our results need to be carefully interpreted due to the lack of methodological quality of studies, the small number of included studies, and the reduced number of participants in each study. However, we suggest that invasive ES may be used as a treatment choice in patients with a FM diagnosis. Further research is still necessary to assess pain, fatigue, and quality of life in patients with FM, ensuring adequate methodological quality, sample size, and long-term follow-up.

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