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NON-INVASIVE CRANIAL ELECTROSTIMULATION INTERVENTIONS ON PAIN, FUNCTIONAL STATUS, AND QUALITY OF LIFE IN PATIENTS WITH FIBROMYALGIA; A SYSTEMATIC REVIEW

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ABSTRACT

Purpose: Examine the effects of non-invasive cranial electrostimulation interventions on pain, functional status, and quality of life in adults with fibromyalgia diagnosis. **Number of Subjects:** 7 articles **Methods:** Literature search was performed using Pubmed, Embase, and PEDro databases. The following search parameters were used for PubMed: ((fibromyalgia) AND (electrical stimulation)). The limits placed on this search were that the search terms must be included in the title, abstract, or keywords of the results. PEDro risk of bias assessment was used. Information taken from the articles includes population, intervention group, comparison group(s), and post-intervention and follow up pain outcomes (VAS). **Results:** Seven studies met the inclusion criteria (PEDro scores 9-10/10). Of the seven studies, 7/7 assessed pain, 4/7 for function, and 4/7 quality of life. Each intervention compared the active intervention to a sham intervention and/or active intervention at a different placement site. Significant improvements in pain (including tender points, pain tolerance, and intensity) were reported for the cranial electrical stimulation group in each of the seven articles when compared to the sham intervention and/or a different placement site. Significant improvements in functional status were also seen in 3 of the studies. Significant improvements in quality of life were reported in one study ($p=0.0015$), with another study showing improvements in the areas of bodily pain ($p=0.02$) and physical functioning ($p=0.05$). **Conclusion:** All studies included in this systematic review determined non-invasive cranial electrostimulation as an effective pain treatment option for patients with fibromyalgia. These findings show that non-invasive cranial electrostimulation is a beneficial tool in the treatment of pain and functional status in patients with fibromyalgia.

Keywords: Electrostimulation, pain, quality of life, fibromyalgia, functional status.

INTRODUCTON

The management of pain continues to be a major focus in the medical clinics and other rehabilitation clinics with varying therapeutic interventions. Probably more challenging is the management of pain and other complications of fibromyalgia (FM). Fibromyalgia is a chronic syndrome with neuropathic tenderness of all four quadrants of the body that results in sleep alterations, mood dysfunction, musculoskeletal stiffness, and chronic fatigue [8]. Pain, that is a major part of the symptom patients present, is said to be perceived differently from the healthy individual [9] but reports from pain studies showed that pain threshold is lowered in FM [10,11]. It is suggested that there is overall decrease in the inhibitory pathways, consequently, low intensity or non-nociceptive stimuli are processed in pre-cortical and cortical structures involved in the effective and cognitive processing of pain [12], which may lead to net increase of pain perception. Evidence from the literature now suggests that FM is a condition associated with brain dysfunction with central pain syndrome [9]. Diagnosing FM may pose difficult clinical challenge. Wide spread of pain for more than three months without underlying course is being advanced but prior College of Rheumatological guidelines suggests a diagnosis of FM if there is 11 tender points if certain pressure is applied to 18 points (nine pairs) of the patient's body [13]. The areas are back of the neck, elbows (below crease of elbow, outside part), front of neck, hips (where buttocks muscle curve to join the thighs), low back and knees (inside of each knee pad). Other areas are upper shoulder (where tendons and muscle meet at the area where muscle connect the shoulder blade), shoulders

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(halfway between edge of the shoulder and the bottom of the neck) and chest (either side of the sternum, few inches below the collar bone). Fibromyalgia is said to affect between 2 and 5% of the general population (14). The management of FM pain is a big challenge in clinical settings as clinical approaches (pharmacological and nonpharmacological including behavioral and other alternative interventions) have not produced clinical efficacy [7]. Other alternative treatments include but not limited to Physical Therapy, Occupational Therapy, Massage Therapy and counselling and they are all intended to improve quality of life, which is considerably impaired in FM [7]. There are conflicting reports in the literature that electrostimulation of the brain or other areas is efficacious in reducing pain and improved quality of life in patients with fibromyalgia. The electrostimulation of the brain may be invasive and noninvasive, and the approaches have ability to modify brain activity in neural networks in area of stimulation and as well as distant, interconnected regions. Of interest is transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) because they are not invasive [7]. Therefore, the purpose of this study is to investigate mon-invasive cranial electrostimulation interventions on pain, functional status, and quality of life in patients with FM. The approach for the study is through systematic reviews of the literature.

