 REVIEW ARTICLE

Effects of transcranial direct current stimulation associated or combined with exercise on musculoskeletal pain: systematic review

Efeitos da estimulação transcraniana por corrente contínua associada ou combinada ao exercício na dor musculoesquelética: revisão sistemática

Ricardo Vinicius Silva Souza[1], Daniel Germano Maciel[1], Mikhail Santos Cerqueira[1]

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ABSTRACT

BACKGROUND AND OBJECTIVES: Aerobic/resistance exercises and transcranial direct current stimulation (tDCS) can produce analgesic effects in patients with musculoskeletal pain, however, the summed effect of these two therapeutic resources remains unclear. The present study aimed to verify the effects of tDCS associated or combined with aerobic/resistance exercise on musculoskeletal pain.
CONTENTS: The search was carried out in the databases: Pubmed, LILACS, Scielo. The intervention considered was tDCS associated or combined with exercises and the comparison was exercise without tDCS or with sham tDCS. Randomized controlled trials enrolling patients with musculoskeletal pain were included. There were no restrictions on the language and year of publication and the methodological quality was verified with PEDro Scale. Three trials were included with a total of 110 participants. The methodological quality was high, with an average of 9 points on the PEDro Scale. The studies used tDCS in the primary motor cortex with an intensity of 1 or 2 mA, for 20 minutes. The participants included were aged between 18 and 75 years and had the following diseases: fibromyalgia, osteoarthritis or chronic low back pain.
CONCLUSION: Overall, tDCS did not overcome the sham tDCS to enhance the effects of exercise in reducing musculoskeletal pain.

Keywords: Aerobic exercise, Analgesia, Musculoskeletal pain, Transcranial direct current stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Os exercícios aeróbios/resistidos e a estimulação transcraniana por corrente contínua (ETCC) podem produzir efeitos analgésicos em pacientes com dores de origem musculoesquelética, porém, o efeito somado destes dois recursos terapêuticos ainda não está claro. O objetivo do presente estudo foi verificar os efeitos da ETCC associada ou combinada ao exercício aeróbio/resistido na dor musculoesquelética.
CONTEÚDO: A busca foi realizada nas bases de dados Pubmed, LILACS e Scielo. A intervenção considerada foi ETCC associada ou combinada a exercícios e a comparação foi exercício sem ETCC ou com ETCC simulada. Foram incluídos ensaios clínicos randomizados envolvendo pacientes com dor musculoesquelética aguda ou crônica. Não houve restrições quanto ao idioma e ano de publicação e a qualidade metodológica dos estudos foi verificada por meio da escala PEDro. Três ensaios foram incluídos com um total de 110 participantes. A qualidade metodológica foi alta, com uma média de 9 pontos na escala PEDro. Os estudos utilizaram a ETCC no córtex motor primário com intensidade de 1 ou 2 mA, por 20min. Os participantes tinham idade entre 18 e 75 anos e eram portadores de fibromialgia, osteoartrite ou lombalgia crônica.
CONCLUSÃO: A ETCC não superou a ETCC simulada para potencializar os efeitos do exercício na redução de dor musculoesquelética.

Descritores: Analgesia, Dor musculoesquelética, Estimulação transcraniana por corrente contínua, Exercício aeróbico.

INTRODUCTION

Musculoskeletal dysfunctions involves several diseases that affect the locomotor apparatus and commonly present pain as an indicator of severity and prognosis1. The estimation is that on average 20 to 30% of people in the world suffer from musculoskeletal pain (MSP) and this number tends to increase with advancing age[1,2]. Non-pharmacological treatment for MSP involves active therapies, such as physical exercise, and passive therapies, such as manual therapy and electrophysical resorts. Among passive therapies, transcranial direct current stimulation (tDCS) has been considered a promising option[3,4].

Physical exercises, in general, have been widely prescribed to control MSP[1,5] through a mechanism known as exercise-induced hypoalgesia. It's believed that this mechanism is regulated by the release of endogenous opioids due to increased motor cortex acti-

Ricardo Vinicius Silva Souza – https://orcid.org/0000-0001-5679-7598;
Daniel Germano Maciel – https://orcid.org/0000-0003-0975-5998;
Mikhail Santos Cerqueira – https://orcid.org/0000-0001-5322-863X.

