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ORIGINAL ARTICLE

Effects of transcranial direct current stimulation in pain and opioid consumption after spine surgery

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Abstract

Background: Transcranial direct current stimulation (tDCS) has shown promising results in alleviating different types of pain. The present study compares the efficacy of three sessions of anodal tDCS applied over primary motor area (M1) or the left dorsolateral prefrontal cortex (DLPFC) or sham on reducing pain and the total opioid consumption in postoperative spine surgery patients.

Materials: Sixty-seven out of 75 eligible patients for postoperative spine surgery were randomly allocated into one of the three experimental groups. Group A received anodal tDCS applied over M1 cortex, group B over left DLPF cortex (2 mA, 20 min) and group C received sham tDCS, all for 3 consecutive postoperative days. Patients were evaluated using a visual analogue scale (VAS) and adynamic visual analogue scale (DVAS) at baseline, and on each of the treatment days. The total morphine consumption over the 3 postoperative days was assessed.

Results: Two-way repeated measures ANOVA showed no statistically significant difference in resting VAS between the three groups. However, there was significant pain improvement ($P < 0.001$) in DVAS in both active groups (group A and B) compared to the sham group (group C) in the postoperative period, with no significant difference between the active groups. Morphine consumption was significantly reduced in both active groups compared with the sham group, but there was no difference in consumption between the active groups.

Conclusion: There was a significant postoperative reduction in morphine consumption and DVAS scores after three sessions of active tDCS.

Significance: tDCS is a promising tool for alleviating pain in the field of postoperative spine surgery.

1 | INTRODUCTION

Spine interventions are usually followed by intense postoperative pain that usually lasts for 72 h, due to massive dissection of the soft tissues and the bones. Successful postoperative pain management has proved to be well correlated with improved functional outcome, short hospital stay and prevention of chronic pain development (Bajwa & Haldar, 2015). Despite its well-known side effects, especially in elderly, opioid analgesics are still the most commonly used medications for postoperative pain relief (Steyaert et al., 2019).

Recently, transcranial direct current stimulation (tDCS) has been proposed as a potential safe and cost-effective treatment for the postoperative pain (Steyaert et al., 2019). Studies have suggested that dampening of the effective

connectivity of the midbrain-medial thalamic pathway using anodal tDCS can ameliorate pain and reduce the amount of opioid required for postoperative pain control (Borckardt et al., 2017; Glaser et al., 2016; Jiang et al., 2018; Khedr, Sharkawy, et al., 2017; Ribeiro et al., 2017).

In pain management, the main targets for tDCS have been primary motor cortex (M1) or dorsolateral prefrontal cortex (DLPFC) (Li et al., 2021). The rationale behind using M1 relies on the connection between M1 with the thalamus, brainstem, cingulate gyrus, prefrontal cortex and insula (Garcia-Larrea et al., 1997, García-Larrea et al., 1999; Peyron et al., 1995). These powerful connections might inhibit the nociceptive signal decreasing pain perception. The rationale for using DLPFC stimulation relies on its connections with areas of brain involved in pain processing. A positron emission tomography (PET) study showed that activity of both left and right DLPFC negatively correlated with perceived pain. High levels of left DLFPC activity were associated with dampening of the effective connectivity of the midbrain-medial thalamic pathway, whereas right DLPFC activation was associated with a weakened relationship of the anterior insula with pain (Lorenz et al., 2003). The implication is that increasing DLPFC excitability using tDCS might also be able to reduce pain (Seminowicz & Moayedi, 2017). Other studies suggested that pain relief could be due to connections from DLPFC to other pain perception areas such as the cingulate cortex, the amygdala and the thalamus (Boggio et al., 2009) or possibly by modulating the response of the limbic system to pain input (Glaser et al., 2016).

Although tDCS over both M1 and DLPFC have been reported to reduce pain perception, there is still debate over its effectiveness. Some studies reported strong positive effects (Borckardt et al., 2013; Borckardt et al., 2017; Khedr, Sharkawy, et al., 2017), while others failed to detect any change (Dubois et al., 2013; O'Connell et al., 2018; Steyaert et al., 2019). Some of these differences could relate to the polarity of the electrode (anodal and cathodal electrodes), site of stimulation (M1 and DLPFC), the site of reference electrode (cephalic or extracephalic), different intensities of stimulation, (1 mA, 1.5 and 3 mA), the duration of stimulation (10 min and 20 min) and the number of sessions (single and repeated sessions).

