

The Effect of Transcranial Direct Current Stimulation on Pain in Knee Osteoarthritis: A Systematic Review and Meta-analysis of Clinical Trials

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Abstract

Background: Knee Osteoarthritis (OA) is a common degenerative joint disease characterized by ongoing pain and reduced physical function.

Objectives: We aimed to systematically review and meta-analyze the clinical trials that evaluated the impact of transcranial Direct Current Stimulation (tDCS) on knee OA pain.

Methods: A comprehensive search was performed on Scopus, Web of Science, PubMed/MEDLINE, EMBASE, ProQuest, CENTRAL via Cochrane, and PEDro from the inception of these databases until May 31, 2023 with no language restrictions. The objective of the search was to find publications that examined the impact of active tDCS compared to sham tDCS or other interventions in individuals with knee OA.

Results: The meta-analysis comprised ten studies including 517 patients with knee OA. Active tDCS resulted in significantly lower pain scores compared to sham tDCS/ Transcutaneous Electrical Nerve Stimulation (TENS) immediately (effect sizes from pre-test–post-test-control design (dppc2) = -0.83, I² = 61.8%), short-term (dppc2 = -0.74, I² = 43.5%), and mid-term (dppc2 = -1.94, I² = 87.8%) follow-ups, but not in the long term (dppc2 = -0.25, I² = 29.6%). However, the certainty of the evidence was assessed as low to very low. Moreover, function was significantly improved with active tDCS immediately after the last treatment session either by McMaster Universities Osteoarthritis Index (WOMAC) or Knee Injury and Osteoarthritis Outcome Score (KOOS) (dppc2 = -0.38, I² = 6.6% and dppc2 = 0.87, I² = 60.1%, respectively). The certainty of the evidence was very low. No serious adverse effects of tDCS were reported by the majority of studies.

Conclusion: More than half of the included trials had unclear or high risk of bias and there were no patient follow-ups beyond three months. Given the criteria of reduced I² and sufficient number of studies, no potential sources of heterogeneity were identified. Further high-quality randomized clinical trials with extended follow-up periods are required to determine the true effects of tDCS on knee OA.

Keywords: Knee Osteoarthritis, Meta-analysis, Pain, Systematic Review, Transcranial Direct Current Stimulation

1. Background

Knee Osteoarthritis (OA) is a prevalent multifactorial degenerative joint disease and is characterized by persistent pain and impaired physical function.¹ Multifactorial etiologies include sports injury, genetic susceptibility, previous knee trauma, old age, female gender, overweight, obesity, knee injury, repetitive joint use, bone density, muscle weakness, and joint laxity.² The worldwide prevalence and incidence rate of knee OA have been estimated at 16% and 203 per 10,000 person-years, respectively.³ The global prevalence of OA is projected to

rise in the coming decades. One significant factor contributing to its increased prevalence in recent decades is the growing elderly population and the prevalence of unhealthy lifestyles.⁴ This can be attributed, in part, to the growing prevalence of risk factors associated with OA, including genetic predisposition, obesity, sedentary lifestyle, and exercise-related injuries.^{5,6}

The study of knee pain caused by OA is challenging due to its fluctuating nature and evolving pattern. The predictability of episodic pain decreases and its distressing nature increases as it progresses from early to

late stages. Several factors have been linked to knee OA pain in longitudinal studies, including younger age, non-white ethnicity, female sex, lower educational attainment, obesity, presence of other medical conditions, psychological factors such as depression, low self-efficacy, pain catastrophizing, and pain sensitization.^{7,8} Aside from younger age, these factors are also associated with an increased risk of functional impairment, which is a precursor to disability and necessitates the treatment of pain in knee osteoarthritis.⁹ Severity of pain, obesity,¹⁰ instability of joints' and 'avoidance of activity'¹¹ are risk factors of functional impairment.

In recent years, there has been a transition from pharmacologic therapy of knee OA to no pharmacologic therapy due to the limited efficacy and side effects such as serious adverse effects such as: falls, nausea, drowsiness, and constipation.^{12,13} Research suggests that nonpharmacologic approaches are more effective in providing long-term symptom relief and can potentially delay or prevent functional decline.¹⁴ Recent studies have shown that individuals with knee OA exhibit changes in central pain processing and increased blood-oxygen-level-dependent activity when exposed to painful stimuli.¹⁵⁻¹⁷ The chronic inflammation and anatomical damage in the joint lead to substantial gray matter atrophy in individuals with OA.^{18,19} These findings highlight the importance of utilizing a treatment intervention that can potentially modify the central pain processing system. Persistent peripheral inputs triggered central nociceptive pathways, cause imbalance in endogenous pain modulation by enhanced synaptic efficacy and reduced inhibition.^{20,21} The continuous repetition of this stimulation cycle with peripheral pain, causes the person to feel pain even when the painful stimulus is not present. Some example of Central sensitization :lower pain thresholds (allodynia), increased and prolonged response to noxious stimuli (hyperalgesia), and enlarger referred pain areas.²² Non-invasive brain stimulation techniques such as transcranial Direct Current Stimulation (tDCS) have garnered significant attention from researchers as a potential treatment for chronic pain conditions.²³

Transcranial direct current stimulation is a method that utilizes a low-intensity current (1-2mA) to modify the excitability of the motor cortex. With electrical stimulation of primary motor cortex (M1), pain modulation occurs through activation of thalamic nuclei directly connected with motor and premotor cortices, as well as activation of medial thalamus, anterior cingulate and upper brainstem.^{24,25} This is achieved by applying the current to the cortex using two or more electrodes. Anodal stimulation of the primary motor cortex enhances cortical excitability through the elevation of the resting membrane potential of neurons.^{26,27} Prior systematic reviews have demonstrated encouraging outcomes of tDCS in the management of

chronic pain, either as a standalone intervention or when used in conjunction with peripheral stimulation.^{28,29} Moreover, tDCS has demonstrated efficacy in the management of fibromyalgia and neuropathic pain.^{30,31} Regarding knee OA, although one systematic review and meta-analysis compared the effectiveness of nonsurgical interventions, there was no mention of tDCS.³² Another review collectively looked at common musculoskeletal conditions, showing significant pain reduction in knee OA with tDCS pooling only the results of two studies.³³

Moreover, a systematic review and meta-analysis which exclusively evaluated the effect of tDCS on knee OA pain and function, revealed significant improvement in both.⁴³ The Randomized Controlled Trial (RCT) articles and searches related to previous systematic reviews were outdated, dating back to 2019. In contrast, the present study includes RCTs from 2023. Additionally, the previous systematic review included only six studies, of which only two were part of the quantitative analysis. The RCT studies in that review were of poor quality, and it was recommended that higher-quality RCTs be conducted in this area. Since then, more RCTs have been performed in this field, highlighting the need for further review.

2. Objectives

We aimed to perform a comprehensive systematic review and meta-analysis of clinical trials assessing the effect of tDCS on knee OA pain.

3. Methods

The protocol for this systematic review has been registered in international prospective register of systematic reviews (PROSPERO) under the code CRD42021251589. The registration details are available at the following URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=251589. The research obtained ethical clearance from the ethics committee of the Iran University of Medical Sciences, with references to the Ethics code: IR.IUMS.FMD.REC.1400.151 (25 Dec 2021). This protocol follows the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).³⁴

3.1. Study Selection Criteria (PICOS criteria for the study)

3.1.1. Population

This study involved individuals of both sexes and all racial backgrounds, aged 18 years or older, who had received a diagnosis of symptomatic knee OA, either in one knee or both knees. The diagnosis was made using radiographic methods or according to the criteria set by the American College of Rheumatology (ACR). Participants with any grade of OA as determined by the Kellgren and Lawrence criteria were included. The patients should

have had knee OA pain in the past three months with an average rating of at least 30 or 3 on a 0-100 or 0-10 Numerical Rating Scale (NRS) or Visual Analogue Scale (VAS) for pain. Moreover, the patients must have had no plan to change medication regimens specifically for pain.