1. Federal University of Rio Grande do Norte, Physiotherapy Department, Natal, RN, Brazil.

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Correspondence to:
Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte
Av. Senador Salgado Filho, 3000 - Campus Universitário, Lagoa Nova
59072-970 Natal, RN, Brasil.
E-mail: mikalsantosc@hotmail.com

vity[6]. Additionally, the exercise-induced hypoalgesia may improve musculoskeletal performance and function[1]. There is evidence suggesting that aerobic and/or resistance exercises are effective in reducing pain in patients with fibromyalgia[7], low back pain[8], knee and hip osteoarthritis[9], femoropatellar pain[10] and tendinopathies[11]. On the other hand, tDCS is a passive and relatively recent technique that consists in the use of a low intensity continuous electric current applied to the scalp in order to stimulate specific cortical areas of the brain[12-14]. This stimulus may cause modulations in neural excitability and inhibit or excite the cortical and subcortical regions, thus inducing the release of endogenous opioids that favor the downward modulation of pain[15-17]. Because it is inexpensive, painless, non-invasive and relatively simple to apply[18], tDCS has been used for MSP treatment. Therefore, it's a reasonable hypothesis that applying tDCS during, before and/or after exercise can potentiate the analgesic effects in the treatment of MSP[4,19-22].

A systematic review[23] evaluated the effects of different non-invasive brain stimulation techniques, repetitive transcranial magnetic stimulation, cranial electrotherapy stimulation, transcranial direct current stimulation, transcranial random noise stimulation and non-invasive cortical electrical stimulation by reduced impedance on chronic pain and concluded that tDCS can improve chronic pain in the short term, however, the specific effect of tDCS combined or associated with exercise on MSP is still unclear. Therefore, the objective of this review was to investigate the effects of tDCS associated or combined with aerobic/resistance exercise on MSP.

CONTENTS

This systematic review followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The search was performed in Pubmed, Scielo and LILACS databases without restrictions regarding language and year of publication of the included studies. The terms used for search were: "transcranial direct current stimulation", "exercise" and "pain". The last search was conducted on December 1, 2020. References from the included articles and also from other systematic reviews on tDCS and pain were checked to track other potentially eligible trials.

The eligibility criteria used in this study were based on the PICOTS strategy - population; intervention; comparison; outcomes; time (moment) of measurement; type of study. Participants should have been diagnosed with musculoskeletal dysfunction and acute or chronic pain; intervention should have been performed through tDCS associated or combined with aerobic or resistance exercises; comparison should have involved exercise without tDCS or associated/combined with sham tDCS, i.e., placebo; the outcome, pain assessed through subjective scales; time of measurement, after at least four weeks of treatment; and the type of studies, randomized clinical trials. Studies involving animals, children or that used a neuromodulation technique different from tDCS were excluded.

Selection of studies

The titles and abstracts were evaluated followed by a full text analysis. The search was carried out independently by two reviewers who later discussed and reached a consensus on the eligibility of the articles found. In case of divergences, a third reviewer was recruited to decide whether or not to include the studies.

Evaluation of the quality of studies

The quality of studies was independently assessed by two reviewers using the PEDro scale, which has good validity and reliability levels. This scale determines the risk of bias and reports on the statistical procedure used in clinical trials. The 11 items analysed were eligibility criteria; sample randomization; allocation concealment; similarity of groups at baseline; blinding of participants; blinding of therapists; blinding of evaluators; measurement of at least one key result obtained in more than 85% of individuals initially allocated into groups; intention-to-treat analysis; intergroup comparison; measurement of effect and variability of treatment. The first item of the scale (eligibility criteria) is not considered for scoring due to its association with external validation. Thus, the total score varies between zero and 10 points. The higher the score, the better the methodological quality of the study. Studies with fewer than 6 points were considered of low methodological quality[24].

Data analysis and extraction

The data extracted from the articles included author; year of publication; objectives; instrument and moments of pain measurement; intervention; comparison; results; conclusion. The analysis of the data was descriptive. In order to characterize the groups, the type of intervention, type of disease, age, gender and sample size were analyzed. To characterize the intervention and the comparison, the number of sessions, duration of stimulation, stimulated brain area, intensity, number of repetitions and series were analyzed.

RESULTS

Sixty-four studies were identified, but only three were eligible for analysis (Figure 1).

