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REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN FIBROMYALGIA: A SYSTEMATIC REVIEW

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ABSTRACT: Introduction: Fibromyalgia is a rheumatologic condition that mainly manifests with chronic and diffuse musculoskeletal pain, as well as neuropsychological symptoms. Recent guidelines point to several treatment modalities, among the main ones: aerobic exercise, pharmacological treatment and cognitive behavioral therapy. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive cerebral cortex neuromodulation technique that has shown positive effects in the control of chronic pain. **Objectives:** Through a systematic review of the literature, this work aims to determine the efficacy and safety of repetitive transcranial magnetic stimulation for the treatment of fibromyalgia. **Methodology:** A systematic review of randomized controlled trials published in English or Portuguese was conducted in the PubMed database. The selected studies compared repetitive transcranial magnetic stimulation (rTMS) with placebo, and the outcomes evaluated were related to the effectiveness of this technique compared to the usual ones. **Results and discussion:** Eight studies were included in this review. There is evidence that repetitive transcranial magnetic stimulation contributes to the improvement of pain and reduction of the social impact caused by fibromyalgia. **Conclusion:**Findings demonstrate an association between rTMS neuronal stimulation therapy and painful and social outcomes caused by fibromyalgia compared to placebo. However, future studies that mainly evaluate the long-term changes with the use of this therapy will be necessary to better evaluate these associations.

Keywords: Fibromyalgia; Diffuse Myofascial Syndrome; Transcranial Magnetic Stimulation; Repetitive Transcranial Magnetic Stimulation; EMTr.

INTRODUCTION

Fibromyalgia (FM) is a rheumatologic clinical condition that manifests as chronic and diffuse pain, mainly musculoskeletal, as well as neuropsychological symptoms such as depression, anxiety, generalized fatigue, non-restorative sleep, sleep and mood disorders, headache and morning stiffness. Its origin is still unknown, but one of the most accepted pathophysiological theories is that there is a pain regulation disorder, being a pain amplification syndrome, where there is an uncoordinated action in the processing of nociception and pain inhibition in the nervous system. central nervous system (CNS), resulting in a perception of the altered painful stimulus, in which the person with FM becomes more sensitive to touch and muscle compression. Fibromyalgia is, then, a complex syndrome of central pain that ends up reflecting in poor quality of life, even causing alexithymia. It must also be noted that multi-causal explanations are preferable to mono-causal explanations, as it is understood that this syndrome is a sum of disorders that are manifested by various symptoms (RIBERTO; PATO, 2004; OLIVEIRA et al., 2017; JONES, 2014; AVILA). et al., 2014; HEYMANN, 2017).

The diagnosis of fibromyalgia is basically defined by clinical criteria, which varies with the experience of each physician. It is essential for the diagnosis of FM to take into account the presence of diffuse pain, sleep disorders, fatigue, changes in cognition and the systematic measurement of mood disorders through appropriate instruments. Painful points can also be used as long as they are associated with other functional disorders. Exclusion diagnosis must not be considered for FM, only differential diagnoses with diseases with similar symptoms or with other syndromes. According to *American College of Reumatology*, the criteria for diagnosing FM

are: 1) Pain during the last week, characterized by being present in at least 11 of 18 body areas (trigger points); 2) Presence of fatigue, non-restorative sleep or cognitive problems; 3) Symptoms must be present for at least 3 months; 4) There is no other disorder that can justify the symptoms presented (HEYMANN et al., 2017; JONES, 2014).

The number of patients diagnosed with fibromyalgia has been growing worldwide, however, this syndrome has a variable epidemiology according to the country analyzed. Research conducted in the United States and Europe describe a prevalence between 2% and 5% and indicate the female sex as the most affected, with about 5% of American women affected and 4.7% of European women (HEYMANN et al., 2017). ; FAGERLUND; HANSEN; ASLAKSEN, 2015).

Brazilian studies estimate a prevalence similar to those described by Americans and Europeans, around 2.5%. However, due to the great population diversity found in Brazil, population studies investigating the prevalence of this pathology in different regions of the country are unknown (HEYMANN et al., 2010).