Anodal stimulation increases cortical excitability and cathodal stimulation decreases it, but the net effects depend on alterations in the overall network balance (Nitsche & Paulus, 2001). Castillo-Saavedra et al. (2016) suggested an increased activation of motor cortex (M1) enhanced pain modulating response to nociceptive sensory stimuli in pain syndromes and has demonstrated that M1 interplays with the areas of brain involved in pain modulation in various types of pain syndromes.

Previous studies reported that anodal tDCS over M1 had positive findings for pain reduction (Borckardt et al., 2013; Glaser et al., 2016; Jiang et al., 2018; Khedr, Sharkawy, et al., 2017; Ribeiro et al., 2017; Stamenkovic et al., 2020). However, few studies used tDCS-DLPFC stimulation in pain relief, most of them applied for chronic pain conditions as fibromyalgia (Fregni, Gimenes, et al., 2006) and only one study used anodal tDCS-DLPFC stimulation for postoperative pain relief after TKA (Borckardt et al., 2017) with positive findings. Kulandaivelan et al. (2018) found that application of anodal tDCS over M1, DLPFC and C2 nerve dermatome, resulted in significant decrease in pain, whereas cathodal stimulation resulted in no significant decrease in pain intensity. Meta-reviews of the analgesic effect of tDCS concluded that there are some positive effects in some pain conditions (Lefaucheur et al., 2008; Lloyd et al., 2020; Pinto et al., 2018), but more mixed results in postoperative pain (Fregni et al., 2021). In order to address this question further, the present study directly compared the efficacy of tDCS over M1 versus DLPFC in postoperative spine surgery. We used high intensity tDCS 2 mA, for 20 min applied over 3 consecutive days and measured the outcome in terms of postoperative pain scores and opioid consumption.

Depending on the previous studies, our hypothesis was that anodal tDCS over either M1 or DLPFC could reduce opioid consumption and severity of postoperative pain after spine surgery.

2 | PATIENTS AND METHODS

This trial was a prospective, double-blinded randomized controlled per-protocol clinical trial that was conducted in Assiut university hospital at the Pain clinic and Neuropsychiatry Department of Assiut University Hospital. Seventy-five participants were scheduled for an elective, spine surgery. Eligibility criteria for participants were males and females aged >18 years and <70 years with an American Society of Anesthesiologists physical status (ASA) I to II; postoperative spine surgery patients (lumbar discectomy and/or laminectomy). Exclusion criteria were patients with a history of epilepsy, frequent headaches or neck pain, patients with implantable devices (ventriculo-peritoneal shunts, pacemakers, intra-thecal pumps, intracranial metal implants), patients with a history of neurological or psychiatric illness. Patients who had taken major centrally acting drugs (anti-epileptics or antidepressants) or high-dose opioid (equivalent or greater than oral morphine 40 mg/24 h), or patients with severe cardio-pulmonary, renal, hepatic diseases, pregnancy or a history of substance abuse including alcohol consumption were also excluded. Eligible patients were

transferred to the postoperative ICU after recovery from anaesthesia. The duration of the operation was recorded for each patient. Postoperative analgesia was started in the ICU on the patient's first analgesic request in the form of morphine sulphate '10 mg/ml, Misr Pharma, Cairo, Egypt' and patient-controlled analgesia (PCA) 'Accumate 1200, Woo Young Medical, Co., Ltd., Seoul, Korea' with a 3 mg loading dose, 0.02 mg/ kg bolus dose and 10-min lock interval, with 20 mg as 4 h limit, and Paracetamol 10 mg/ kg was administered every 6 h.

2.1 | Ethics and consent

The study was approved by the Assiut Medical School Ethical Review Board with (IRB no.17300690), with clinicaltrial.gov registration ID NCT03278184. Written informed consent was obtained from patients in the preoperative visit.

2.2 | Randomization

Seventy-five patients were eligible for spine surgery, eight patients out of them refused to participate in the study and only 67 were randomly allocated into one of three groups using closed envelopes. Sixty patients were included in the analysis as seven out of 67 dropped-out after the 2nd session and were excluded from the analysis (see flow chart Figure 1).

Group A:—received anodal tDCS (2 mA, 20 min, with anodal stimulation applied over M1 of the lower limbs cortex postoperatively for 3 consecutive days).

Group B:—received anodal tDCS (2 mA, 20 min, with anodal stimulation applied over left DLPFC postoperatively for 3 consecutive days).

Group C:—received sham tDCS (over M1 cortex postoperatively for 3 consecutive days).