Description of studies

The three included articles were published between 2016 and 2018. The sample size varied from 30 to 45 volunteers, totaling 110 individuals of both sexes. The detailed description of included studies is presented in table 1.

Quality of studies

The studies had high methodological quality, with an average of 9 points, with a total score of 8-10 on the PEDro scale (Table 2). The study[25] scored 10 on the PEDro scale, the study[6] scored 9, and the study[26] scored 8. All three met the requirements for randomization and sample concealment, similarity between groups at baseline, blinding of participants and evaluators, analysis of intent to treat, intergroup comparison and point estimates and variability. Blinding of therapists was the least met item. The sample calculation[25,26] was performed and all studies were registered and funded (Table 3).

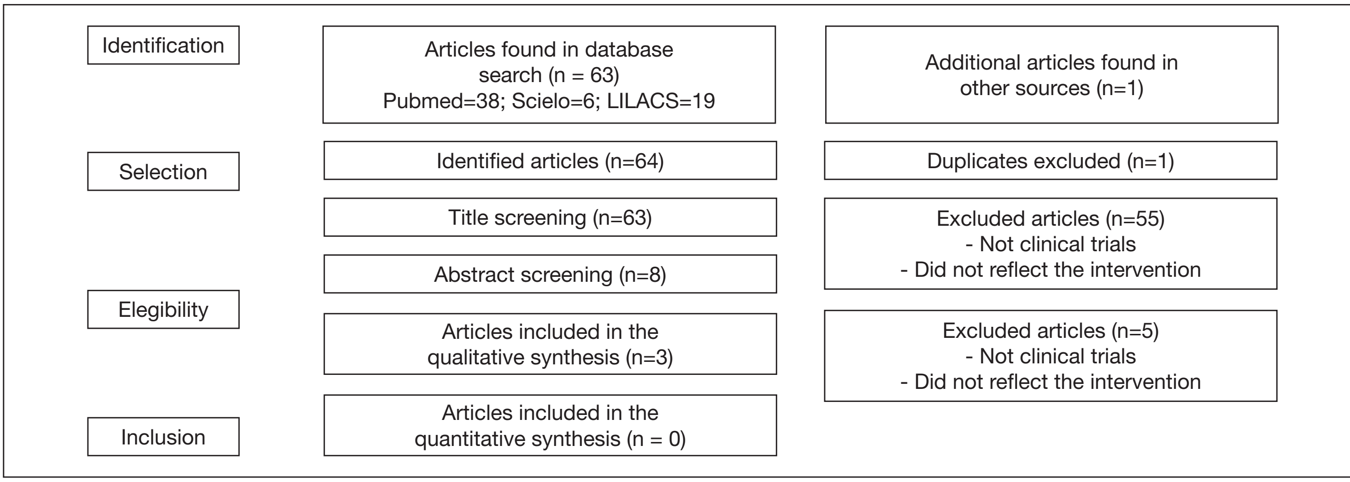

Figure 1. Flowchart for inclusion of studies

Table 1. Description of studies included in the review

Study	Population	Intervention			Comparison
		General protocol	tDCS parameters	Exercise parameters	
Mendonça et al.[6]	45 patients with fibromyalgia; Age between 18 and 65 years. G1 (n=15): ACT tDCS combined with ACT aerobic exercises. G2 (n=15): S tDCS combined with ACT aerobic exercises. G3 (n=15): ACT tDCS combined with S aerobic exercises.	4 weeks OF treatment (tDCS during aerobic exercise). Week 1: tDCS for 5 consecutive days and aerobic exercises 3 days a week. Weeks 2 to 4: aerobic exercises only, 3x per week.	20 minutes of application with 2mA intensity. Anodic electrode at point C3 of the M1 region. Cathodic electrode positioned on the supraorbital region, contralateral to the anodic electrode.	30 minutes on treadmill with 60% MHR intensity.	S tDCS: same parameters as the active group, but tDCS were applied only for the first 30s. S Aerobic exercise: same parameters as the active group, but with minimum treadmill speed.
Chang et al.[26]	30 patients with knee osteoarthritis. Age over 50 years. G1 (n=15): ACT tDCS associated with resistance exercise. G2 (n=15): S tDCS associated with resistance exercise.	8 weeks of treatment. 2 days a week (tDCS associated with resistance exercise). Application of tDCS 30 minutes before the exercise program.	20 minutes with 1 mA intensity. Anodic electrode positioned at M1, contralateral to the most symptomatic knee. Cathodic electrode positioned on the contralateral supraorbital region.	30 minutes of strengthening with ankle braces or elastic bands. 3 series of 10 repetitions; 30s interval between series for each of the following exercises: 1) knee extension, 2) hip abduction, 3) partial squatting on the wall, 4) knee flexion while sitting, 5) step ups/ step downs.	S tDCS: same parameters as the active group, but tDCS were applied only for the first 15s. Exercise protocol and guidelines similar to the intervention group.
Straudi et al.[25]	35 patients with chronic low back pain. Age between 18 and 75 years. G1 (n=18): ACT tDCS associated with resistance and stretching exercises (in groups). G2 (n=17): S tDCS associated with resistance and stretching exercises (in groups).	4 weeks of treatment (tDCS associated with resistance exercise). Application of tDCS for 5 consecutive days before the exercise program.	20 minutes with 2mA intensity. In central or bilateral low back pain: anodic electrode positioned at M1 (dominant hemisphere). In unilateral pain: anodic electrode positioned in the M1 region, contralateral to the pain side. The cathode electrode was positioned in the contralateral supraorbital area.	Resistance exercises (8 to 10 submaximal actions maintained for 5 to 6s with intensity of 40 to 60% of the maximum voluntary contraction) for extensors of the spine, buttocks, abdomens, iliopsoas and paraspinals. Stretching maintained for 15 to 20s, with intensity controlled through subjective perception.	S tDCS: same parameters as the active group, but tDCS was applied only for the first 30s. Exercise protocol and guidelines similar to the intervention group.