A study carried out in Montes Claros showed that fibromyalgia was the second most prevalent rheumatologic disease among the analyzed population, behind only osteoarthritis, with 2.5% of the population affected, the majority being female, of which 40.8% were were between 35 and 44 years of age (SENNA et al., 2004).

However, it is worth mentioning that fibromyalgia is not the most prevalent chronic pain in Brazil or in the world, however, it is estimated that the patient with this syndrome generates direct costs 2 to 3 times higher than other patients with chronic pain. In Brazil, this situation worries the authorities, as the great geographical distance and different socioeconomic realities between the States make it difficult to access health care, both for the confirmation of the diagnosis and for the treatment of these patients (SOUZA; DIRCE, 2018).

According to the guidelines, the benefits of aerobic exercise, pharmacological treatment, cognitive behavioral therapy and multidisciplinary treatments have been demonstrated (BELLATO et al., 2012).

Drug treatment aims to control the patient's symptoms, highlighting antidepressants as the most used to maintain the disease. Among the tricyclics, amitriptyline stands out, which has an important role in improving pain and decreasing fatigue and sleep, other options are the norepinephrine and serotonin reuptake inhibitors (FITZCHARLES et al., 2013). Among the anticonvulsants, pregabalin and gabapentin are the most used, but it is not known for sure how they work for the benefit of the clinical manifestations of these patients (ARNOLD et al., 2018).

Interestingly, opioids do not have good efficacy in the treatment of this syndrome, when prescribed, tramadol is chosen, which is more effective than other drugs in this class. As well as non-steroidal anti-inflammatory drugs, which also have a very limited indication for these patients (KIA; CHOY, 2017).

On the other hand, non-drug treatments include: acupuncture, cognitive-behavioral therapies, massages, exercises, hydrotherapy, hyperbaric oxygen therapy, ozone therapy, transcranial magnetic stimulation, among others, such as transcranial direct current stimulation (tDCS). (OLIVEIRA; ALMEIDA, 2018). When it comes to tDCS, there is evidence that it reduces pain intensity in patients with fibromyalgia (SAAVEDRA et al., 2015).

Stimulation of this brain area can induce significant analgesic effects, mainly through modification in sensory pain processing by

thalamic inhibitory networks (BOYER et al., 2012). The transcranial direct current stimulation technique uses a low-amplitude direct current applied to the scalp to modify the underlying neural activity and promises to be a promising therapeutic approach for fibromyalgia as this syndrome causes functional changes in the patient's brain. HANSEN; ASLAKSEN, 2015).

Transcranial magnetic stimulation (TMS) is a non-invasive brain neuromodulation technique that induces an electrical current in certain regions of the brain through magnetic pulses. In TMS, an electromagnetic field strong enough to generate an action potential is formed under a coil positioned on the patient's head and is responsible for depolarizing local neurons through electromagnetic induction, when used repetitively, in repetitive transcranial magnetic stimulation (rTMS)., the alternating speed of the electric current orientation is quickly high, reversing between positive and negative in a matter of microseconds and giving rise to brief and repetitive electromagnetic pulses, which in turn, create an extremely powerful electromagnetic induction, causing not only neuromodulatory changes but also of local neuroplasticity (VALIENGO et al., 2013; HOU et al., 2016). It is known that, during rTMS, in the stimulated area, there is a temporary suspension of the function equivalent to the unit of measurement of the frequency used in the therapy (Hertz - Hz). In addition, depending on the stimulation frequency, excitation or inhibition may occur. High frequencies (between 5 and 20 Hz) have an excitatory potential while lower frequencies (<1 Hz) have an inhibitory potential in the modulation of cortical function (BOGGIO et al., 2006). By having neuronal modulatory action, this therapy has the ability to cause lasting effects used to study and treat neuropsychiatric diseases and pain syndromes (BRIGHINA et al., 2019).

