REVIEW PAPER

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Effectiveness of transcranial direct current stimulation on pain and function in knee osteoarthritis: a systematic review with meta-analysis based on PRISMA guidelines

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Abstract

Introduction. To evaluate the effectiveness of transcranial direct current stimulation (tDCS) on pain and function in patients with knee osteoarthritis (OA).

Methods. The meta-analysis data source were PubMed (MEDLINE) and Cochrane (Central). Randomized controlled trials comparing active tDCS (in combination with other interventions or alone in knee OA patients) with sham tDCS published in English till July 2019 were analysed. The outcome measures were pain intensity (visual analogue scale and numeric rating scale) and function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]). Mean difference with 95% confidence interval for the active tDCS and sham groups were investigated.

Results. Four articles with 171 patients were included in the qualitative systematic review and 2 articles with 55 patients were included in the quantitative meta-analysis. The results revealed a statistically significant reduction in pain (visual analogue scale) in the active tDCS group compared with the sham group ($Z = 7.32$, $p < 0.00001$) and a significant improvement in WOMAC scores ($Z = 2.31$, $p = 0.02$), with high heterogeneity of 83%.

Conclusions. There is a significant improvement in pain and function in patients with knee OA after the application of active tDCS either alone or in combination. However, more studies are required to confirm the effectiveness of tDCS in knee OA. Owing to the promising results of tDCS in various pain conditions and in knee OA, it can be seen as a future tool for managing pain in the field of physiotherapy.

Key words: transcranial direct current stimulation, pain, functional improvement, WOMAC, meta-analysis

Introduction

The Global Burden of Disease 2010 study revealed that knee osteoarthritis (OA) was the prominent cause of disability and was ranked 11th highest contributor of global disability [1]. The prevalence of knee OA is 28.7% in India [2]; around 20% of the population above 30 years of age experience knee symptoms in India [3]. Persistent pain is a common problem associated with knee OA that causes maladaptive changes in the brain and spinal cord [4, 5]. Analogous findings have been described in patients with chronic regional pain syndrome and low back pain, thereby suggesting a positive correlation of a decrease in the grey matter and the chronicity of pain [6]. Recent literature has also indicated that patients with knee OA have altered central pain processing [7–10] and increased blood-oxygen-level-dependent activity in response to painful stimuli [11–13]. Also, the persistent inflammatory processes in the joint and anatomic lesions cause significant atrophy in grey matter in OA patients [14, 15]. All these findings reinforce the need for using a treatment intervention that has a potential to modulate the central pain processing system. Therefore, non-invasive brain stimulation techniques have gained considerable interest among researchers to treat chronic pain conditions.

Transcranial direct current stimulation (tDCS) is a simple and safe non-invasive brain stimulation technique that involves the application of weak electrical currents to the scalp with the use of a surface electrode [16], which results in altering the excitability of the motor cortex [17–19] by increasing the firing of neurons underneath the electrodes. The magnitude of change in excitability depends on various factors, such as positioning of the electrodes, intensity of the current applied, and duration of the application. Anodal stimulation of primary motor cortex raises the cortical excitability by increasing the neuronal resting membrane potential, while cathodal stimulation reverses the effect by decreasing the neuronal firing. Various studies have also suggested an analgesic effect with anodal stimulation via modulation of neuronal membrane channels and thus producing local and distant plastic changes in the brain, thereby demonstrating the potential of tDCS to treat a variety of chronic pain conditions. The effectiveness of tDCS has already been proved in different chronic pain conditions like fibromyalgia, low back pain, etc. [20–22]. However, there is a scarcity of literature that describes the effectiveness of tDCS in musculoskeletal conditions like OA.

Usually, transcutaneous electrical nerve stimulation has been used to relieve pain through the pain gate mechanism [23]. However, recent physical therapy guidelines for knee OA put more emphasis on exercises and less on electrotherapy interventions like transcutaneous electrical nerve stimulation [24, 25]. Hence, tDCS could be used to modulate pain through the central pain mechanism. Moreover, literature advocates the use of tDCS along with exercises to produce pronounced impact owing to the motor learning through the priming effect in knee OA patients [26]. Hence, the effective-

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ness of tDCS must be explored further to establish the role of tDCS in treating musculoskeletal pain with altered central pain processing. Therefore, the primary objective of this review is to encapsulate the data available on the effectiveness of tDCS in knee OA on pain and function in order to evaluate the efficacy of this therapy and verify if tDCS utilization can be explored as a new approach to treat OA.