2.3 | Procedure

The patients and the assessors were blind to the study groups.

The distance between the anatomical landmarks nasion and inion as well as the distance between the preauricular points were measured for each participant and a cross mark was placed halfway both lines at the central midline (CZ localization). Then, the EEG cap was placed on the head of the participants. To stimulate the M1 of the lower limbs, the anodal electrode (size: 24 cm^2) was placed over Cz; according to the 10–20 EEG system, according to the international 10–20 EEG system (Homan et al., 1987). The reference electrode (size: 35 cm^2) was fixed over the contralateral arm (extracephalic). To stimulate the left DLPFC; the anodal electrode (size: 24 cm^2) was located at F3; according to 10–20 EEG system (Herwig et al., 2003).

tDCS was applied with an Eldith DC stimulator (neuro- Conn GmbH, Ilmenau, Germany). The screen report of the Eldith DC stimulator was identical whether

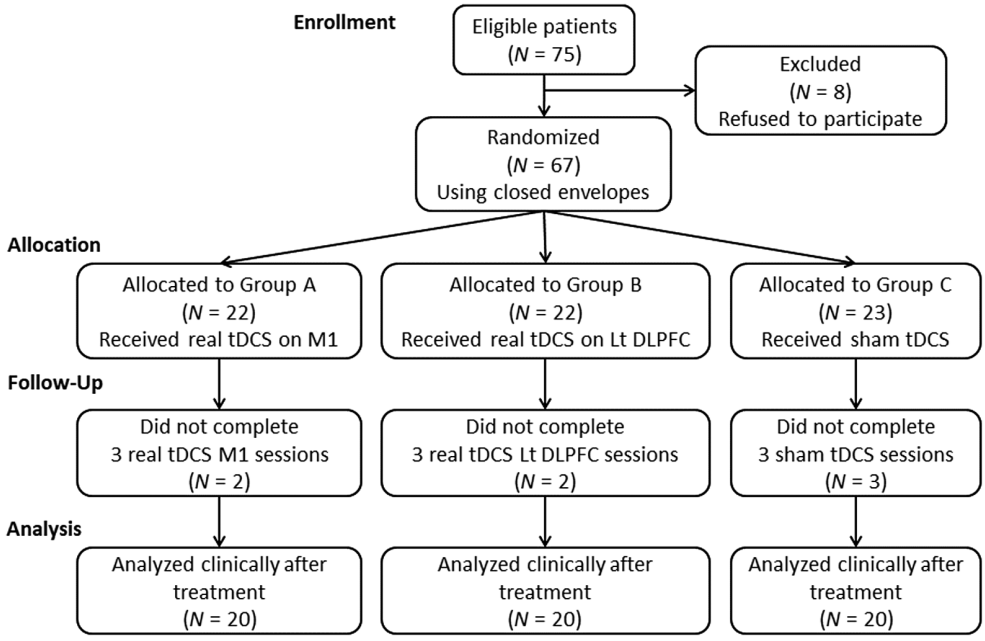

FIGURE 1 Flow chart showing the distribution of the studied groups and follow-up sessions. Sixty patients were included in the per-protocol analysis.

delivering real or sham tDCS, assuring the double-blind nature of the experiment. Direct current was transferred by a saline-soaked pair of surface sponge electrodes and delivered by specially developed, battery-driven, constant current stimulator, with maximum output of 10 mA (see Figure 2).

For active stimulation anodal tDCS was applied over M1 or DLPFC and the current was adjusted to deliver 2 mA for 20 min. For sham stimulation anodal tDCS was applied over M1 as above except that the current was adjusted to deliver 2 mA for only 30 s at the beginning and end of the session with the same duration of session. This produces a sensation similar to continuous stimulation since the sensation is mainly due to the change in stimulus current at the start and end of application (Fregni, Boggio, et al., 2006; Fregni, Gimenes, et al., 2006; Khedr, El Gamal, et al., 2014; Khedr, Elfetoh, et al., 2014; Khedr, Sharkawy, et al., 2017). The impedance levels were kept below 5 k ohms to ensure good contact of the electrodes with the scalp and to ensure that stimulation has not failed as prescribed by DaSilva (DaSilva et al., 2011). The impedance levels were checked by monitoring them when displayed on the stimulator screen.