JUSTIFICATION

Fibromyalgia syndrome is a chronic clinical condition with a complex approach and symptoms that are difficult to manage and, recently, neuromodulation techniques such as repetitive transcranial magnetic stimulation have been considered a promising option in the management of these symptoms due to their ability to modulate the nociceptive stimulus in the nervous system. central.

OBJECTIVES

GENERAL OBJECTIVES

To determine the effectiveness of repetitive transcranial magnetic stimulation for the treatment of fibromyalgia through a meta-analysis of randomized clinical trials extracted from the consulted database.

SPECIFIC OBJECTIVES

Assess quality of life as measured by the Fibromyalgia Impact Questionnaire (FIQ) or equivalent.

METHODOLOGY

PROTOCOL AND REGISTRATION

This systematic review was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (LIBERATI et al., 2009).

ELIGIBILITY CRITERIA

a) Study types: Randomized controlled trials comparing repetitive transcranial magnetic stimulation with placebo for the treatment of patients with fibromyalgia. Texts written in English and Portuguese were considered for this review. There is no publication date restriction.

b) Patients: Patients diagnosed with fibromyalgia by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the American College of Rheumatology (ACR).

c) Types of intervention: Studies were included that evaluated the new treatment of fibromyalgia with repetitive transcranial magnetic stimulation, an inhibitory or excitatory neuromodulation technique that allows the induction of a magnetic field in the brain in a painless and non-invasive way, comparing it with placebo.

d) Evaluated outcomes: The evaluated outcomes are related to the efficacy, through the visual analogue pain scale (VNS) and safety of the new therapeutic method, through the analysis of the Fibromyalgia Social Impact Questionnaire (FIQ), compared to standard treatments.

DATA SOURCE

Studies were identified by searching electronic databases and article reference lists. The database used was PubMed.

SEARCH

The search strategy used for PubMed databases was as follows: "((Fibromyalgia OR Diffuse Myofascial Pain Syndrome)) AND (Transcranial Magnetic Stimulation OR Transcranial Magnetic Stimulation, Repetitive OR RTMS)". As part of the article search process, the search strategies were reviewed by XAVIER C., FERRARI J.P. and SHOCK R.F.

SELECTION OF STUDIES

Eligibility analysis and screening of the studies found were performed independently and standardized by three reviewers (XAVIER C., FERRARI J.P. and CHOCAIR R.F.). Differences between the reviewers were resolved by debates and consensus among them, together with the advisor (BARACAT F.I.). A flowchart adapted from PRISMA was used to summarize the study selection process.

DATA COLLECTION PROCESS

The method of extracting data from each included clinical trial consisted of filling out information forms. After the analysis of each clinical trial, a list of criteria based on the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) was used to report a randomized clinical trial. Subsequently, the reviewers extracted data from each included study through the standardized form and worked with a second reviewer to verify the extracted data. Disagreements were resolved by discussion and consensus among reviewers. Information extracted from each trial included: patient characteristics and inclusion and exclusion criteria; methods of randomization and allocation of patients; intervention and control groups, outcomes and losses.

INDIVIDUAL ANALYSIS OF THE RISK OF BIAS IN STUDIES

To examine the quality of selected randomized controlled trials, reviewers worked independently detailing the adequacy of randomization and patient allocation; blinding patients, healthcare professionals, data collectors and outcome evaluators; as well as transparent reporting and the extent of losses to follow-up. These items meet the criteria applied by the Jadad scale to assess the risk of bias in randomized clinical trials, which was calculated for each study. The scale score ranges from 0 to 5, according to figure 1. A clinical trial is considered to have high methodological quality if its score is greater than or equal to 3 points on the scale (JADAD et al., 1996). In each study, it was also evaluated whether the repetitive transcranial magnetic stimulation technique was properly described or if it was poorly

reported, or still insufficiently described, making reproduction unfeasible.

In addition, it was also determined in each outcome if they were properly defined in each study. There was no hope that the outcomes would be homogeneously defined in all studies, however, they must have a clear description. For the preparation of this review, there was no intention to exclude any article based on a higher risk of bias presented.