Subjects and methods

Eligibility criteria

This meta-analysis and systematic review was performed in accordance with the PRISMA guidelines. Articles comparing the effectiveness of active tDCS with sham tDCS and following the diagnostic criteria for OA provided by the American College of Rheumatology (1990 or 2010 ACR) [27] were included. All published articles in English till July 2019 were eligible. The search was restricted to randomized controlled trials performed in humans. This systematic review was conducted in July 2019; the use of tDCS is recently evolving very rapidly and hence the number of articles available in databases is very low, so the systematic review was not recorded in the PROSPERO register.

Information sources

Information was collected from 2 electronic databases: PubMed (MEDLINE) and Cochrane (Central) from inception to July 2019.

Search strategy

For searching the relevant literature in PubMed, the following keywords were used: "Transcranial direct current stimulation" OR "tDCS" AND "Osteoarthritis" OR "OA" AND "knee" for the title/abstract in the advanced search options; during the filter search, "Clinical trial" and "Humans" were used to scrutinize the articles. For searching in Cochrane, ("Transcranial direct current stimulation"): ti, ab, kw OR ("tDCS"): ti, ab, kw AND ("Osteoarthritis"): ti, ab, kw were used.

Study selection

We applied the PICOS strategy where the population was knee OA. The intervention was tDCS; the comparator group was either active tDCS or sham (placebo) tDCS or control group; the outcome measures were pain, evaluated either with the visual analogue scale (VAS) or with the numeric rating scale (NRS), and function, assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Studies which included both active tDCS