The study's exclusion criteria were prosthetic knee replacement, non-arthroscopic surgery to the affected knee, or major trauma to the knee region, secondary OA, history of intra-articular injection within the last two weeks or prolotherapy within the last year, serious medical illnesses, such as uncontrolled diabetes or hypertension, heart failure, chronic kidney or hepatic insufficiency, or history of acute myocardial infarction, peripheral neuropathy, systemic rheumatic disorders, including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia, systemic neuromuscular diseases such as myasthenia gravis, Lambert-Eaton syndrome, and gout, any neurological condition that could affect lower limb function, including Parkinson's disease and multiple sclerosis, alcohol/substance abuse, cognitive impairment, history of brain surgery, tumor, seizure, traumatic brain injury, or stroke, implanted metal or electrical device in the head or chest, physical therapy within the last 30 days, pregnancy or lactation, active skin lesions under the site of electrodes, and hospitalization within the preceding year for psychiatric disorders.

3.1.2. Intervention and Comparator

The inclusion criteria for this study involved the selection of research investigations with two or more than two arms, wherein at least one arm was subjected to active tDCS treatment while other arms received sham tDCS or an alternative treatment for knee OA. The tDCS was defined as the passing of constant current from an anode to a cathode placed on the head for a certain duration with variable ramp-up/down periods. Studies that used any other physical interventions such as ultrasound in combination with active tDCS in the intervention arm were excluded. Articles that combined tDCS with other modalities were excluded from the study. Only those studies that had only utilized tDCS were included. In the study by Sajadi et al.,⁷⁴ tDCS was applied to one arm while TENS was applied to the other. Since the arm receiving tDCS was not combined with TENS, it was included in our study. However, those which used other types of non-physical interventions like Mindful-Based Meditation (MBM) or knee strengthening exercise were included.

3.1.3. Outcomes

The primary outcome of the present systematic review pertained to the pain assessed by VAS, NRS, or any other pain rating scales. The secondary outcomes were function by the Western Ontario and McMaster Universities

Osteoarthritis Index (WOMAC) or Knee Injury and Osteoarthritis Outcome Score (KOOS) and adverse events.

3.1.4. Study Design

This systematic review included all clinical trials that investigated the comparative impact of active tDCS versus sham tDCS or other interventions on knee OA. The inclusion criteria for study designs encompassed randomized or non-randomized, parallel or cross-over, single-blind, double-blind, or open-label designs. One-arm studies with pre-post designs were excluded. Case reports, narrative reviews, systematic reviews with/without meta-analyses, animal studies, case series, study protocols, scoping reviews, books and book chapters/sections, retrospective chart reviews, cohorts, and cross-sectional studies were excluded. Furthermore, conference or meeting abstracts that did not yield usable data as well as registered trials with no published reports were excluded.

3.2. Eligibility Criteria

Following the completion of the search, all references were imported into the Mendeley Desktop software and subsequently duplicated. Eligibility for inclusion was determined by reviewing the titles and abstracts of the primary articles obtained through the search strategy. Two independent reviewers (S.S, L.J) evaluated the full-text of the articles that were considered potentially relevant. A consensus was achieved through discussion when the reviewers held conflicting opinions. When there was a lack of agreement among the reviewers, the final decision was made by a third evaluator (M.BC), who possessed more expertise in the relevant field.

3.3. Search Strategy

A comprehensive search was conducted in seven databases, including Scopus, Web of Science, PubMed/MEDLINE, EMBASE, ProQuest, CENTRAL via Cochrane, and PEDro. The search covered the period from the inception of these databases until May 31, 2023, and no language restrictions were applied. Also, the National Institute of Health Clinical Trials Register (<https://ClinicalTrials.gov/>), the IRCTN registry (<https://www.isrctn.com/>), and the World Health Organization (WHO) ICTRP Search Portal (<https://trialsearch.who.int/>) were thoroughly searched to identify unpublished studies meeting the inclusion criteria.

This systematic review identified relevant search terms from Emtree and Medical Subject Headings (MeSH), as well as free text words, focusing on the patient (knee osteoarthritis) and intervention (tDCS). Supplementary 2 presents the search strategies used for Scopus, Web of Science, PubMed, CENTRAL, EMBASE, and ProQuest. Furthermore, a comprehensive evaluation

of relevant primary research and reviews was conducted to examine bibliographies for any additional pertinent studies.

3.4. Data Extraction

Data extraction was performed by two reviewers (S.S, K.M) using a pre-designed data extraction form. After the process was completed, the extracted data was cross checked by one of the authors (S.Sa) to minimize any possible inaccuracies.

3.5. Quality and Risk of Bias Assessment

The quality assessment of the studies was conducted using the Cochrane Collaboration's tool for assessing risk of bias,³⁵ including the following parameters: random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, and reporting bias. The quality assessment was conducted by two authors (S.S, M.BC) and any disagreements were resolved through discussion. A third author (S.Sa) was consulted in instances where no consensus was reached.

Two independent authors (S.S, M.BC) utilized the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) tool to evaluate the overall quality of evidence (<https://gdt.gradepro.org>).

3.6. Statistical Analysis

The statistical analysis was done using the Stata software (version 14.2, StataCorp LP, College Station, TX, USA). The quantitative synthesis of data was conducted using the random effect model to observe a conservative approach and displayed in a forest plot. Heterogeneity was assessed using the Q Cochrane test and the I^2 test.³⁶ The degree of heterogeneity was classified into four categories: mild (0 – 39.9), moderate (40 – 69.9), severe (70 – 89.9), and highly severe (90 – 100).³⁷

We used *dppc2* (effect sizes from pretest–posttest-control designs) as the effect size with interpretation as follows: 0.2-0.5, small effect; 0.5-0.8, medium effect; and >0.8, large effect.³⁸ The online effect size calculator provided by the Campbell Collaboration available at <https://campbellcollaboration.org/research-resources/effect-size-calculator.html> was employed with $r = 0.3$. Accordingly, the METAN command for three variables was applied for analysis. Also, the WebPlotDigitizer was used to extract numerical data from plots and graphs.

One study had four parallel arms, including sham tDCS, M1 tDCS, S1 tDCS, and dorsolateral prefrontal cortex (DLPFC) tDCS.³⁹ Since all other studies had placed the anode electrode over M1, we only included the M1 tDCS and sham tDCS arms of this trial in the meta-analysis. Furthermore, the studies by da Graca-Tarrago et al., and Chaturvedi et al., had four arms and used intramuscular electrical stimulation (EIMS) and TENS in combination with tDCS, respectively.^{40,41} Thus, in order

to isolate the effect of tDCS we only included two arms from each study; active tDCS + sham EIMS vs. sham tDCS + sham EIMS from the former and active tDCS + sham TENS vs. sham tDCS + sham TENS from the latter. To evaluate the effects of tDCS on pain, the follow-up time points were divided as follows to include the highest number of studies:

- Immediately (Immediately post intervention until at most one week after the last treatment session);
- Two weeks after the last treatment session (Short-term);
- Three weeks to less than two months after the last session (Mid-term); and
- Two to three months after the last treatment session (Long-term).

3.6.1. Subgroup Analysis

Subgroup analysis was employed to identify the sources of heterogeneity. The subgroup variables included the country in which the study was carried out, year of publication, sex, mean age and Body Mass Index (BMI) of patients in the active tDCS groups, study and control groups, method of tDCS administration, tDCS ramp-up/down duration, the total number of tDCS session and duration of each session, overall quality of the included studies (risk of bias), and total sample size.