PLANNED METHODS FOR ANALYSIS

Meta-analyses were performed using the random effects model to obtain mean differences and 95% confidence intervals (95%CI) for each outcome. All analyzes were performed using the software *Review Manager* 5.4. Data on risk differences and 95% confidence intervals for each outcome will be calculated using the Mantel-Haenszel test and inconsistency (heterogeneity) was calculated using the chi-square method (Chi^2) and by the Higgins method. This last method (designated I^2) represents the percentage of the total variation of an effect estimated by studies that is due to heterogeneity rather than true probability (HIGGINS, J. *et al*., 2003).

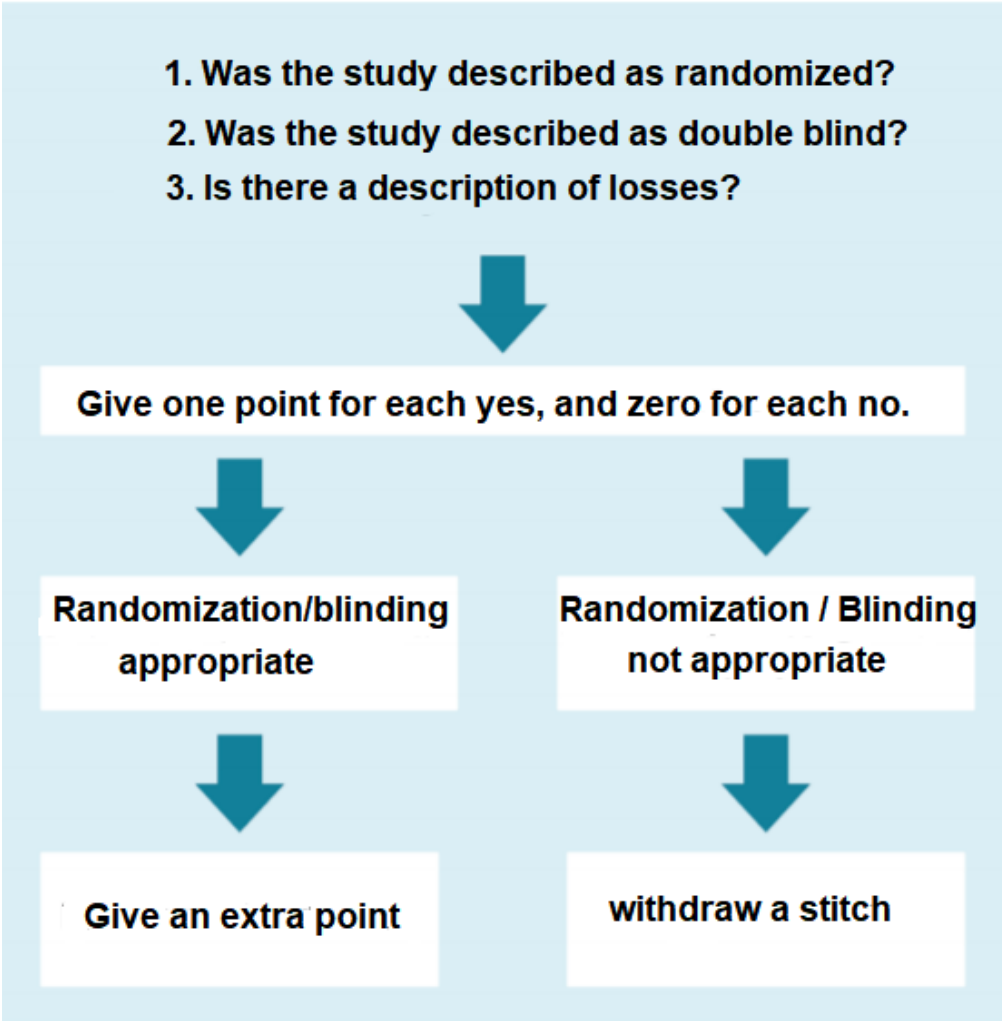

Figure 1. Brief explanation of the Jadad Scale (Risk of Bias Assessment of Randomized Clinical Trials) (BARACAT, FI; 2017).