Each patient received tDCS session for three consecutive days after operation, the 1st session of tDCS 3 h after operation, the 2nd and 3rd session at the same time of 1st session. Before session, we explained the three different tDCS configurations to the patients. At the end of session, the assessor asked the patient to guess what type of stimulation (real or sham) did he/ she receive? The patients were blind to the type of stimulation. We checked if the participants recognized the type of stimulation. Most of the patients were unable to recognize the type of tDCS as they had never previously received it, however five cases out of 60 (8.2%) recognized it (2 in M1 group, 2 in DLPFC group and 1 in sham) with no statistical significance difference between groups.

Patients were evaluated using a visual analogue scale (VAS) and a dynamic visual analogue scale (DVAS) at baseline (3 h after the operation immediately before the first session). Re-assessment of pain using (VAS and DVAS) was applied after the 1st, 2nd and 3rd tDCS sessions (Day 1, 2 and 3). The investigator who applied the sessions not involved in the static or Dynamic VAS assessment and the assessor was blind to the group or type of stimulations.

2.4 | Outcome measures

The primary outcome measures were Visual Analogue Scale (VAS) and dynamic VAS scores before the first session (baseline), then after the sessions on the first, second and third days postoperative. VAS score is a subjective scale from 0 to 10, where 0 means no pain, while 10 is the worst pain ever, and patient point to a number on the scale represents his level of pain during rest. DVAS score was the same as VAS score, but the pain was evaluated during walking for 10 m. The secondary outcome was cumulative morphine consumption at 72 h postoperative. This included 3 mg loading dose, 0.02 mg/kg bolus dose and 10 min lock interval, with 20 mg as 4 h limit. At the end of each 24 h, the total amount of morphine consumed was recorded.

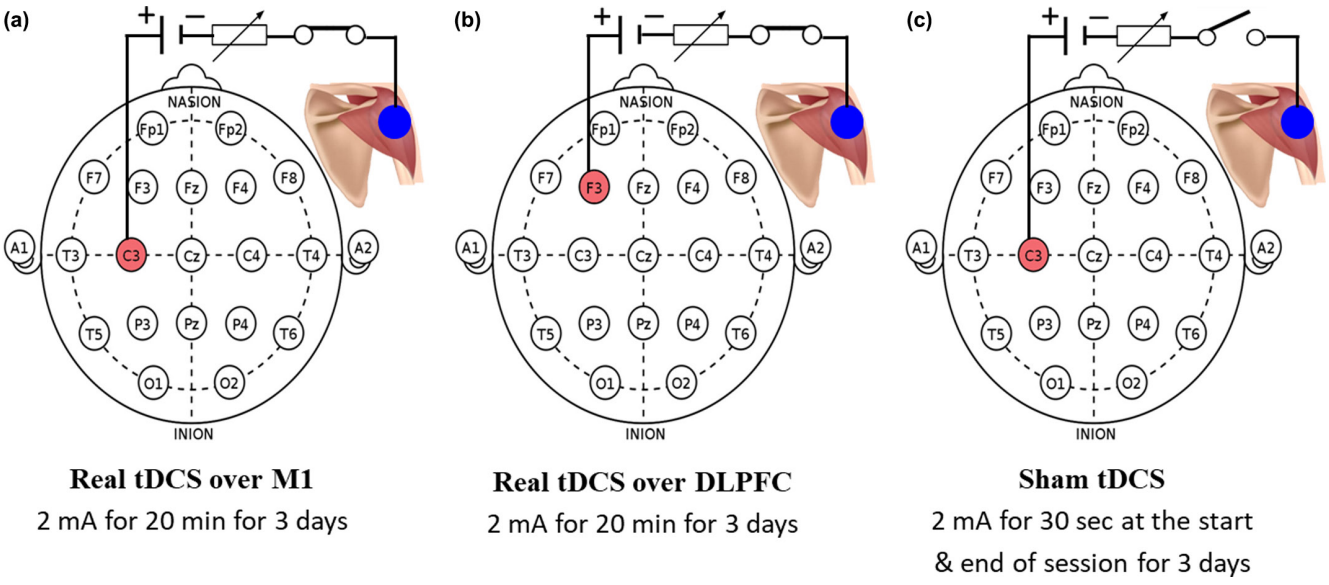

FIGURE 2 tDCS procedure showing anode and cathode electrodes placement during real tDCS over M1 (a), real tDCS over DLPFC (b) and sham tDCS over M1 (c).

2.5 | Sample size calculation

The sample size calculation was conducted using G*Power statistical program v. 3.1.9.2 and was based on the result of a previous study conducted by Dubois and colleagues (Dubois et al., 2013), where the mean of baseline VAS score was 4.5, assuming that the SD is 1.1 the minimum required size was 51 (17 in each group). To compensate for attrition rate and the dropouts of the patients, we increased the sample size to 25 patients in each group.