3.6.2. Assessment of Publication Bias

Reporting bias was assessed using Egger's weighted regression test (P -value < 0.05).⁴² Furthermore, the "trim-and-fill" technique was utilized to evaluate the potential influence of publication bias on the overall results.⁴³

3.6.3. Sensitivity Analysis

This study employed the jackknife (leave-one-out) approach to conduct sensitivity analysis. This was performed to evaluate the impact of individual studies on the overall findings.⁴⁴

4. Results

4.1. Identification of Studies

Figure 1 depicts the procedure for research selection. A total of 1286 publications were obtained from the research databases. After eliminating duplicate publications, the total number of remaining publications was 1129. Afterwards, 1080 publications were excluded from the study based on an evaluation of their titles and abstracts. The eligibility of the remaining 49 publications was assessed using their full-text.

Harvey MP et al., included a small number of patients with chronic pain anywhere in the musculoskeletal system.⁴⁵ One trial evaluated the effects of tDCS on experimental pain intensity,⁴⁶ whose participants were the same as another.⁴⁷ Two others were Bayesian analyses of the effect of tDCS on experimental pain sensitivity and

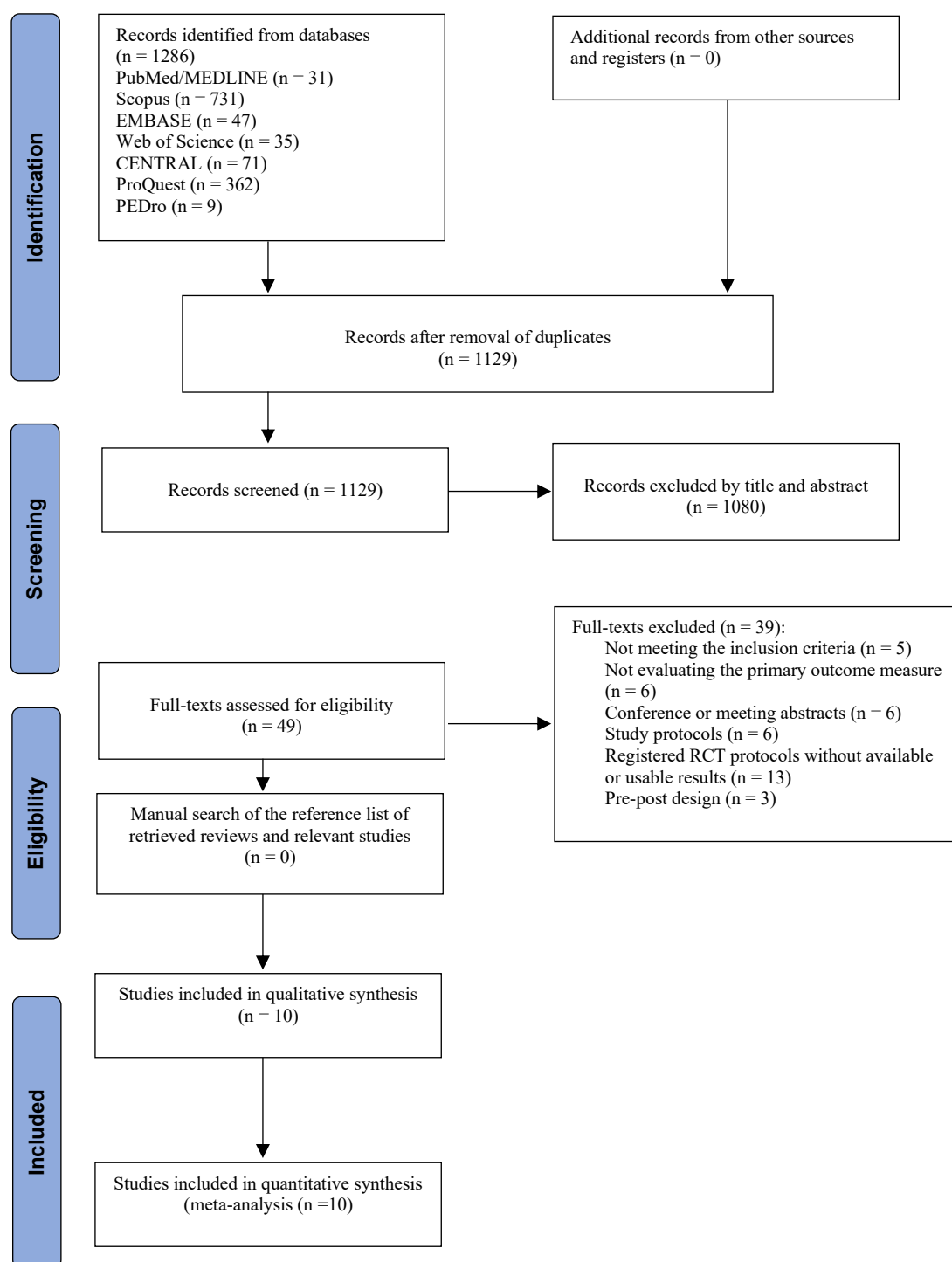


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

inflammation,^{48,49} and the main trial has been included.⁵⁰ Brain-derived neurotrophic factor levels were the main outcome of another trial and there was no pain assessment.⁵¹ In other studies, alternating current stimulation was used instead of direct current, but they did not report the pain experienced by participants.⁵²⁻⁵⁴ One study used a subset of patients from another trial and did not report baseline NRS values.⁵⁵ Some were before-after trials.⁵⁶⁻⁵⁸ Six papers were conference or meeting abstracts⁵⁹⁻⁶⁴ and six were published as study protocols.⁶⁵⁻⁷⁰ Another study had

performed secondary analysis on the tDCS group of an already included trial by Tavares et al.⁷¹ There was also a pilot study, the full results of which were later published.⁷²

Moreover, no data or results were published for three trials (TCTR20210802001, NCT02330315, and NCT01404052). Some were still recruiting patients (NCT04375072, NCT05138471, ChiCTR2200055650, and ACTRN12621000787886). The recruitment status of three trials was pending (ChiCTR2200064735, IRCT20131225015932N18,