RESULTS

SELECTION OF STUDIES

The eighty-one studies were screened and assessed for eligibility using the following descriptors: "((Fibromyalgia OR Diffuse Myofascial Pain Syndrome)) AND (Transcranial Magnetic Stimulation OR Transcranial Magnetic Stimulation, Repetitive OR RTMS)" in the PubMed database. Ten were discarded because they were duplicates or because, after reading the title and abstract, the article clearly did not meet the eligibility criteria. A total of 33 studies were accessed for full-text evaluation, of which 25 were excluded because they had any of the following characteristics: outcomes different from those evaluated; studies that evaluated other causes of pain syndromes; clinical trials that used intervention therapy different from the one evaluated, impossibility of extracting data or that were not randomized clinical trials. Therefore, 8 studies were included in the systematic review. A total of 199 participants were evaluated for the social impact outcome and 125 participants for the pain intensity outcome. Figure 2 shows a flowchart adapted from PRISMA, which illustrates the study selection process.

CHARACTERISTICS OF THE STUDIES

a) methods: The eight randomized controlled trials extracted from the PubMed database and selected for review were published in English.

b) patients: A total of 253 patients were involved in this review. Although all patients were diagnosed with fibromyalgia,

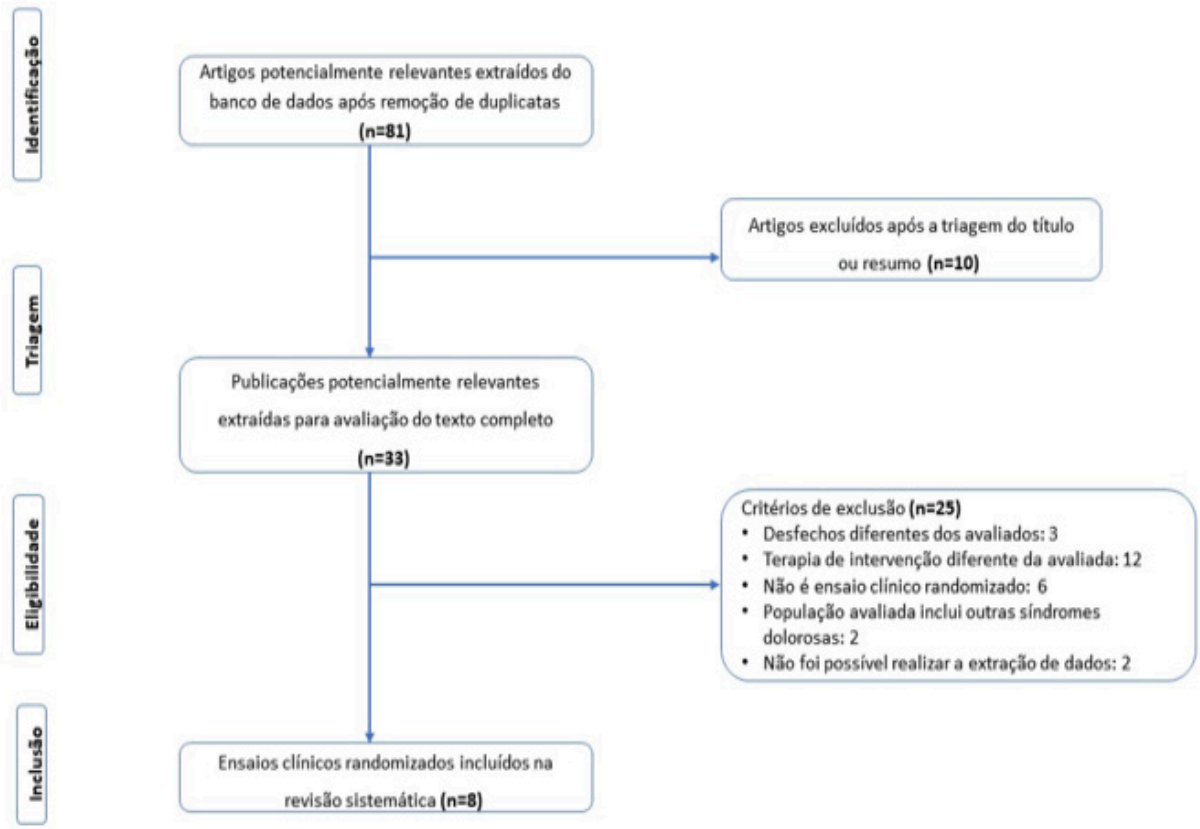

Figure 2 – Flowchart adapted from PRISMA that illustrates the selection of studies (LIBERATI *et al.*, 2009).