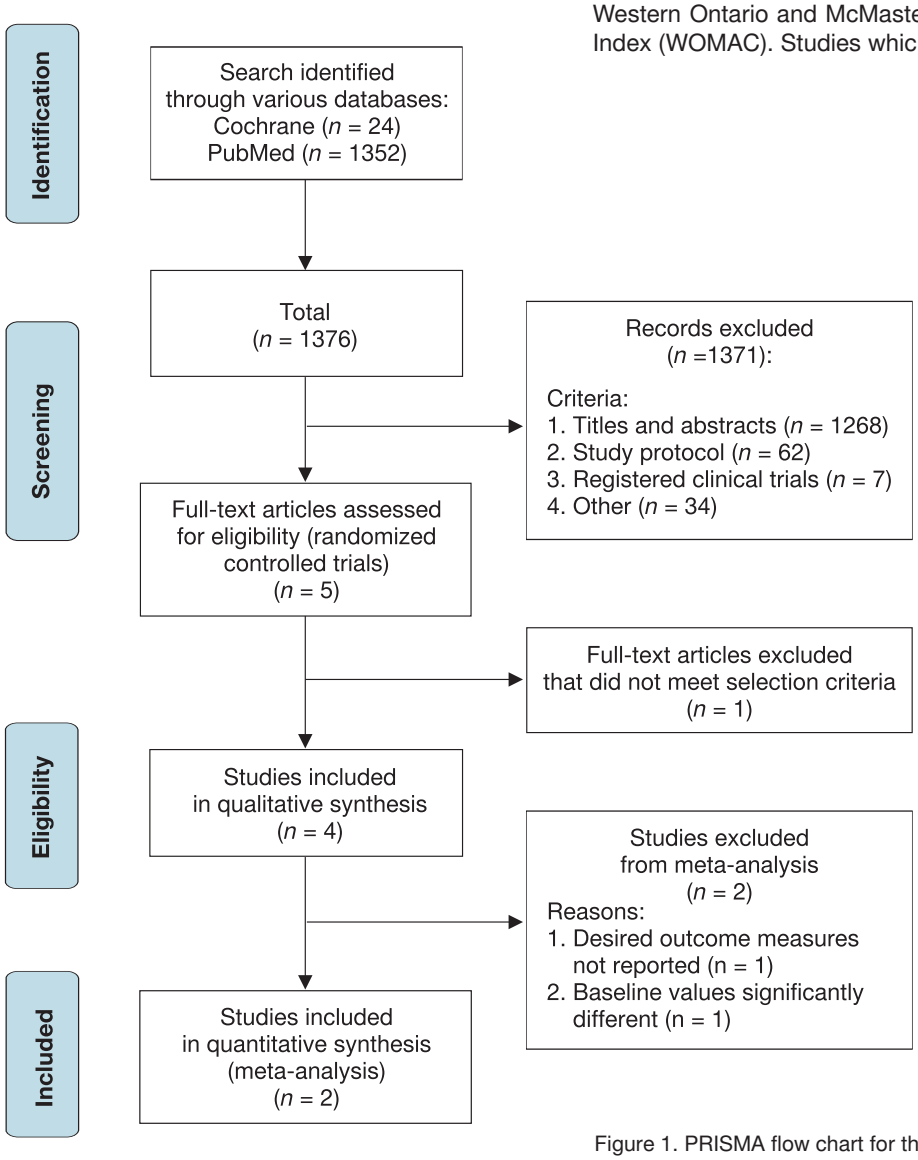


Figure 1. PRISMA flow chart for the selection of the studies

(in combination with other interventions or in isolation) and sham tDCS in patients with knee OA were selected.

Eligible relevant studies were scrutinized by 2 reviewers (SK and RC) first by the title, then by the title and abstract, and finally by the availability of full text. Studies that were not experimental; that did not provide values of the investigated variables, i.e. pain and function; and that did not refer data in terms of mean and standard deviation were excluded from this systematic review and meta-analysis.

A total of 1352 studies from PubMed and 24 studies from Cochrane were obtained by using the search strategy mentioned above. After the removal of duplicates, 4 studies were selected for the systematic review. Only 2 studies were included in the for meta-analysis; 2 were excluded: 1 article involved significant differences between groups in the baseline values of VAS and WOMAC, and in 1 study the required data could not be retrieved (it presented only values of pressure pain threshold and not the desired VAS and WOMAC scores). Figure 1 illustrates the PRISMA flow chart for the selection of the studies.

Data collection process

Two authors (RC and SK) autonomously searched and extracted the data in accordance with the MeSH terms and related keywords. The extracted information was cross-checked for any disparity. Any disagreement was resolved through discussion with SJ and the decision of SJ was final.

To find out the effectiveness of the intervention, mean and standard deviation of pain (VAS or NRS) and function (WOMAC) along with other sample characteristics like age, height, weight, body mass index (BMI) were extracted from both the experimental and control group. Data concerning author, year, continent/country, the total number of subjects for both the experimental and control group were also extracted and compared.

Risk bias in individual studies

Methodological study quality was assessed with the Physiotherapy Evidence Database (PEDro) and the Downs and Black checklist for randomized controlled trials [28]. Studies were considered of higher quality if they met the criteria for randomization and allocation concealment, assessor blinding, and intention-to-treat analysis. The quality assessment was performed independently by 2 investigators (SK, RC).

Synthesis of results

This was done by using the Review Manager 5 (RevMan 5) software, which is a Cochrane Collaboration software for systematic reviews and meta-analyses. Mean difference and 95% confidence interval were computed by entering the data for mean, standard deviation, and total number of subjects for both the active tDCS group and the sham group. Forest plots for pain and WOMAC were also produced with RevMan 5. The significance level was 0.05. The analysis was performed by 2 independent investigators (SK, SJ).

Ethical approval

The conducted research is not related to either human or animal use.