Table 1. The General Characteristics of the Included Studies

Author, Year	Additional treatment	Sample size	Sex (No. of females)	Age (years), Mean	BMI (kg/m ²), Mean	K/L radiographic score (No.)		Outcome measures	Adverse effects	Follow-ups
						tDCS	Control			
Ahn, 2017 (40)	No change in pain medication, N/R	40 tDCS (n=20) Sham (n=20)	tDCS, 10 Sham, 11	tDCS, 60.60 Sham, 59.30	tDCS, 27.00 Sham, 26.00	Grade 0, 5 Grade 1, 5 Grade 2, 5 Grade 3, 4 Grade 4, 1	Grade 0, 8 Grade 1, 3 Grade 2, 5 Grade 3, 4 Grade 4, 0	Pain (NRS), WOMAC, SF-MPQ-2, 6MWT, SPPB, side effects + PROMIS version 1.0-Applied Cognition-Abilities-Short Form 8a	No serious adverse effects or cognitive impairment	1 day 2 days 3 days 4 days 5 days (immediate) 1 week 2 weeks 3 weeks
Chang, 2017 (65)	Usual medications (N/R), standard quadriceps strengthening exercise	30 tDCS (n=15) Sham (n=15)	tDCS, 11 Sham, 9	tDCS, 59.8 Sham, 64.1	tDCS, 31.3 Sham, 30.5	N/R	N/R	Pain (VAS), WOMAC, adverse events	One case of headache in the tDCS group and one case of painful sensation under electrode in the sham group	8 weeks (immediate)
Ahn, 2019 (63)	No change in pain medication, N/R	30 tDCS (n=15) Sham (n=15)	tDCS, 8 Sham, 10	tDCS, 59.47 Sham, 59.47	tDCS, 27.90 Sham, 27.17	N/R	N/R	Pain (NRS), WOMAC, patient satisfaction, side effects	No serious adverse effects or side effects	2 weeks (immediate)
da Graca-Tarrago (31)	Analgesics	30 tDCS (n=15) Sham (n=15)	Female only	tDCS, 64.14 Sham, 63.87	tDCS, 29.47 Sham, 28.83	Grade 3-4	Grade 3-4	Pain (VAS), WOMAC, side effects	No significant side effects, minor side effects of tDCS <12% of patients, similar between groups	1 day 2 days 3 days 4 days 5 days (immediate)
Sajadi, 2020 (64)	Strengthening exercises of knee muscles, acetaminophen in case of pain intensity >60 on VAS	40 tDCS (n=20) TENS (n=20)	tDCS, 15 TENS, 19	tDCS, 59.30 TENS, 56.85	tDCS, 30.29 TENS, 31.76	Grade 2-3	Grade 2-3	Pain (VAS), WOMAC, adverse effects	No adverse effects	1 week (immediate) 1 month 3 months
Tavares, 2021 (67)	No change in usual medications, N/R	104 tDCS (n=51) Sham (n=53)	tDCS, 42 Sham, 46	tDCS, 74.78 Sham, 73.13	N/R	Grade 1, 15 Grade 2, 15 Grade 3, 12 Grade 4, 8	Grade 1, 11 Grade 2, 17 Grade 3, 18 Grade 4, 6	Pain (BPI, VAS), WOMAC, Lequesne, SF-12, TUGT, one-leg stance, self-rated health, adverse effects	Headache, scalp pain, neck pain, tingling, skin redness, sleepiness, acute mood changes, trouble concentrating Only scalp pain and skin redness significantly higher with active tDCS	1 week (after 5 sessions) 2 weeks (after 10 sessions) 3 weeks (immediate) 5 weeks (15 days after end) 7 weeks (1 month after end) 11 weeks (2 months after end)
Rahimi, 2021 (29)	Physiotherapy: TENS, ultrasound, infrared, patellofemoral and tibiofemoral mobilization, exercise therapy	80 tDCS, M1 (n=20) tDCS, S1 (n=20) tDCS, DLPFC (n=20) Sham (n=20)	tDCS (M1), 18 tDCS (S1), 18 tDCS (DLPFC), 18 Sham, 18	Total sample, 58.8	tDCS (M1), 27.69 tDCS (S1), 27.33 tDCS (DLPFC), 28.30 Sham, 28.30	Grade 2-3	Grade 2-3	Pain (VAS), KOOS, ROM, quadriceps strength, stepping, chair stand, 10m-walking	N/R	2 weeks (immediate) 1 month
Chaturvedi, 2021	Physiotherapy including	36	tDCS, 11	tDCS, 52.78	tDCS, 29.57	Grade 1, 3	Grade 1, 0	Pain (VAS), KOOS,	N/R	1 week (immediate)

(30)	hot packs + hamstring & quadriceps stretching	tDCS (n=18) Sham (n=18)	Sham, 14	Sham, 51.75	Sham, 27.48	Grade 2, 6 Grade 3, 9	Grade 2, 10 Grade 3, 8	6MWT, adverse effects		2 weeks 6 weeks
Azizi, 2021 (66)	Acetaminophen 325 mg daily	54 tDCS (n=27) Sham (n=27)	tDCS, 21 Sham, 18	tDCS, 61.3 Sham, 56.4	tDCS, 26.8 Sham, 25.2	Grade 1-2	Grade 1-2	Pain (VAS), KOOS, side effects	No important side effects	5 days (immediate) 3 months
Martorella, 2022 (37)	No change in pain medication, N/R	120 tDCS (n=60) Sham (n=60)	tDCS, 40 Sham, 42	tDCS, 65.32 Sham, 66.60	tDCS, 32.70 Sham, 32.52	Grade 1, 9 Grade 2, 20 Grade 3, 22 Grade 4, 9	Grade 1, 7 Grade 2, 20 Grade 3, 29 Grade 4, 4	Pain (NRS), WOMAC, adverse events, tDCS experience questionnaire	No serious adverse effects	1 week 2 weeks 3 weeks (immediate) 3 months

6MWT, 6-Minute Walk Test; BMI, body mass index; BPI, Brief Pain Inventory; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalogram; EIMS, intramuscular electrical stimulation; K/L, Kellgren and Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; MBM, mindfulness-based meditation; N/R, not reported; NRS, numerical rating scale; ROM, range of motion; SF-12, 12-Item Short Form Health Survey questionnaire; SF-MPQ-2, Short-Form McGill Pain Questionnaire-2; SPPB, Short Physical Performance Battery; tDCS, transcranial direct current stimulation; TUGT, timed up and go test; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. The General tDCS Characteristics of the Included Studies

Author, Year	Country	tDCS group											Control group(s)
		Administration	Type	Device	Electrodes	Electrode positioning	Anode position	Cathode position	Current intensity	Duration per session	Other characteristics	Treatment period	
Ahn, 2017 (40)	USA	Other-administered	Active tDCS	Soterix CT direct current stimulator (Soterix Medical Inc., NY)	A pair of thick (0.3 cm) rectangular surface sponge electrodes (5x7 cm) saturated with 10 ml saline	10-20 EEG system	M1 (C3 or C4) contralateral to the affected knee	Supraorbital region ipsilateral to the affected knee	2 mA	20 min	10 s ramp-up and 10 s ramp-down	Once daily, 5 consecutive days, total=5 sessions	Sham tDCS, electrodes in the same position, 2 mA current for only 30 s with the same ramp-up and ramp-down of 10 s
Chang, 2017 (65)	Australia	Other-administered	Active tDCS	DC-STIMULATOR (neuroConn, Ilmenau, Germany)	Two 35-cm ² surface sponge electrodes	N/R	M1 contralateral to the side of the worst knee	Contralateral supraorbital region	1 mA	20 min	10 s ramp-up and 10 s ramp-down	Twice weekly, 8 weeks, total=16 sessions	Sham tDCS, identical position, stimulation turned on for 15 s then off
Ahn, 2019 (63)	USA	Self-administered	Active tDCS + active MBM	Soterix 1x1 tDCS mini-CT Stimulator (Soterix Medical Inc., NY)	Headgear and 5x7 cm saline-soaked surface sponge electrodes	N/R	Primary motor cortex contralateral to the affected knee	Supraorbital region ipsilateral to the affected knee	2 mA	20 min	10 s ramp-up and 10 s ramp-down	5 days a week, 2 weeks, total=10 sessions	Sham tDCS, identical position, 30 s of 2mA stimulation at the beginning and end + sham MBM (relaxation and deep breaths)
da Graca-Tarrago (31)	Brazil	Other-administered	Active tDCS + sham EIMS	N/R	Rubber electrodes attached to a sponge soaked in 0.9% saline with a size of 35 cm ² (5x7 cm), 7-8 cm apart	N/R	Primary motor cortex (M1) contralateral to the affected knee	Contralateral supraorbital region	2 mA	30 min	Ramp-up/down duration 30 s	Once daily, 5 consecutive days, total=5 sessions	Sham tDCS, same way, device would turn off after 30 s of ramp-up + sham EIMS, 30 min right after active tDCS with electroacupuncture device (Sikuro) with no electrical stimulation but with blinking diode, 12 needles along the spinous processes
Sajadi, 2020 (64)	Iran	Other-administered	Active tDCS	Battery driven stimulator	2 rubber electrodes	10-20 EEG system	M1 (C3 or C4)	Supraorbital region	2 mA	20 min	N/R	3 sessions per week, 2	TENS, 4 rubber electrodes with 35 cm ²