2.6 | Statistical analysis

The statistical analysis for the data in the current study was done using SPSS version 22 and prism program for graphs. Shapiro–Wilk test was used to detect the normal distribution of the variable. Two-way repeated measures ANOVA was used to analyse the main effect of time in each group (motor, DLPFC and sham tDCS), as well as the group X time interaction (pre-session, 1st, 2nd day, 3rd day after surgery) X group (Group A, B and C). Follow-up two-way ANOVAs were used to determine the source of significant interaction terms.

Non-sphericity was compensated using the Greenhouse–Geisser correction. The percent improvement in each rating scale (VAS and DVAS) was calculated as follows: (Baseline pre-session—Day 3 post-session/ Baseline pre-session) * 100. Percent reduction of morphine consumption was calculated as follows: (total consumption of morphine at Day 1)—total consumption of morphine of Day 2/ Day 1* 100. A *P*-value of <0.05 was considered statistically significant. The total morphine consumption included total morphine administered both on request and patient controlled.

3 | RESULTS

In this per-protocol study, 60 out of 67 patients were included in the analysis. There were no statistical differences in demographic data or duration of surgery between the study groups (Table 1).

Table 2 showed the mean value of resting VAS scores over the three postoperative days. Two-way ANOVA analysing the main effect of time for each group showed significant improvement in VAS score in the three studied groups ($P \leq 0.001$). However, the two-way ANOVA for the interaction time between groups (time x group) showed no significant differences between the three groups.

Table 3 showed the mean value of dynamic VAS scores over the three postoperative days. As with the resting VAS scores, Two-way ANOVA analysing the main effect of time for each group showed significant improvement in the DVAS in each group separately ($P \leq 0.001$). Moreover, two-way ANOVA revealed significant difference in the main interaction time x3 groups ($P < 0.001$). The effect size of time x group interaction was large ($\eta^2 = 0.218$). To determine the source of difference, two-to-two comparisons were performed using two-way ANOVA resulting insignificant more pain improvement in both active groups than the sham group in postsurgery period ($P < 0.001$), with no significant difference between active groups.

Table 4 showed the total morphine consumption over the postoperative period (mg). Two-way ANOVA revealed significant difference in main interaction time x 3 groups ($P < 0.001$). The effect size of time x group interaction was large ($\eta^2 = 0.419$). To determine the source of difference, two-to-two comparisons were performed using two-way ANOVA resulting in significant less morphine consumption in both active groups than sham group. However, there was no difference in total morphine consumption between active groups (M1 or DLPFC) tDCS. The total

TABLE 1 Demographic and clinical data of studied groups

	Motor tDCS	DLPFC tDCS	Sham	*P* value[a]
Age (years)	45 ± 12	42 ± 12	41 ± 11	0.6
Sex				
Male	11	8	14	
Female	9	12	6	0.2
Sciatica				
Right	7	8	9	
Left	9	9	8	0.9
Bilateral	4	3	3	
Surgery duration (min)	109 ± 12	108 ± 10	108 ± 11	0.9

Abbreviations: DLPFC, dorsolateral prefrontal cortex; tDCS, transcranial direct current stimulation.

[a]Categorical data analysed by Chi-Square test; non-categorical data analysed by Kruskal–Wallis test.

TABLE 2 VAS score comparison between the studied groups

	Baseline VAS	Day one VAS	Day two VAS	Day three VAS	Two-way ANOVA Time effect for each group	Two-way ANOVA Time effect ×2 groups	Interaction Time ×3 groups
Motor tDCS	7.3 ±0.9	4 ±0.7	3.6 ±0.5	2.6 ±0.5	df = 1.7, F = 196.6, $P \leq 0.001$	Motor & Sham df = 1.7, F = 2.55, $P2$ = 0.09	df = 3.37 F = 1.42 P = 0.23 η^2 = 0.048
DLPFC tDCS	7.2 ±1	3.8 ±0.6	3.5 ±0.5	2.5 ±0.5	df = 1.6, F = 169.0, $P \leq 0.001$	DLPFC & Sham df = 1.6, F = 1.83, $P3$ = 0.17	
Sham	7.4 ±0.9	4.2 ±0.5	3.7 ±0.5	3.3 ±0.5	df = 1.6, F = 210.6, $P \leq 0.001$	Motor & DLPFC df = 1.7, F = 0.12, $P1$ = 0.85	

Abbreviations: df, Degree of freedom; DLPFC, dorsolateral prefrontal cortex; η^2, Partial Eta Squared of Time * group interaction; tDCS, transcranial direct current stimulation; VAS, Visual analogue score.