n = sample size; tDCS = transcranial direct current stimulation; ACT = active; S = sham; M1 = primary motor cortex; mA = miliampère; MHR = maximum heart rate; EX = exercise; VAS = visual analog scale; OA = osteoarthritis; G1 = group 1; G2 = group 2; G3 = group 3.

Table 2. Methodological quality of eligible studies

Studies	PEDro Scale Items 1 2 3 4 5 6 7 8 9 10 11	PEDro Scale (0-10)	Registered	Declared primary outcome	Funded	Sample size calculation
Mendonça et al.[6]	Y Y Y Y Y N Y Y Y Y Y	9	Y	Y	Y	N
Chang et al.[26]	Y Y Y Y Y N Y N Y Y Y	8	Y	Y	Y	Y
Straudi et al.[25]	Y Y Y Y Y Y Y Y Y Y Y	10	Y	Y	Y	Y

Y= Yes; N = No.
1: eligibility criteria and participant source; 2: randomized allocation; 3: concealed allocation; 4: baseline comparability; 5: blinded participants; 6: blinded therapists; 7: blinded evaluators; 8: adequate follow-up; 9: analysis of intention to treat; 10: comparison between groups; 11: point estimate and variability.
Item 1 does not contribute to the total score.

Table 3. Results and conclusions of studies analyzing the effects of tDCS associated or combined with exercise on MSP

Studies and disease	Instrument and pain measurement moments	Results	Conclusions
Mendonça et al.[6] Fibromyalgia	VAS 1 week before treatment. After 1 and 4 weeks of treatment. 1 and 2 months after the end of treatment.	Decrease in pain intensity at the end of the first and fourth week of intervention in all groups, but the greatest was in the tDCS + ACT EX group. There was no reduction in pain 1 and 2 months after the end of treatment. There was no significant difference in pain intensity between groups.	Authors' conclusion: tDCS + ACT EX produces a greater reduction in pain intensity than the individual use of tDCS or ACT EX. Conclusion of the review: There was no difference between ACT tDCS and S tDCS to improve pain in patients with fibromyalgia. Therefore, the benefits in both groups were probably due to ACT EX.
Chang et al.[26] Osteoarthritis	VAS 1 week before treatment After 8 weeks of treatment	Pain during walking decreased in both groups after 8 weeks of treatment. The reduction of pain in the ACT tDCS + EX group was twice that observed in the S tDCS + EX group. There was no significant difference between groups.	Authors' conclusion: There was pain reduction after 8 weeks of treatment in both groups. The effect in the ACT tDCS + EX group was more than double compared to the simulated group. However, there was no significant difference in pain reduction compared to the S tDCS + EX group. Conclusion of the review: There was no difference between ACT tDCS and S tDCS to improve pain in patients with osteoarthritis. Therefore, the benefits in both groups were probably due to exercise.
Straudi et al.[25] Chronic low back pain	VAS; Before treatment; After tDCS application and after group exercise; After 1 month of treatment.	In both groups there was no significant reduction in pain intensity immediately after tDCS, however, there was reduction in pain from the first session on. There was difference between groups after 1 month of treatment, favoring the tDCS + EX group.	Authors' conclusion: tDCS can increase the analgesic effects of the exercise group in patients with chronic low back pain. Conclusion of the review: There was a difference in favor of ACT tDCS compared to S tDCS to improve pain in patients with chronic low back pain. Therefore, the use of tDCS can increase the analgesic effects of exercise in patients with chronic low back pain.