				(ActivaDose II)	with 35 cm ² surface covered with 0.89% saline soaked sponges		contralateral to the affected knee	ipsilateral to the affected knee				weeks, total=6 sessions	in square pattern around the kneecap, 5 cm apart, 100 Hz frequency, 100 µs pulse width, 10% below patient motor threshold for 25 min
Tavares, 2021 (67)	Brazil	Other-administered	Active tDCS	Soterix 1×1 Low-Intensity Stimulator	Two 35-cm ² surface sponge electrodes (EASYPad™ Soterix Medical Inc.) soaked with 10 ml physiologic saline	10-20 EEG system	M1 (C3/C4) contralateral to the affected knee	Supraorbital region contralateral to the anode	2 mA	20 min	Ramp-up/down duration 30 s	5 sessions per week, 3 weeks, total=15 sessions	Sham tDCS, identical position, 30 s of each ramp-up/down period
Rahimi, 2021 (29)	Iran	Other-administered	Active tDCS	OASIS Pro (Mind Alive Inc., Canada)	2 saline-soaked 4×4 cm surface electrodes	10-20 EEG system	Left M1, left S1, left DLPFC	Contralateral (right) supraorbital region	1 mA	20 min	Ramp-up/down duration 30 s	5 sessions per week, 2 weeks, total=10 sessions	Sham tDCS, active electrode center of the head, cathode on supraorbital area
Chaturvedi, 2021 (30)	India	Other-administered	Active tDCS + sham TENS	Medicaid (serial No.: TD216209, India)	Circular sponge soaked in normal saline	10-20 EEG system	Primary motor cortex (M1, C3, or C4) contralateral to the more painful knee	Opposite supraorbital region, ipsilateral to the affected knee	2 mA	20 min	N/R	Once daily, 5 consecutive days, total=5 sessions	Sham tDCS, same position, turned on for 30 s and then turned off + sham TENS, surface electrodes at the medial and lateral side of the knee joint for 20 min, stimulator turned on for 30 s and then turned off
Azizi, 2021 (66)	Iran	Other-administered	Active tDCS	EndoMed (ENRAF Co., Netherlands)	Inserted in a 16 cm ² sponge, soaked in 1% saline solution, with Velcro	10-20 EEG system	Contralateral primary motor cortex (C3 or C4)	Ipsilateral supraorbital region (Fp1 or Fp2)	2 mA	20 min	10 s ramp-up from zero and 10 s ramp-down	Once daily, 5 days, total=5 sessions	Sham tDCS, 10 s ramp-up of the current from zero to 2 mA, 30 s stimulation, 10 s ramp-down to zero, 20 min no current
Martorella, 2022 (37)	USA	Self-administered	Active tDCS	Soterix 1×1 tDCS mini-CT Stimulator (Soterix Medical Inc., NY, 6.5-inch-long, 3-inch-wide, 0.7-inch-thick)	Headgear and 5×7 cm saline-soaked surface sponge electrodes	Headgear (fixed)	Primary motor cortex (M1)	Supraorbital region	2 mA	20 min	Ramp-up and ramp-down over 30 s	5 session per week, 3 weeks, total=15 sessions	Sham tDCS, electrodes in the same position, stimulator delivered only 2 mA current for 30 s

6MWT, 6-Minute Walk Test; BMI, body mass index; BPI, Brief Pain Inventory; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalogram; EIMS, intramuscular electrical stimulation; K/L, Kellgren and Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; MBM, mindfulness-based meditation; N/R, not reported; NRS, numerical rating scale; ROM, range of motion; SF-12, 12-Item Short Form Health Survey questionnaire; SF-MPQ-2, Short-Form McGill Pain Questionnaire-2; SPPB, Short Physical Performance Battery; tDCS, transcranial direct current stimulation; TUGT, timed up and go test; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

and IRCT20160423027554N3), and two were not yet recruiting (NCT04321655 and NCT04320875). Another trial (NCT02723929) had reported results at Clinical Trials.gov; however, a combination of active tDCS and active transcranial ultrasound (a physical intervention) were employed in the intervention group, unlike the study by Ahn et al., who used active MBM, a non-physical intervention, in combination with active tDCS.⁷³ After reviewing relevant studies and reviews, no publications were found in the references. In total, the qualitative and quantitative synthesis included ten studies.

4.2. Overview of the Included Studies

Table 1 provides a summary of the overall characteristics of the included studies. All studies compared active tDCS with sham except for the study by Sajadi et al., who compared it with TENS.⁷⁴ Moreover, Ahn et al., combined active tDCS with active MBM.⁷³ In two studies, tDCS was self-administered.^{47,73} Table 2 provides a summary of the tDCS characteristics of the included studies. The anode was placed on the primary motor cortex (M1), contralateral to the affected knee, and the cathode on the ipsilateral supraorbital region in all studies. Most studies used a current intensity of 2 mA,^{40,41,47,50,73-76} except two that applied a 1 mA current

intensity.^{39,77} One study utilized 30-minute tDCS sessions,⁴¹ while the others employed 20-minute sessions.^{39,40,47,50,73-77} The total number of tDCS sessions ranged from 5 to 21. Furthermore, the ramp-up/down period was either 10 or 30s.

This meta-analysis included a total of 517 patients, with one study including only female patients.⁴¹ The mean age of the participants in the active tDCS groups ranged from 52.78 to 74.78 years and from 51.75 to 73.13 years in the control groups. Pain was measured using VAS in seven trials^{39-41,74-77} and NRS in three.^{47,50,73} However, in one study by Tavares et al., in addition to VAS, pain was also measured using the Brief Pain Inventory (BPI).⁷⁶ On the other hand, function was evaluated by the WOMAC scale in seven studies^{41,47,50,73,74,76,77} and KOOS scale in three.^{39,40,75} Tavares et al., also used the Lequesne index scale as a measure of function in knee OA.⁷⁶ Other outcome measures included the 6-minute walk test (6MWT),^{40,50} Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2) and Short Physical Performance Battery (SPPB),⁵⁰ patient satisfaction,⁷³ 12-Item Short Form Health Survey questionnaire (SF-12), timed up and go test (TUGT), one-leg stance, and self-rated health,⁷⁶ Range Of Motion (ROM), quadriceps strength, stepping, chair stand, and 10m-walking,³⁹ as well as the tDCS experience questionnaire.⁴⁷

	Allocation concealment	Attrition bias	Detection bias	Performance bias	Random sequence generation	Reporting bias	Total
Ahn, 2017	+	-	+	+	+	+	-
Chang, 2017	+	+	+	+	+	+	+
Ahn, 2019	+	+	+	+	+	+	+
da Graca-Tarrago, 2019	+	+	+	+	+	+	+
Sajadi, 2020	+	+	-	-	+	+	-
Tavares, 2021	+	+	+	+	+	+	+
Rahimi, 2021	?	+	+	+	+	+	?
Chaturvedi, 2021	+	+	-	+	+	+	-
Azizi, 2021	+	+	-	+	+	+	-
Martorella, 2022	+	-	+	+	+	+	-

Figure 2. Risk of bias assessment by different items using the Cochrane's Collaboration tool.