TABLE 3 Dynamic VAS (DVAS) score comparison between the study groups

	Baseline DVAS	Day one DVAS	Day two DVAS	Day three DVAS	Two-way ANOVA Time effect for each group	Two-way ANOVA Time effect ×2 groups	Interaction Time ×3 groups
Motor tDCS	8.45 ± 0.5	7.3 ±0.7	6.6 ± 0.5	4.5 ± 0.5	df = 2.6, F = 228.8, $P \leq 0.001$	Motor & Sham df = 2.6, F = 11, $P2 < 0.001$	df = 5.54 F = 7.92 $P \leq 0.001$ η^2 = 0.218
DLPFC tDCS	8.40 ± 0.5	7.5 ±0.6	6.7 ± 0.7	4.5 ± 0.5	df = 2.6, F = 256.1, $P \leq 0.001$	DLPFC & Sham df = 2.7, F = 11, $P3 < 0.001$	
Sham	8.45 ± 0.6	7.6 ±0.6	6.6 ± 0.6	5.6 ± 0.8	df = 2.4, F = 109.3, $P \leq 0.001$	Motor & DLPFC df = 2.7, F = 0.5, $P1$ = 0.66	

Abbreviations: df, Degree of freedom; DLPFC, dorsolateral prefrontal cortex; DVAS, Dynamic Visual analogue score; η^2, Partial Eta Squared of Time * group interaction; tDCS, transcranial direct current stimulation.

TABLE 4 Morphine consumption (mg) among study groups

	Morphine day one (mg)	Morphine day 2&3 (mg)	Total morphine consumption (mg)	Two-way ANOVA Time effect for each group	Two-way ANOVA Time effect ×2 groups	Interaction Time ×3 groups
Motor tDCS	9.6 ±1	6.7 ±0.7	16.3 ± 1.5	Motor df = 1, $F = 270.8$, $P \leq 0.001$	Motor & Sham df = 1, $F = 40$, $P \leq 0.001$	df = 2 $F = 20$ $P \leq 0.001$ $\eta^2 = 0.419$
DLPFC tDCS	9.7 ±0.9	6.8 ±0.8	16.6 ± 1.1	DLPFC df = 1, $F = 132.5$, $P \leq 0.001$	DLPFC & Sham df = 1, $F = 184$, $P \leq 0.001$	
Sham	9.6 ±0.8	8.3 ±0.6	18 ± 1.1	Sham df = 1, $F = 52.6$, $P \leq 0.001$	Motor & DLPFC df = 1, $F = 0.03$, $P = 0.8$	

Abbreviations: CI 95%, Confidence interval 95%; df, Degree of freedom; DLPFC, dorsolateral prefrontal cortex; η^2, Partial Eta Squared of Time * group interaction; tDCS, transcranial direct current stimulation.

amount of consumed morphine was recorded at the end of each 24 h.

To confirm the results, we calculated the percent of improvement of pain rating scales using the formula; base line pre-session 1—Day 3 after the 3rd session/baseline pre-session ×100 (Table 5 and Figure 3a,b).

The active tDCS of both groups improved the resting and dynamic VAS scores, and the total consumption of morphine was significantly reduced in the two active groups, in comparison to sham group. There was no significant difference in the effectiveness of M1 or DLPFC tDCS (Table 5 and Figure 3c).

The Absolute risk reduction (ARR) was calculated using the formula (percent of reduction in active tDCS – percent of reduction in sham group). The number need to treat (NNT) was calculated using the formula (1/ARR * 100) (Table 5).

4 | DISCUSSION

Multimodal analgesia relies on the combination of drugs and behavioural techniques to control pain while reducing the adverse effects of opioids analgesics. Multimodal analgesia is becoming the standard of care for pain control, both in the operating room and during the postoperative period (Dubois et al., 2013). There were some controversies in the effect of tDCS in reducing the postoperative pain in many studies. The difference in the findings could be related to the heterogeneous stimulation's parameters (intensity, frequency and duration).