Table 1. Characteristics of the included studies

Study number	Reference article	Participants	Study origin	Study design	Treatment group	Control group	Outcome measures	Findings
1	Chang et al. [26]	30 patients with knee OA (ACR criteria)	Australia	Randomized, assessor- and participant-blinded, controlled pilot trial	Active tDCS + exercise, tDCS of 0–1 mA for 20 min plus supervised strengthening exercises twice weekly for 8 weeks	Sham tDCS + exercise	VAS, WOMAC, PPT, HPT, CPM, NFR	Pain during walking reduced, improvement in QoL (WOMAC), PPT increased, CPM improved from baseline in the active tDCS + exercise group as compared with the sham tDCS + exercise group
2	Ahn et al. [29]	41 participants with knee OA (ACR criteria)	United States	Experimenter- and participant-blinded, randomized, sham-controlled pilot study	Active tDCS of 2 mA for 20 min once daily for 5 consecutive days, follow-up for 3 weeks	Sham tDCS	NRS, WOMAC, SF-MPQ-2, 6-minute walk test, SPPB	The active tDCS group showed greater reduction in pain scores, increase in 6-minute walk distance, increase in mobility performance in SPPB scores, no statistically significant improvement in WOMAC or SF-MPQ-2 subscales
3	Graca-Tarragó et al. [31]	60 women with knee OA (ACR criteria)	Brazil	Randomized, double-blind, factorial, 4-group parallel clinical trial	Active tDCS + active IMES, active tDCS + sham IMES, sham tDCS + active IMES	Sham tDCS + sham IMES	VAS, CPM, PPT, WOMAC	The active tDCS + active IMES group showed larger reduction in pain scores, significant increase in CPM, PPT, WOMAC values, implying increase in DPMS function, and decrease in analgesic use
4	Ahn et al. [30]	40 participants with knee OA (ACR criteria)	Houston, United States	Double-blind, randomized, sham-controlled pilot study	Active tDCS of 2 mA for 20 min once a day for 5 consecutive days	Sham tDCS	HPT, PPT, punctate mechanical pain, CPM	Active tDCS: reduced experimental pain sensitivity, increase in heat pain threshold and reduction in punctate pain as compared with sham tDCS

ACR –American College of Rheumatology, CPM – conditioned pain modulation, DPMS – descending pain modulatory system, HPT – heat pain threshold, IMES – intramuscular electrical stimulation, NFR – nociceptive flexor withdrawal reflex, NRS – numeric rating scale, OA – osteoarthritis, PPT – pressure pain threshold, QoL – quality of life, SF-MPQ-2 – Short-Form McGill Pain Questionnaire, SPPB – Short Physical Performance Battery, tDCS – transcranial direct current stimulation, VAS – visual analogue scale, WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index

Table 2. Quality assessment of the selected randomized controlled trials with the Physiotherapy Evidence Database (PEDro) scoring (higher score implies higher quality)

Criterion number	Criteria	Chang et al. [26]	Ahn et al. [29]	Graca-Tarragó et al. [31]	Ahn et al. [30]
1	Specified eligibility criteria	Yes	Yes	Yes	Yes
2	Random allocation	Yes	Yes	Yes	Yes
3	Concealed allocation	Yes	Yes	Yes	Yes
4	Similar baseline	Yes	No	Yes	Yes
5	Subjects blinding	Yes	Yes	Yes	Yes
6	Therapists blinding	No	Yes	Yes	Yes
7	Assessors blinding	Yes	Yes	Yes	Yes
8	Measures of key outcomes for more than 85% of subjects	Yes	Yes	Yes	Yes
9	Intention-to-treat analysis of 1 key outcome	Yes	No	No	No
10	Between-group statistical comparisons of at least 1 key outcome	Yes	Yes	Yes	Yes
11	Variability for at least 1 key outcome	Yes	Yes	Yes	Yes
Total		10/11	9/11	10/11	10/11

Results

Study characteristics

All the studies included in this review were pilot studies investigating 131 patients in total. One study was from Australia [26], 2 from the United States [29, 30], and 1 from Brazil [31]. All these studies used tDCS (either in combination with other intervention or alone) in comparison with a sham group.