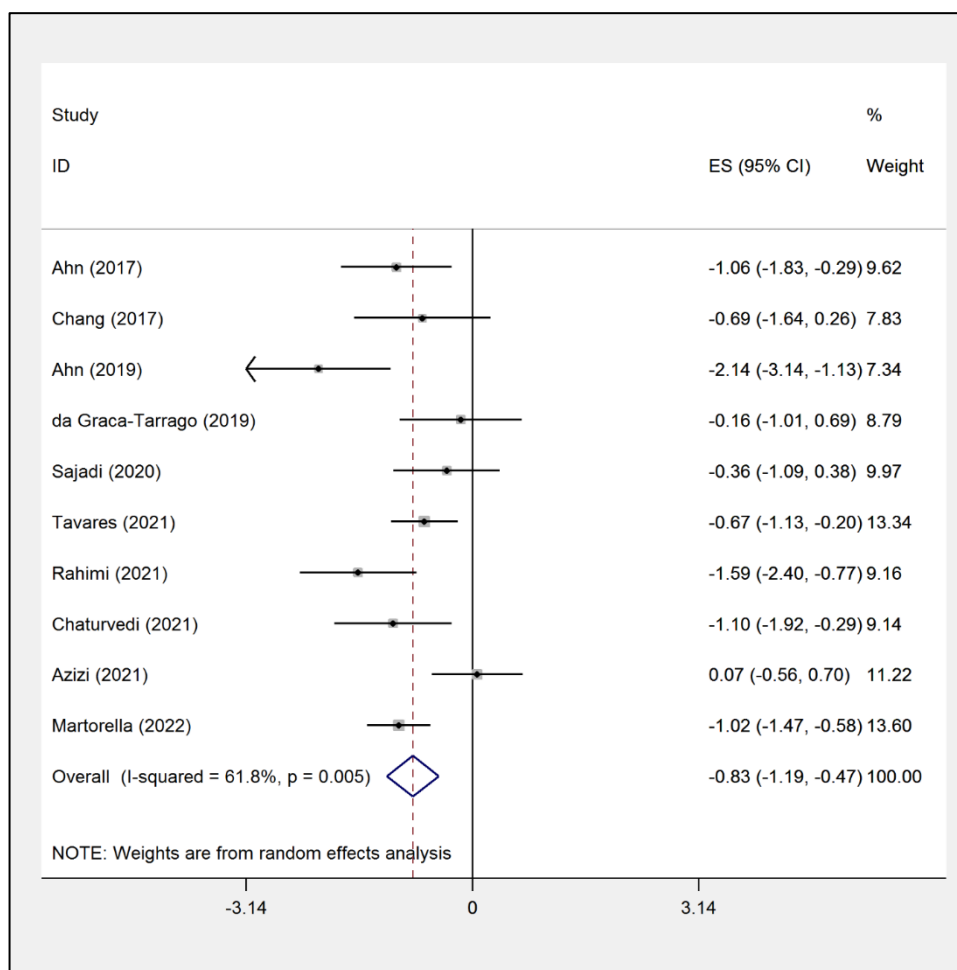


Figure 3. Forest Plot of Comparison: Active transcranial direct current stimulation (tDCS) vs. sham tDCS/transcutaneous electrical nerve stimulation (TENS) for the primary outcome “pain” immediately.

4.3. Quality Assessment

Figure 2 displays the results of quality assessment. With low risk in all the items of the Cochrane’s Collaboration tool, four studies had an overall low risk of bias.^{41,73,76,77} Moreover, all the studies had low risk of bias in terms of reporting and random sequence generation. Only one trial had an unclear allocation concealment which resulted in an overall unclear risk of bias.³⁹ Sajadi et al.’s study had a high risk of detection and performance biases.⁷⁴ Two studies only had a high risk of detection bias,^{40,75} while two others only had a high risk of attrition bias.^{47,50}

4.4. Outcomes

4.4.1. Immediate Effects on Pain

Taking before-intervention values into account, five trials reported significantly lower pain with active tDCS compared to sham,^{39,40,47,50,73,76} while others showed no significant difference in terms of pain reduction when comparing active tDCS with sham tDCS/TENS.^{41,74,75,77} Overall, active tDCS was superior to sham tDCS/TENS for pain reduction in knee OA with moderate heterogeneity (dppc2 = -0.83, 95% confidence interval [CI] -1.19; -0.47, I² = 61.8%) (Figure 3). However, it is important to

note that the certainty of the evidence was assessed as very low. We downgraded the evidence by one level for risk of bias, indirectness, and imprecision (Supplement 3).

4.4.2. Short-term Effects on Pain

Only three studies looked at pain in short-term, out of which two showed a significant reduction in pain at this point.^{40,73} Overall, active tDCS resulted in significantly lower knee OA pain compared to sham in the short-term, with moderate heterogeneity (dppc2 = -0.74, 95% CI -1.25; -0.22, I² = 43.5%) (Figure 4a). The certainty of the evidence was assessed as low because the evidence was downgraded by one level for risk of bias, and imprecision (Supplement 3).

4.4.3. Mid-term Effects on Pain

Three of the five trials that tested the mid-term effects of tDCS on pain showed a significant reduction compared to the sham.^{39,40,50} Moreover, the general impact of active tDCS on knee OA pain was significantly better than the sham tDCS/TENS. However, there was high heterogeneity (dppc2 = -1.94, 95% CI -1.94; -0.09, I² = 87.8%) (Figure 4b). The certainty of the evidence was assessed as very

low because the evidence downgraded by one level for risk of bias, inconsistency, indirectness, and imprecision (Supplement 3).

4.4.4. Long-term Effects on Pain

Only one study demonstrated significantly lower pain with

active tDCS than sham in the long term.⁴⁷ Additionally, the overall effect on knee OA pain was non-significant at this time point (dppc2 = -0.25, 95% CI -0.57; -0.07, I² = 29.6%) (Figure 4c). The certainty of the evidence was assessed as very low because the evidence downgraded by one level for risk of bias, indirectness, and imprecision (Supplement 3).