METHODS

Information Sources/Search: Databases, including Pubmed, Embase and PEDro databases were searched in October 2017. The following search parameters were used for PubMed: ((fibromyalgia) AND (electrical stimulation)). The search parameters for Embase were: ('fibromyalgia':ti,ab,kw AND 'electrical stimulation':ti,ab,kw). The limits placed on this search were that the search terms must be included in the title, abstract, or keywords of the results. A hand search of the article's references was done in order to ensure that all appropriate articles were included.
Eligibility Criteria: In order to be included in this review, the articles must meet the following criteria:
(1) participants in each study were defined by the researchers as having been diagnosed by a physician with fibromyalgia, (2) the outcomes measured in each study included pain, functional status, and/or quality of life, (3) the intervention was considered non-invasive (no surgical procedures), and (5) study must be on original research (no follow-up or continuation studies). Each article must also have full text available, be published in a peer-reviewed journal, and must be offered in English.
Study Selection: A stepwise selection method was used to determine which articles would be included in the review. Study quality was evaluated using PEDro criteria. The PEDro is a 10-point scale for assessing internal validity (higher scores indicating higher quality). PEDro risk of bias assessment was used.

RESULTS AND DISCUSSION

Seven studies met the inclusion criteria (PEDro scores 9-10/10). Of the seven studies: 7/7 assessed pain [1,2,3,4,5,6, 7]; 4/7 assessed function pain [2,3,4,5]; and 4/7 assessed quality of life pain [2,4,6,7]. Two studies included active cranial electrostimulation (CES) at earlobes [1,5]; four included active transcranial direct current stimulation (tDCS) at left primary motor cortex (M1) [2,4,6,7]; and one included active non-invasive cranial electrostimulation (NICE) at the parietal midline pain [3]. Each intervention compared the active intervention to a sham intervention and/or active intervention at a different placement site. Significant improvement in pain (including tender points, pain tolerance, and intensity) were reported for the cranial electrical stimulation group in each of the seven articles when compared to the sham intervention and/or a different placement site [1,2,3,4,5,6,7]. Significant improvements in functional status were also seen in three of the studies [2,3,5] with one study reporting a tendency towards a significant increase in function due to decrease in FIQ seen in the study [4]. It is important to note that the other studies [1,6,7] did not measure functional changes but pain and QoL outcomes. Significant improvement in quality of life were reported in one study ($p=0.0015$) [6], with another study [2] showing improvements in the areas of bodily pain ($p=0.02$) and physical functioning ($p=0.05$) but not overall. However, three of the studies [1,5,3] did not measure any data relating to QoL. What is not very clear is why all the studies showed significant decrease in pain and the pain reduction did not transfer to functional improvement or QoL in all the groups? Could it be that function and improved QoL come later after sustained pain reduction in patients with chronic disease like FM? The study by Sator-Katzenschlage *et al*. [15] showed that therapy that significantly reduce pain intensity and improve social dimension of chronic pain, such as avoidance behavior, cognitive control, and physical activity but not enough to improve

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psychological well-being, which is said to affect quality of life. Another study by Schiesser *et al*. [16] reported that psychological well-being and mood were not improved despite the reduction in pain intensity.

There are different devices used to modulate electrical activities in the brain. The device, tDCS, apply weak direct current densities on the order of 0.1 mA/cm2 to the scalp via two relatively large anode and cathode electrodes to modulate the activity of brain neurons [17]. Closely related to this is cranial electrotherapy stimulation (CES), which generally uses alternating current unlike the direct current used in tDCS but the methods of application are the same way. Transcranial magnetic stimulation (TMS) uses pulsing external magnetic fields to induce current flow at controllable frequencies in the brain. Therapeutic magnetic stimulation (TMS) can be administered one pulse (or stimulus) at a time, or, the pulses can be given in rapid succession (called rTMS), originally designed for mood control. All these are noninvasive cortical electrostimulation (NICS). On the other hand, epidural motor cortex stimulation (MCS) entails implantation of electrodes over the primary motor cortex, and this is an invasive procedure where one or more electrodes are placed extra-durally over the motor cortex via a burr hole or a small craniotomy, and these electrodes are then connected to an implantable, battery-powered, neurostimulator.