VAS = visual analog scale; tDCS = transcranial direct current stimulation; ACT = active; S = sham; EX = exercise.

DISCUSSION

All included articles compared the combination or association of exercise with simulated tDCS[6,25,26]. The studies[6,25] did not show significant difference in pain intensity in patients with fibromyalgia and osteoarthritis between ACT tDCS and S tDCS. tDCS seems to add analgesic effects to exercise specifically for low back pain[26].

Unlike the present results, two recent meta-analyses have shown significant benefits of the synergistic use of tDCS with pain control exercises in chronic diseases[27,28]. The results of these meta-analyses were probably influenced by the inclusion of studies involving manual therapy, cognitive-behavioral therapy and electrical muscle stimulation. The present review adds more specific information on the synergistic use of tDCS and resistance or aerobic exercises.

There are methodological issues that need to be carefully observed regarding the use of tDCS and its stimulation parameters. For example, all included studies performed the stimulation of the primary motor cortex[6,25,26]. As pain can also be related to emotional factors, the application of tDCS in another brain area, such as the dorsolateral prefrontal cortex, for example, may have better effects than when applied to the primary motor cortex[29]. It's important to note that the primary motor cortex is a brain area capable of releasing neurotransmitters that can increase the production of endogenous opioids and consequently reduce pain[6,15,19] and tDCS, as well as therapeutic exercises, act on this cortical area. Therefore, the stimulation of a same cortical area by the association or combination of these two resources can explain the limited analgesic effect of the use of exercise alone[6]. It's reasonable to consider that stimulating the primary motor cortex through exercise and another cortical area through tDCS may be more effective in potentiating the analgesic effects of exercise.

Regarding the parameters of stimuli intensity and duration, the studies presented two different types of stimulation: 2mA for 20 minutes[6,25] and 1mA for 20 minutes[26]. Despite discrepancies, the literature states that after stimulation with tDCS for 20 minu-

tes and with intensity between 1 and 2mA it's possible to verify changes in cortical excitability[30]. This may be the reason why most studies have opted for this dosimetry.
As for the moment of application, the studies were heterogeneous in relation to associating[25,26] or combining[6] tDCS and exercise. The study that presented significant results favorable to tDCS is a pilot trial that did the application before the exercise[25]. Although based on studies with low risk of bias, data from this review suggest that the associated or combined use of exercise and tDCS for MSP control is discordant.
This review's results are based on only three studies that are homogeneous regarding the cortical area of tDCS application, but heterogeneous regarding the parameters of application of tDCS and types of disease. However, due to these limitations and to the small number of articles and participants included, since only three databases were searched, the results should be interpreted with caution.
To evaluate whether tDCS used synergistically with exercise programs reduces or not MSP, studies with adequate sample size, longer follow-up periods, different times, durations, frequencies, and application parameters should be conducted.

CONCLUSION

Combining or associating tDCS with exercise has limited additional effect on the reduction of MSP in relation to treatment with exercise individually, and part of these effects may be due to the placebo effect.

AUTHORS' CONTRIBUTION

Ricardo Vinicius Silva Souza
Data Collection, Conceptualization, Methodology, Writing - Review and Edition
Daniel Germano Maciel
Methodology, Writing - Preparation of the original, Writing - Review and Editing
Mikhail Santos Cerqueira
Data Collection, Conceptualization, Project Management, Methodology, Writing - Review and Editing, Supervision

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