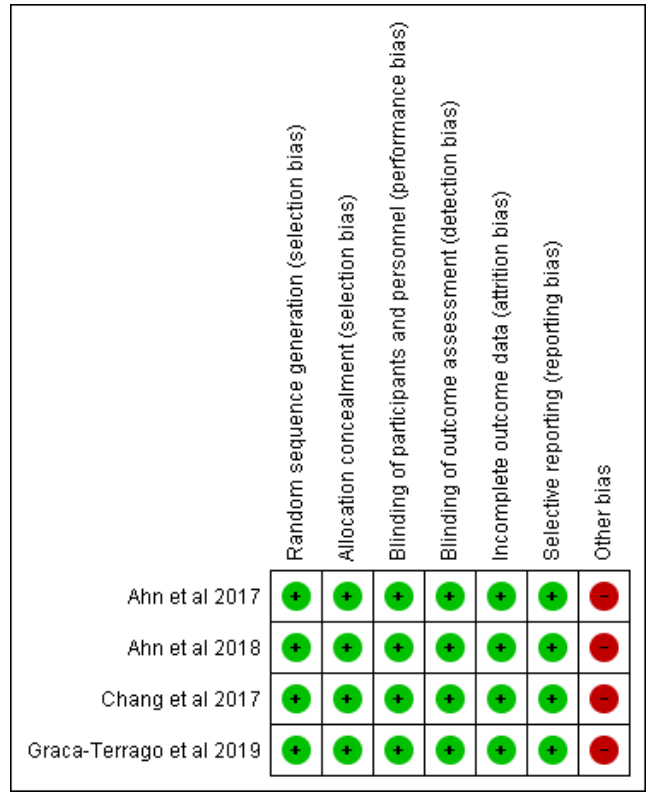
The study by Chang et al. [26] involved active tDCS in combination with exercises twice weekly for 8 weeks. Ahn et al. [29] applied only active tDCS and compared it with sham tDCS. The study by da Graca-Tarragó et al. [31] concerned tDCS in combination with intramuscular electrical stimulation. All the studies measured changes in pain (VAS or NRS) and function (WOMAC scale). Table 1 presents the overview of the included studies.

Quality assessment

Table 2 summarizes the quality of the studies included in this review. Three of them had a PEDro score of 10 out of 11, depicting their high quality, and one study was scored 9 of 11. Table 3 summarizes the methodological quality assessment of the included studies in accordance with the Downs and Black checklist.

Risk of bias

The risk of bias is explained in Figure 2. All the studies included showed a low risk in random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias), as well as a high risk in other bias. The overall risk of bias was low in all the included studies.



The green colour indicates low risk of bias and the red colour shows high risk of bias

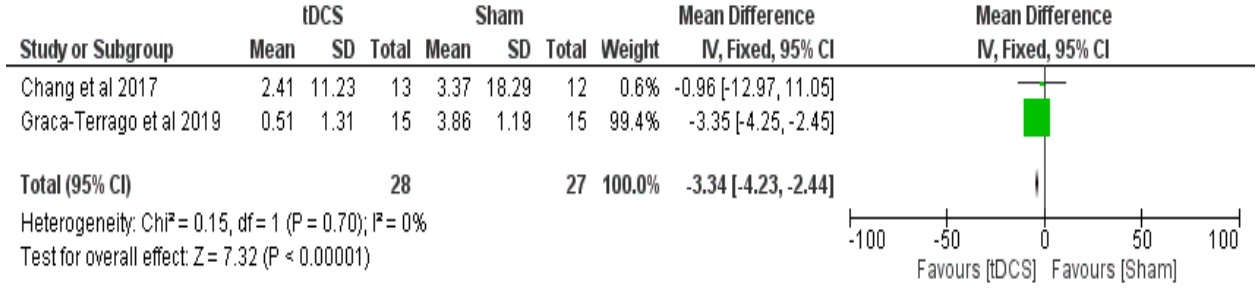
Figure 2. Risk of bias summary

Result summary

The result of the meta-analysis showed that the reduction in pain was statistically significant in the active tDCS groups as compared with the sham groups ($Z = 7.32$, $p < 0.00001$), with no heterogeneity of the included studies (Figure 3). The meta-analysis also indicates that function improvement was in favour of active tDCS ($Z = 2.31$, $p = 0.02$), with high heterogeneity of 83% in the included studies (Figure 4).

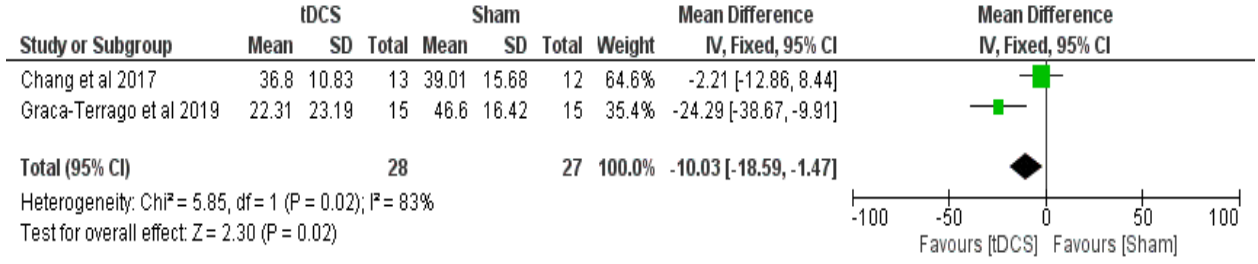
Table 3. Downs and Black checklist for assessing the methodological quality of the studies