exclusion criteria were different between clinical trials. Some articles excluded patients who had another pain syndrome, inflammatory rheumatologic diseases, secondary fibromyalgia, autoimmune diseases, other medical or psychiatric diseases such as depression, neurological disorders, history of substance abuse, pregnancy, breastfeeding, contraindications to brain stimulation, seizures., epilepsy, presence of a cardiac pacemaker, implanted medication pump, metallic devices implanted in the patient's head, blood tests with altered results, tendency to bleed or use of anticoagulants, non-interruption of medication use in less than 1 month, except medications for pain and sleep disorders provided that the dose has been stable for at least 1 month, patients with active infection or cancer, with intracranial hypertension, recent traumatic brain injury, brain surgery or with hearing problems. Regarding the inclusion criteria, most studies specified that the diagnosis of fibromyalgia was defined by the ACR (American College of Rheumatology), with a minimum pain intensity of 4 points on a scale of 0-10, age over 18 years, being right-handed, have persistent pain for more than 6 months before enrollment, have been on stable treatment for more than 1 month before enrollment and remain on it during the study, are not aware of rTMS therapy, who have experienced generalized pain and tenderness at 11 or more of the 18 trial sites specific tender points, diagnosed at least 12 months before the start of the clinical trial, be female, with the exception of 1 study that included male patients and only one study defined that the included patient must have French as their native language.

c) interventions: In each clinical trial, one group was placed on repetitive transcranial magnetic stimulation while the other group was subjected to placebo stimulation. After organizing the clinical trials, 2 comparison groups were obtained from the computed data, which will be presented in Tables 1 and 3.

d) outcomes: Most clinical trials evaluated at least one of the outcomes we intended to assess (visual analogue pain scale and fibromyalgia impact questionnaire). However, a few studies expressed their results through other outcomes and were excluded for that reason.

A summary of the characteristics of the included clinical trials is shown in Table 1 below.

RISK OF BIAS IN STUDIES

As mentioned earlier, the individual analysis of the risk of bias in the studies was performed by applying the Jadad scale that assesses whether repetitive transcranial magnetic stimulation techniques in fibromyalgia and the definitions of outcomes were properly described by each author, assigning a score of 0 to 5 for each study. All studies achieved good methodological quality: Jadad ≥ 3 with 1 of the studies achieving a score of three points due to the absence of blinding during the clinical trial while 7 of the 8 clinical trials achieved a maximum score of five points.

Data regarding the risk of bias for each study are described in Table 2.

INDIVIDUAL STUDY RESULTS

The results of each outcome evaluated by the studies are shown in Table 3 and Table 4, being represented by a score of the mean of the intervention and control groups, in addition to the respective standard deviations.

SUMMARY OF RESULTS, RISK OF BIAS BETWEEN STUDIES AND ADDITIONAL ANALYZES

Data expressed by risk difference and confidence intervals for each study are

Author, year	Country	n	Number of sessions	Outcome and follow-up
Altas *et al.* (2019)	Turkey	30	15	VNS and FIQ 3 weeks
Boyer *et al.* (2014)	France	38	14	FIG 11 weeks
Fitzgibbon *et al.* (2013)	Australia	26	20	VNS and FIQ 1 month
Lee *et al.* (2012)	South Korea	15	10	VNS e FIQ 1 month
Maestú *et al.* (2013)	Spain	54	8	VNS 8 weeks
Mhalla *et al.* (2011)	France	40	21	FIQ 25 weeks
Passard *et al.* (2007)	France	30	10	FIQ 8 weeks
Short *et al.* (2011)	USA	20	10	FIQ 2 weeks

Table 1. Characteristics of included clinical trials.