The main results of the current per-protocol study showed that active anodal tDCS over M1 or DLPFC for 3 consecutive days can improve DVAS pain scores and reduce opioid consumption in patients following spine surgery. Most previous studies have investigated the effect of tDCS on pain relief in chronic pain conditions (De Icco et al., 2021; Lloyd et al., 2020; O'Connell et al., 2018; Pacheco-Barrios et al., 2020; Pinto et al., 2018). Only a few studies have investigated the effect of tDCS on acute postoperative pain. Most of these studies have reported a beneficial effect in terms of reduced pain scores and postoperative opioid use in a variety of surgical interventions such as endoscopic retrograde cholangiopancreatography (ERCP) (Borckardt et al., 2011), total knee arthroplasty (TKA) (Borckardt et al., 2013, 2017; Khedr, Sharkawy, et al., 2017), hallux valgus surgery (Ribeiro et al., 2017), spine surgery (Glaser et al., 2016; Jiang et al., 2018) and thoracotomy (Stamenkovic et al., 2020).

4.1 | Effect of tDCS over M1

In the present study, the effectiveness of repeated sessions of active anodal tDCS over M1 on reducing pain scores

TABLE 5 Percent of morphine reduction and percent of pain reduction using VAS and DVAS

	Morphine			Percent of VAS reduction			Percent of DVAS reduction		
	ER	ARR	NNT	ER	ARR	NNT	ER	ARR	NNT
Motor tDCS	29.97	16.86	6	64.57	9.89	11	47.08	13.50	8
DLPFC tDCS	29.70	16.59	7	63.34	8.66	12	46.38	12.80	8
Sham	13.11			54.68			33.58		

Abbreviations: ARR, Absolute risk reduction (Motor-ER or DLPFC-ER – Sham-ER); DVAS, Dynamic visual analogue scale; ER, Event reduction %: ER for VAS and DVAS = (Baseline – Day 3/Baseline * 100); NNT, Number needed to treat (1/ARR * 100) rounded up; VAS; Visual analogue scale.