Criterion number	Criteria	Chang et al. [26]	Ahn et al. [29]	Graca-Tarragó et al. [31]	Ahn et al. [30]
1	Reporting Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes	Yes	Yes
2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes	Yes	Yes
3	Are the characteristics of the patients included in the study clearly described?	Yes	Yes	Yes	Yes
4	Are the interventions of interest clearly described?	Yes	Yes	Yes	Yes
5	Are the distributions of principal confounders in each group of subjects to be compared clearly described?	No	Yes	Yes	Yes
6	Are the main findings of the study clearly described?	Yes	Yes	Yes	Yes
7	Does the study provide estimates of the random variability in the data for the main outcomes?	Yes	Yes	Yes	Yes
8	Have all important adverse events that may be a consequence of the intervention been reported?	Yes	Yes	No	Yes
9	Have the characteristics of patients lost to follow-up been described?	Yes	Yes	Yes	Yes
10	Have actual probability values been reported (e.g. 0.035 rather than < 0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	Yes	Yes	Yes
11	External validity Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes	Yes	Yes	Yes
12	Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Unable to determine	Unable to determine	Unable to determine	Unable to determine
13	Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	No	No	Unable to determine	No
14	Internal validity – bias Was an attempt made to blind study subjects to the intervention they received?	Yes	Yes	Yes	Yes
15	Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	Yes	Yes	Yes
16	If any of the results of the study were based on 'data dredging,' was this made clear?	Yes	Yes	Yes	Yes
17	In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time between the intervention and outcome the same for cases and controls?	Yes	Yes	Yes	Yes
18	Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes	Yes	Yes
19	Was compliance with the intervention(s) reliable?	Yes	Yes	Yes	Yes
20	Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes	Yes	Yes
21	Internal validity – confounding (selection bias) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes	Yes	Yes
22	Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period?	Yes	Yes	Unable to determine	Yes
23	Were study subjects randomized to intervention groups?	Yes	Yes	Yes	Yes
24	Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes	Yes	Yes	Yes
25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes	Yes	Yes	Yes
26	Were losses of patients to follow-up taken into account?	Yes	Unable to determine	Unable to determine	Unable to determine
27	Power Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Yes	Yes	Yes
Total		24/27	24/27	22/27	24/27



tDCS – transcranial direct current stimulation

Figure 3. Forest plot for pain in patients with knee osteoarthritis



tDCS – transcranial direct current stimulation

Figure 4. Forest plot for function (WOMAC) in patients with knee osteoarthritis

Discussion

The results of the meta-analysis suggest that there was a statistically significant improvement in pain (VAS) and functional improvement (WOMAC) in the patients with knee OA after the application of active tDCS, whether in combination with other interventions or used in isolation. The results of individual studies included in this review favour the application of active tDCS in improving pain (VAS) and function (WOMAC) in patients with knee OA. It can be inferred from the results of the meta-analysis that tDCS is an effective intervention in knee OA management.

This systematic review includes 4 moderate-to-high quality studies with a low risk of bias. However, the review addresses some limitations, which include a small number of studies (n = 4) with small samples (of around 170 patients). The majority of the included studies reported preliminary (pilot study) findings. We also observed high heterogeneity in function, with I^2 of 83%. We could not perform sensitivity analysis because of the small sample size. So, in order to generalize the effectiveness of tDCS, more randomized controlled trials with larger sample sizes are required to establish the role of active tDCS in knee OA treatment.

Taking into account the initial promising results of tDCS application in various conditions like low back pain, fibromyalgia, many psychological disorders [19, 20, 25], and, to some extent, knee OA, its effectiveness can be further explored and the use of tDCS can be seen as a potential tool in the management of knee OA.

Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

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