The noninvasive cranial stimulation (NICS) used is this study has been used to treat chronic pain disorders because of their ability to modify brain activity in neural network in the area of stimulation and as well as other interconnected regions further away [7]. When applied to primary motor cortex (M1), it is stated that they are capable of modifying sensory aspect of pain via modulation of M1-thalamic inhibitory networks [13]. They can also modify other cortico-cortical and cortico-subcortical projections in pain processing pathways [13,18]. In FM, pain can be due to lack of inhibitory control over somatosensory processing (19, 20). Stimulation of the M1 through the NICE techniques may modulate the sensory aspect of pain, independent of the affective component, and this may target one of the pathophysiological mechanisms of FM [7]. The pain reduction effects seen in this study of noninvasive cranial stimulation in FM are in accord with many studies in the literature that used tDCS [20,21] and rTMS ([22,23] of M1 in FM setting. Apart from pain modulation, these techniques may also modulate symptoms such as anxiety [1] mood [15] and improved sleep patterns [3]. The lack of widespread of improved QoL in the study as compared to the pain reduction may necessitate the inclusion of psychological therapy intervention in addition to the pain reduction therapies of NICS. Pain pathways affected by stimulation may be different from pathways that modulate mood and psychological well-beings.

There are some limitations of this study and these include but not limited to different frequency of treatment, duration of treatment and application of the treatment devices even though they were all noninvasive cranial stimulation. The studies were not homogenous in design.

Study Summary Table 1.

Study and Design	Participant Characteristics	Exclusion Criteria	Experimental Group Intervention	Comparator Group Intervention(s)	Outcomes	Results/Conclusions
Cork et al., 2004 double-blind crossover study	Sex: F = 70 M = 4 Age: 53.0	Pregnancy, presence of implanted pacemakers, pumps, or stimulators, as well as presence of superficial or internal ear infections	CES at earlobes for 1 hour/day for 3 weeks at 100 µA, 50% duty cycle at 0.5 Hz	Sham CES at earlobes with device appearing to turn on but no active stimulation given; 1 hour/day for 3 weeks.	**Pain** (Pain Intensity) Baseline: No statistical difference in baseline mean values. (CES and Sham)	Pain intensity improved significantly for the CES group after 3 weeks. **p < 0.01** (CES vs Sham)
					Pain (McGill) Baseline: No statistical difference in baseline mean values.	Pain intensity did not improve significantly for the CES and Sham groups using McGill measure **p >0.05** (CES and Sham vs Baseline)
						Pain intensity improved significantly for Sham group after crossover (from Sham to CES) **p < 0.001** (Sham vs Baseline)
Fregni et al., 2006 randomized, sham-controlled, proof of	Sex: F = 32 Age: 53.4±8.4	Any uncontrolled clinical disease, alcohol or substance abuse, pregnant or lactating, & any	Active tDCS at M1 for 20 min/day for 5 consecutive days at 2 mA. Active tDCS at left DLPFC for 20	Sham tDCS for 20 min/day for 5 consecutive days, but the device was turned off after 30 seconds	**Pain** (VAS) Baseline: M1: 8.5 ± 1.4 DLPFC: 8.0 ± 1.6 Sham: 7.5 ± 1.9 p-value not reported.	Significant decrease in pain over time in the M1 group compared to the Sham group. No significant difference in pain for DLFPC group compared to Sham group. **p = 0.25** (DLPFC vs Sham) **p = 0.027** (M1 vs Sham)