Author, year	Blinding	Randomization	Losses	Total
Altas *et al.* (2019)	2	2	1	5
Boyer *et al.* (2014)	2	2	1	5
Fitzgibbon *et al.* (2013)	2	2	1	5
Lee *et al.* (2012)	0	2	1	3
Maestú *et al.* (2013)	2	2	1	5
Mhalla *et al.* (2011)	2	2	1	5
Passard *et al.* (2007)	2	2	1	5
Short *et al.* (2011)	2	2	1	5

Table 2. Analysis of the risk of bias in the studies.

Author, year	Average Intervention	Standard Deviation Intervention	Sample Intervention	Average Control	Standard Deviation Control	Control sample	Average Control 2	Deviation Control 2	Control Sample 2
Altas *et al.* (2019)	48.75	7.94	10	39.97	15.88	10	39,02	14,4	10
Boyer *et al.* (2014)	-9.6	16.7	16	2.0	9.3	13			
Fitzgibbon *et al.* (2013)	39.70	21.3	14	51.28	20,1	12			
Lee *et al.* (2012)	47.8	10.2	10	48,7	35.5	5			
Mhalla *et al.* (2011)	56.0	17.7	16	63.3	15.0	14			
Passard *et al.* (2007)	47.4	8.1	15	57.8	6.8	15			
Short *et al.* (2011)	38.99	19.44	10	47.93	14.70	10			

Table 3. Results regarding the outcome of the fibromyalgia impact questionnaire.

Author, Year	Average Intervention	Standard Deviation Intervention	Sample Intervention	Average Control	Standard Deviation Control	Control sample
Altas *et al.* (2019)	55.5	15.3	20	56	17.1	10
Fitzgibbon *et al.* (2013)	50.6	21.7	14	55.4	20.9	12
Lee *et al.* (2012)	55.15	15.7	10	60.3	24.8	5
Maestú *et al.* (2013)	-39	29.7	28	-8	48.13	26

Table 4. Results regarding the visual pain scale outcome calculated from 0 to 100.

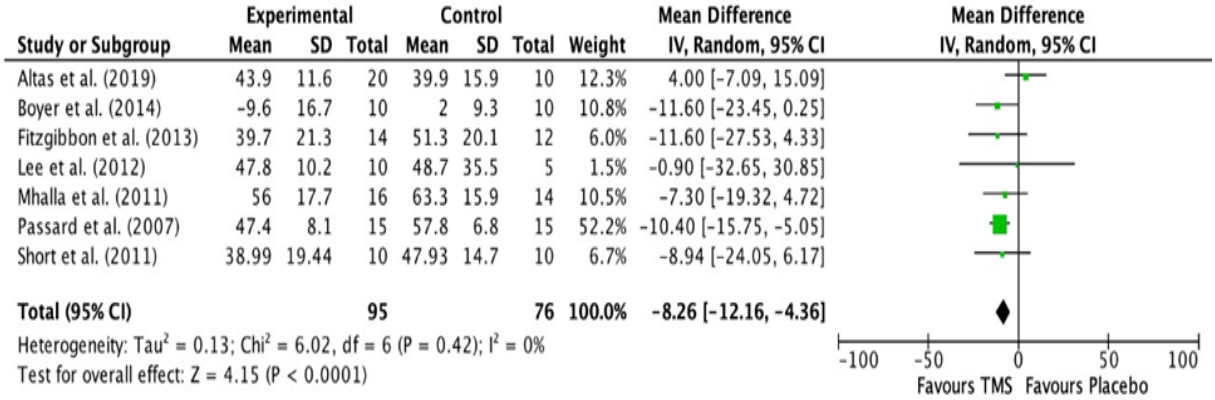

Figure 3- Social impact outcome analysis comparing transcranial magnetic stimulation in fibromyalgia versus placebo.