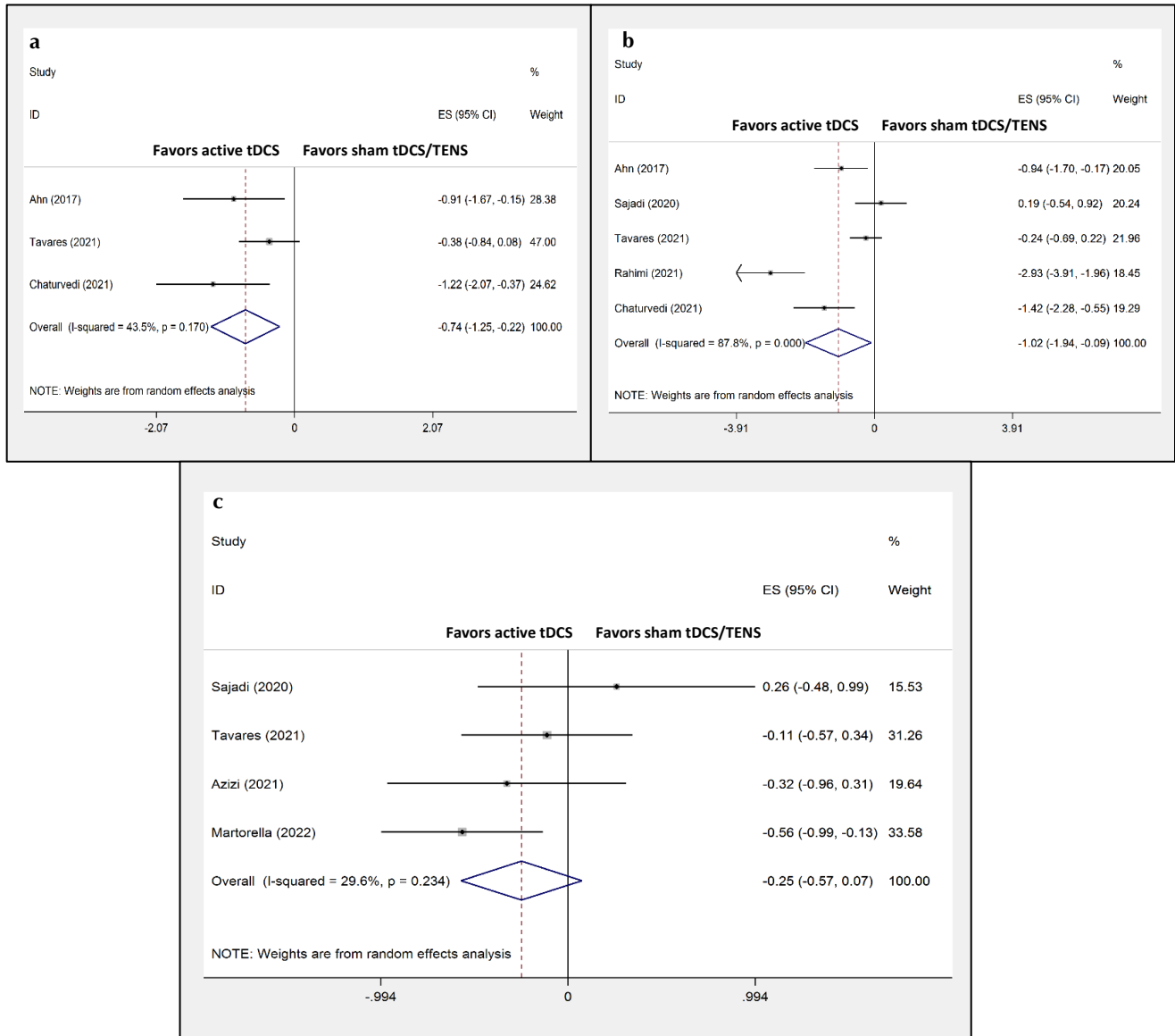


Figure 4. Forest Plot of Comparison: active transcranial direct current stimulation (tDCS) vs. sham tDCS/transcutaneous electrical nerve stimulation (TENS) for the primary outcome “pain” in knee osteoarthritis **a**) short-term, **b**) mid-term, and **c**) long-term follow-up.

4.4.5. Effects on Function

The WOMAC scale was used in seven and the KOOS scale in three trials for the assessment of function. Since the two scales had opposite interpretations, i.e. the higher WOMAC score but lower KOOS score translating into worse function, the results could not be pooled and are reported separately. Furthermore, the quantity of research studies available was only adequate for quantitative analysis in the short-term and immediate periods.

Although most studies showed that active tDCS was not superior to sham tDCS/TENS in terms of knee OA function improvement (WOMAC), the overall estimate

demonstrated a significantly better function immediately with mild heterogeneity (dppc2 = -0.38, 95% CI -0.63; -0.13, I² = 6.6%) (Figure 5a). The certainty of the evidence was assessed as very low because the evidence downgraded by one level for risk of bias, inconsistency, indirectness, and imprecision (Supplement 4).

Active tDCS led to significantly improved function compared to sham by KOOS scale (dppc2 = 0.87, 95% CI 0.18; 1.55, I² = 60.1%) (Figure 5b). The certainty of the evidence was assessed as very low because the evidence downgraded by one level for risk of bias, indirectness, and imprecision (Supplement 4).

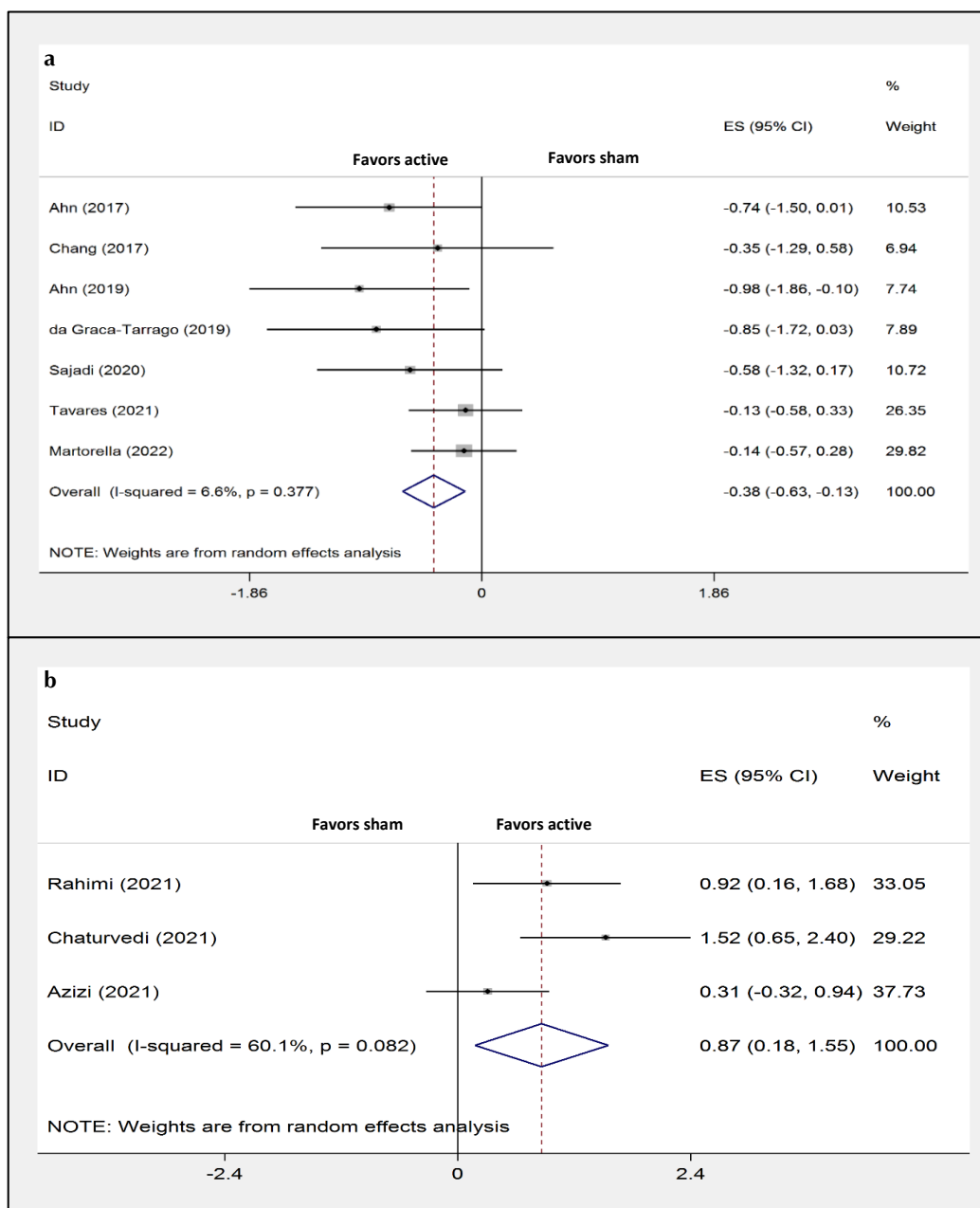


Figure 5. Forest Plot of Comparison: active transcranial direct current stimulation (tDCS) vs. sham tDCS/transcutaneous electrical nerve stimulation (TENS) for the outcome “function” in knee osteoarthritis a) WOMAC and b) KOOS.

4.4.6. Adverse Effects

Most studies reported no important or serious adverse effects associated with tDCS. Nevertheless, there was a case of headache in the active tDCS group and one case of painful sensation under the electrodes in the sham group of a previous study.⁷⁷ Furthermore, Tavares et al., reported a number of side effects, among which scalp pain and skin redness were significantly more frequent with active tDCS.⁷⁶ Also, minor side effects were reported by less than 12% of the patients in da Graca-Tarrago et al.’s study but the rate was similar between the two groups.⁴¹

4.5. Potential Sources of Heterogeneity

The maximum number of studies was included in the meta-analysis when immediate effects on pain were

evaluated; therefore, this time point was chosen for subgroup analysis. The mean BMI of patients in the active tDCS group, the interventions used, the control group, the method of administration, the ramp-up/down duration, and the number of sessions could be regarded as potential sources of heterogeneity (Supplement 5); however, in none of the subgroups, the I² decreased to less than 50%, and in those with 0% I², the number of studies was insufficient.