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principle study		neuropsychiatric disorders	min/day for 5 consecutive days at 2 mA. All patients reported 3 weeks later for follow up evaluation.	All patients reported 3 weeks later for follow up evaluation.	**Function** (FIQ) Baseline: No statistical difference in baseline mean values.	Significant decrease in FIQ scores for M1 group compared to Sham & DLPFC groups. **p = 0.018** (M1 vs DLPFC) **p = 0.023** (M1 vs Sham)
					QoL (SF-36) Baseline (Physical Functioning; 0–57.1): M1: 32.1 ± 7.9 DLPFC: 30.4 ± 10.1 Sham: 30.3 ± 8.1 Baseline (Bodily Pain; 0–62.7): M1: 38.9 ± 4.8 DLPFC: 37.2 ± 5.9 Sham: 37.5 ± 5.6 p-value not reported	Absolute values suggest improvement in all domains, but only significant decreases in overall scores for physical functioning and bodily pain. Pre- to post-intervention p-values: **p = 0.02** (physical functioning) **p = 0.05** (bodily pain)
Hargrove et al., 2012 randomized placebo-controlled study	Sex: F = 71 M = 6 Age: 52.65	Subjects with other pain related diagnoses, chronic neurological disorder or significant systemic disorders, psychiatric disorders other than depression and anxiety	NICE 11 min/day 2x/week with 2 days between treatments at 40 Hz (22 total treatments)	Sham NICE 11 min/day 2x/week with 2 days between treatments at 40 Hz (22 total treatments) with no stimulation signal	**Pain** (Tender points) Baseline: Active: 17.4 (17.0, 17.7) Sham: 16.8 (16.2, 17.5) **p = 0.16**	Significant reduction in tender points for active. **p < 0.001** (Active) **p = 0.68** (Sham) **p < 0.001** (MCFB*)
					Pain (PPT) Baseline: Active: 36.7 (33.6, 39.9) Sham: 38.9 (35.0, 42.9) **p = 0.38**	Significant increase in pain tolerance, while the sham group presented with a decrease in pain tolerance after trial. **p < 0.001** (Active) **p = 0.04** (Sham) **p < 0.001** (MCFB*)
					Function (FIQ) - Overall Baseline: Active: 61.5 (57.4, 65.5) Sham: 58.6 (52.3, 63.7) **p = 0.45**	Significant improvement for both groups. **p < 0.001** (Active) **p = 0.05** (Sham)
					Function (FIQ) - Pain Baseline: Active: 6.6 (6.0, 7.2) Sham: 6.6 (5.9, 7.3) **p = 0.89**	Significant improvement for active. **p < 0.001** (Active) **p = 0.20** (Sham)
					Function (FIQ)- Function Baseline: Active: 4.0 (3.2, 4.8) Sham: 4.0 (3.2, 4.8) **p = 0.97**	Significant improvement for active. **p < 0.001** (Active) **p = 0.59** (Sham)
Riberto et al., 2011 randomized, double-blinded controlled trial	Sex: F = 23 Age: 58.3±12.1 (Active) 52.4±11.5 (Sham)	Any patient with psychiatric or behavioral conditions, & any patient with cardiovascular limitations	Active tDCS at left M1 (motor cortex) for 20 min/week for 10 weeks at 2 mA	Sham tDCS at left M1 with stimulation turned off after 30 seconds	**Pain** (SF-36) Baseline: No statistical difference in baseline mean values.	Significant reduction in bodily pain for Active tDCS but not Sham tDCS. **p = 0.006** (Active) **p = 0.15** (Sham)
					Function (FIQ) Baseline: No statistical difference in baseline mean values.	Tendency for significant decrease in FIQ scores after Active tDCS. **p = 0.056** (Active) **p = 0.18** (Sham)
					QoL (SF-36; all scores except pain) Baseline: No statistical difference in baseline mean values.	No significant change. **p = 0.97**
Taylor et al., 2013 Three groups, double-blind study	Sex: F = 43 M = 3 Age: 50.8±10.4	Pregnant or breastfeeding, epilepsy or history of seizures, and pacemaker or other implanted devices such as insulin pump or opioid pump.	Active CES at earlobes for 60 min/day for 8 weeks at 0.5 HZ & 100 μA	Sham CES at earlobes appeared to be activated but no stimulation given. Usual Care Alone (UCA)	**Pain** (NRS) Baseline: Active CES: 5.8 ± 1.9 Sham: 5.7 ± 1.6 UCA: 6.0 ± 2.1 **p = 0.88**	Significant decrease in average pain for Active CES group compared to the Sham and UCA groups. **p = 0.023**
					Function (FIQ) Baseline: Active CES: 61.36 ± 18.2 Sham: 65.98 ± 17.9 UCA: 66.31 ± 16.9. **p = 0.65**	Significant decrease in score on FIQ for Active CES group compared to the Sham and UCA groups. **p = 0.028**
Valle et al., 2009 randomized, sham-controlled longitudinal clinical trial	Sex: F = 41 Age: 54.8±9.6	Pregnancy or lactating, history of substance abuse or dependence, brain surgery or intercrainial implantation, & significant	Active tDCS at left M1 for 20 min/day for 10 sessions (over 2-week period) at 2 mA	Active tDCS at left DLPFC for 20 min/day for 10 sessions over a 2-week period. Sham tDCS at left M1 turned off after 20	**Pain** (VAS) Baseline: No statistical difference in baseline mean values.	Significant decrease in pain lasting up to 2 months. M1 vs baseline Post-treatment (**p = 0.012**) 30-day follow-up (**p = 0.02**) 60-day follow-up (**p = 0.03**)