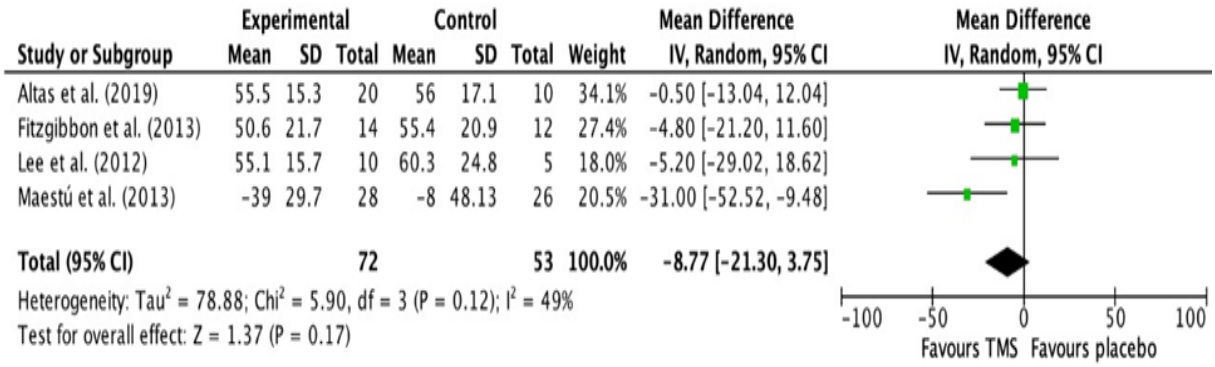

Figure 4- Analysis of visual pain scale outcome, comparing transcranial magnetic stimulation in fibromyalgia versus placebo.

graphically displayed, together with the results of the meta-analyses, including the respective measures of heterogeneity, in the figures below. The graphs are organized in each comparison group, according to the sequence presented in the previous tables.

Surveying the data extracted from the eight included studies, it can be seen that the meta-analysis demonstrated the efficacy of transcranial magnetic stimulation treatment in the social impact outcome (Figure 3), and a trend towards improvement in the pain outcome (Figure 4). However, this result must be interpreted with caution due to the heterogeneity of the studies, which used different frequencies and coils in different positions during stimulation therapy.

DISCUSSION

The present systematic review quantitatively evaluates the reported changes in pain and quality of life in patients with fibromyalgia after receiving repeated transcranial magnetic stimulation, capable of causing not only neuromodulatory changes but also local neuroplasticity [17],[18]. By having neuronal modulatory action, this therapy has the ability to cause lasting effects used to study and treat neuropsychiatric diseases and pain syndromes [20]. The data collected support the hypothesis of an improvement in quality of life and a tendency to decrease pain intensity. The research carried out for this review revealed that despite the high number of articles initially found (81) during the search, only eight of them met all the eligibility criteria. The methodological quality of the included clinical trials was satisfactory, since all studies achieved Jadad scores greater than or equal to 3, a fact that may explain the detection of the association between the therapy used and the effect of improvement in quality of life and intensity. of pain despite the small sample of patients (n=253). On the other hand, the strict patient exclusion criteria (predominance of women in the combined sample, exclusion of patients with psychiatric disorders, minors, among others) for randomized clinical trials end up interfering with the validation of the clinical applicability of the results extracted from these trials. studies in the population with fibromyalgia. There were some differences between the rTMS frequencies and intervals in the analyzed studies, which could potentially weaken the generalizability of the results. Although several studies support a significant difference between the effects of stimulation compared to placebo, most studies report only the short and medium-term effects of the therapy used on the evaluated outcomes, thus requiring more studies to evaluate larger populations, with fewer exclusion criteria and the duration and intensity of these long-term effects, which could then change the conclusions of this review and reveal other potentially existing effects of RTMS.

CONCLUSION

Therefore, it can be concluded that the findings demonstrate an association between rTMS and painful and social outcomes caused by fibromyalgia compared to placebo stimulation. However, future studies that mainly evaluate the long-term changes with the use of this therapy will be necessary to better evaluate these associations.

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