4.6. Assessment of Publication Bias

The results of the Egger’s linear regression analysis suggested a low probability of publication bias (intercept = -1.08, standard error = 1.91, 95% CI -5.48 to 3.34, P = 0.588). Additionally, the trim-and-fill technique did not

identify any missing studies, thus preserving the pooled estimates without alteration (Supplement 6).

4.7. Sensitivity Analysis

We conducted a leave-one-out sensitivity analysis to assess the influence of each individual study on the overall effect of active tDCS compared to sham tDCS/TENS regarding knee OA pain, immediately or in short-term (Supplement 7). Based on the analysis, none of the included studies had a significant impact on the pooled I^2 value for the specific outcome in question.

5. Discussion

This systematic review and meta-analysis included 10 RCTs to evaluate the effect of tDCS on pain and function in patients with knee OA. The findings suggest that tDCS is effective in reducing pain both immediately and up to two months after treatment (mid-term), as well as in improving function in patients with knee OA. These findings align with the results of other review studies.^{78,79} According to Rahimi et al., placing the anode electrode on primary motor cortex (M1) can help to reduce knee OA pain. However, it's worth noting that the study only analysed the results qualitatively, and the benefit of tDCS in reducing pain is uncertain.⁷⁸

In a study conducted by Comino-Suárez et al.,⁷⁹ the effects of tDCS on pain, function, Pressure Pain Threshold (PPT), Conditioned Pain Modulation (CPM), and side effects were examined through a systematic review and meta-analysis. This investigation assessed the effect of tDCS before and after a 3-week follow-up period. The findings indicated that tDCS generally resulted in a reduction of pain compared to the sham group; however, this reduction was significant only during the follow-up period of less than three weeks. Notably, tDCS demonstrated a comparable effect in pain reduction when compared to other interventions.

In the present study, we found that tDCS led to a decrease in pain relative to the control group, with this reduction being significant only in the mid-term (within two months) but not during the long-term follow-up (beyond two months). It is important to note that the estimated effect size decreased in the short term and increased in the mid-term compared to the immediate effects. This variation can be attributed to the higher number of treatment sessions in some of the studies.^{39,74,76} Additionally, in three trials, specific types of physiotherapy were applied to the study groups.^{39,40,74}

Comino-Suárez et al. also performed a subgroup analysis based on stimulation point, current density, number of sessions, and follow-up duration.⁷⁹ Their results indicated that these factors did not significantly reduce heterogeneity or alter the overall findings. In our study, subgroup analysis was performed to determine the potential sources of heterogeneity among the included

studies. Consequently, some tDCS characteristics, including the number of treatment sessions, the method of administration, and the ramp-up/down duration, were identified as potential sources. Moreover, the intervention used, the control group (sham or other interventions), the country where the study was carried out, and the mean BMI of patients in the active tDCS group were other potential sources of heterogeneity. Nevertheless, in none of the subgroups, I^2 decreased to lower than 50% and in those with 0% I^2 , the number of studies was not sufficient.

A key distinction between our study and that of Comino-Suárez et al. lies in the selection of the control group. While Comino-Suárez et al. compared tDCS with sham and other interventions, our study compared tDCS with a control group that included both sham and other interventions.⁷⁹ This approach was informed by two studies conducted by da Graca-Tarrago et al.,⁴¹ and Chaturvedi et al.,⁴⁰ which utilized a four-arm design incorporating EIMS and TENS in conjunction with tDCS. Since the effects of these interventions appeared indistinguishable, we opted not to differentiate within the control group.

Another finding of the current study was the significant knee function improvement with active tDCS compared to sham tDCS/TENS. Interestingly, by including seven studies, there was only mild heterogeneity ($I^2 = 6.6\%$) when the WOMAC score was used, but the estimated effect size fell under the category of small effects. As for KOOS score, a large effect was demonstrated for active tDCS; however, only three studies were included in this meta-analysis and there was moderate heterogeneity. The study conducted by Comino-Suárez et al.⁷⁹ revealed significant functional improvements across nine studies comparing tDCS with sham treatment. These improvements were particularly pronounced in follow-up periods of less than three weeks and when the number of treatment sessions was fewer than ten. While our study analyzed the results of the WOMAC and KOOS questionnaires separately, the Comino-Suárez et al.⁷⁹ study assessed the outcomes of both questionnaires simultaneously; nonetheless, the results were comparable.

Transcranial direct current stimulation has been found to promote the development of long-term motor memory, which is a result of experience-dependent plasticity.⁸⁰ It also enhances motor performance in older individuals by increasing facilitation and reducing inhibition.⁸¹ Additionally, when applied at short intervals, tDCS induces excitability enhancements similar to long-term potentiation in healthy participants.⁸² These findings suggest that tDCS has notable positive effects on neuronal plasticity, potentially enhancing the speed of recovery from, or preventing the occurrence of, maladaptive plasticity,⁸³ which can be responsible for function improvement in knee OA patients, especially when employed on the primary motor cortex as it was the case in all the included studies in the

current meta-analysis.

Regarding side effects, most studies found no significant or severe adverse effects associated with tDCS. Three studies reported some side effects. Except for the study by Chang et al., in which there were five treatment sessions,⁷⁷ the two other studies applied at least 15 tDCS treatment sessions.^{41,76} Nevertheless, according to a 2016 evidence-based update, there have been no reports of serious adverse effects or irreversible injuries resulting from conventional tDCS protocols in human trials. These trials have included over 33,200 sessions and 1,000 subjects who underwent repeated sessions.⁸⁴

The main advantage of this study was the use of dppc2 as the effect size, allowing the inclusion of pre-intervention measurements. Also, a publication bias assessment was conducted, and the findings suggest a low probability of its occurrence. Furthermore, the sensitivity analysis using the leave-one-out technique indicated that the aggregated dppc2 of pain remained unaffected by the inclusion of individual studies.

This research was subject to various limitations. Since multiple studies had only reported total WOMAC and KOOS scores, we could not evaluate the effect of tDCS on the subscales. Another limitation was that other interventions (i.e., MBM, exercise therapy, sham TENS, etc.) in combination with active tDCS were included in this study.⁷³ Hence, it is challenging to discern the distinct effects of tDCS in isolation. However, the sensitivity analysis showed that no individuals' studies, including this one, had a significant effect on the overall estimates. Moreover, this study couldn't evaluate long-term effects of tDCS on function due to the lack of data. Only two studies had a sample size of over 50 people in each group.^{47,76} So, the statistical power to detect differences was less than optimal.

6. Conclusion

The results of the study suggest that tDCS is a potent intervention for individuals with knee OA, exhibiting a substantial effect size in alleviating pain and enhancing functionality both immediately and up to two months' post-treatment. Over 50% of the trials included in the study had either unclear or high risk of bias, and there was a lack of patient follow-up beyond a three-month period. No sources of heterogeneity were found when considering the criteria of reduced I^2 and an adequate number of studies. Additional rigorous randomized clinical trials with longer follow-up durations are necessary to ascertain the actual impact of tDCS on knee OA.

Author Contributions

Authors contributed equally to this work. All authors reviewed and approved the final version of the manuscript.

Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

Research Highlights

What Is Already Known?

Drugs failed knee OA pain treatment; research now focuses on brain-based pain control, positioning tDCS as a key alternative.

What Does This Study Add?

The tDCS is a potent intervention for knee OA, significantly reducing pain and improving functionality both immediately and for up to two months' post-treatment.

Ethical Approval

The research obtained ethical clearance from the Ethics Committee of Iran University of Medical Sciences, with reference to the ethics code: IR.IUMS.FMD.REC.1400.151. The protocol for this systematic review has been registered in the international prospective register of systematic reviews (PROSPERO) under the code CRD42021251589. The registration details are available at the following URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=251589

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