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		medical, neuropsychiatric or chronic pain disorder		seconds of stimulation; 20 min/day for 10 sessions over a 2-week period		Significant decrease in pain immediately, but not a lasting effect. DLPFC vs baseline Post-treatment **(p = 0.035)** 30-day follow-up **(p = 0.17)** 60-day follow-up **(p = 0.27)**
					QoL (FIQ) Baseline: No statistical difference in baseline mean values.	Significant decrease in FIQ score showing improved QoL. M1 vs baseline 28.3% ±37.1 reduction **p = 0.0015**
						Significant decrease in FIQ score showing improved QoL. DLPFC vs baseline 27.6% ±26.8 reduction **p = 0.02**
						Improved QoL, but no significant change from baseline. Sham vs baseline 13.8% ±39.4 reduction **p = 0.15**
Villamar et al., 2013 patient- and assessor-blind, sham-controlled, randomized crossover trial	Sex: F = 15 M = 3 Age: 50.3±8.5	Current pregnancy, presence of metallic implants in head, history of substance abuse within past 6 months, use of carbamazepine within past 6 months, severe depression, & any history of epilepsy, stroke, mod-severe TBI, severe migraines, or brain surgery	Anodal 4x1 Ring HD tDCS placed at left M1 for 20 minutes at 2 mA (single treatment)	Sham 4x1 Ring HD tDCS with stimulation turned off after 30 seconds. Cathodal 4x1 Ring HD tDCS placed at left M1 for 20 minutes at 2 mA (single treatment)	**Pain** (VNS) Baseline: Sham: 5.09 ± 1.72 Anodal: 5.47± 1.94 Cathodal: 5.03 ± 2.23 **p = 0.767**	Significant decrease in pain for both Anodal and Cathodal vs sham groups. **p = 0.004** (global test) vs Baseline)
					Pain (McGill) Baseline: No statistical difference in baseline mean values.	Pain intensity improved significantly for Sham group after crossover. **p < 0.001** (Sham vs Baseline)
						Tender point scores significantly improved compared to baseline after sham group crossover. **p < 0.001** (Sham vs Baseline)
					QoL (Adapted QoL Scale for Persons with Chronic Illness) Baseline: No statistical difference in baseline mean values.	No significant interaction found. **p = NS****

Keys: tDCS: Transcranial direct current stimulation (tDCS); CES: Cranial electrostimulation; M1: Primary motor cortex; DLPFC: Dorsolateral prefrontal cortex; Sham: Nonactive group; DLPFC: Dorsolateral prefrontal cortex; MI: Primary motor cortex; QoL: Quality of life; UCA: Usual care alone; FIQ: Fibromyalgia impact questionnaire; VAS: Visual analog scale; MCFB: Mean changes from baseline between group; PPT: Pressure pain threshold.

CONCLUSION

All studies included in this systematic review determined non-invasive cranial electrostimulation as an effective pain treatment option for patients with fibromyalgia. Multiple studies also demonstrated a significant improvement on the patients' functional status. However, only one of the studies showed a significant improvement in quality of life. These findings show that non-invasive cranial electrostimulation is a beneficial tool in the treatment of pain and functional status in patients with fibromyalgia. Pain reduction may not immediately transfer to improved quality of life. Additional research is needed to incorporate non-invasive cranial electrostimulation and psychological therapy to possibly provide pain reduction and improved quality of life.

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