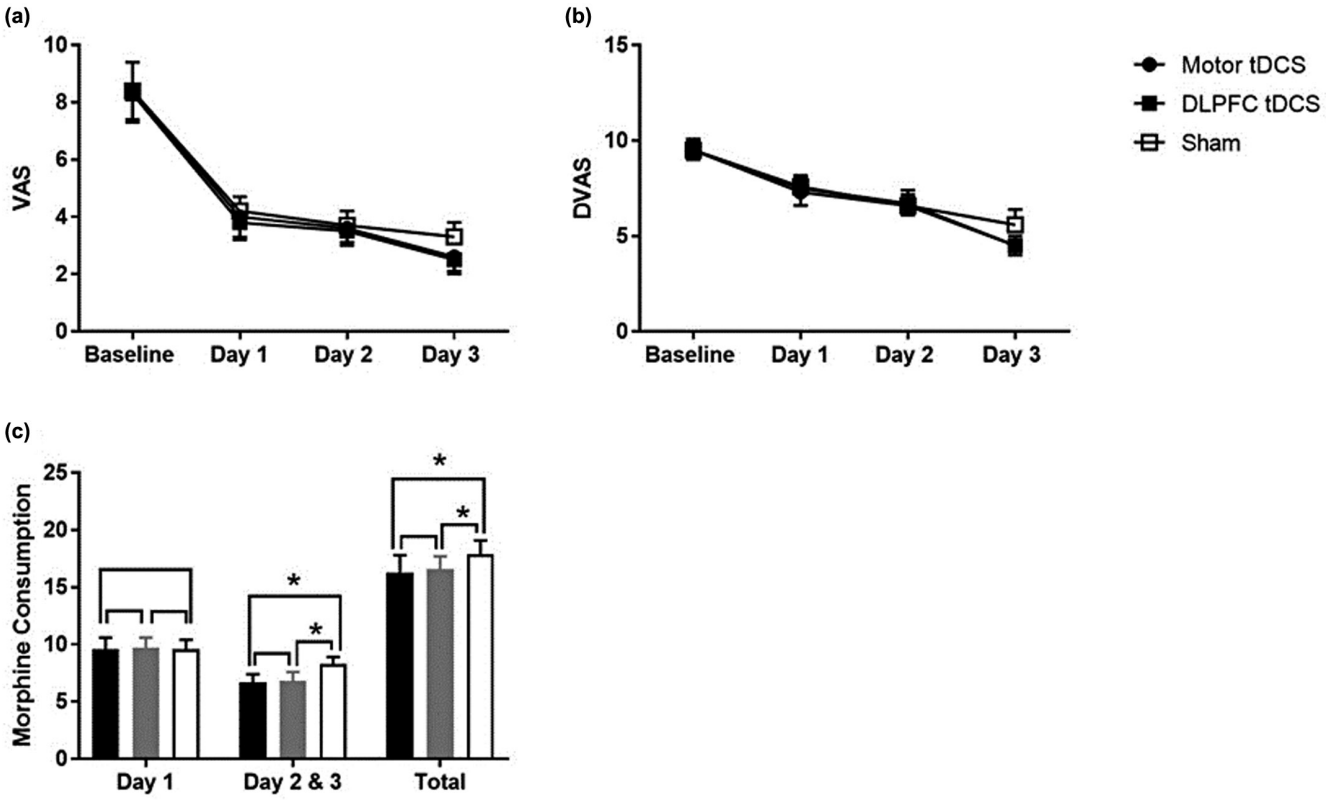

FIGURE 3 The mean values and standard errors of VAS score (a), and DVAS score (b) along the course of follow-up of the studied groups. (c) The mean value of total amount of the postoperative morphine consumption at day 1 and day 2& 3 and the total morphine consumption over the 3 postoperative days. Two-way ANOVA interaction time x groups showed significant changes in DVAS and morphine consumption between the three groups ($P \leq 0.001$ for each) with no significant difference in VAS score.

and opioid consumption can possibly be explained as follows: One possible mechanism is that tDCS augments the effectiveness of the exogenously used morphine, thus reducing its consumption while enhancing the analgesic effect. This is supported by the findings of Khedr, Omran, et al. (2017) and Khedr, Sharkawy, et al. (2017) in a study of patients with fibromyalgia. They found that the reduction in pain and improved mood was related to changes in serum endorphin levels (Khedr, Omran, et al., 2017). Similarly, DosSantos et al. (2012) suggested that a single tDCS session causes an immediate increase in endogenous μ-opioid release stimulation. A second possible explanation is that tDCS reduces pain perception (Pacheco-Barrios et al., 2020), so less morphine is needed to achieve the same level of analgesia.

The positive effect of tDCS over M1 (M1-tDCS) in the present study was consistent with the findings of most previous studies that used M1-tDCS for postoperative pain relief (Borckardt et al., 2013; Glaser et al., 2016; Jiang et al., 2018; Khedr, Sharkawy, et al., 2017; Ribeiro et al., 2017; Stamenkovic et al., 2020). There was just one exception which reported no relief of postoperative pain after total knee arthropathy (TKA) even though they used a very similar protocol but with a cephalic reference

unlike the extra-cephalic reference used here (Borckardt et al., 2017). Interestingly, the same study reported a positive effect of Left DLPFC-tDCS.

4.2 | Effect of tDCS over DLPFC

One possible mechanism of pain relief after tDCS stimulation of the DLPFC is an increase in pain thresholds similar to that reported in healthy subjects (Boggio et al., 2008), which would reduce both pain and morphine consumption. The second possibility may be due to tDCS modulates the connections from DLPFC to other pain perception areas such as the cingulate cortex, the amygdala and the thalamus (Boggio et al., 2009), A third possibility is that tDCS of DLPFC stimulation modulates the emotional component of pain (Mylius et al., 2012). The present study replicates the positive effect of DLPFC stimulation reported by Borckardt et al. (2017),

The present study found no significant difference between M1 and DLPFC-tDCS in pain relief and thus supports the use of DLPFC-tDCS in postoperative pain control. Our equally positive effect of M1 stimulation and DLPFC is quite different compared with Borckardt et al. (2017), The most likely explanation for this difference is the location of the extracephalic reference electrode as mentioned above. Indeed, we found a similarly positive effect of M1-tDCS in a previous study of pain relief after total knee replacement surgery (TKS) using the same extra-cephalic reference position (Khedr, Sharkawy, et al., 2017). We used an extracephalic cathodal electrode as a reference electrode (over the deltoid) to avoid the confounding effects of two electrodes with opposite polarities over the brain (Accornero et al., 2007; Vandermeeren et al., 2010). The extracephalic reference may prevent shunting and overall improve current delivery (Fregni et al., 2021).

In the view of previous studies and current study, tDCS was found to result in pain relief after surgery and its effect in the postoperative analgesia was confirmed. The results of the current study helped us in changing the classic postoperative analgesia and use the multimodal one by adding tDCS in the protocol of postoperative pain relief. This will help in avoiding the opioid side effects especially in elderly and shorten the hospital stay.

5 | CONCLUSION

Repeated sessions of tDCS either over M1 or DLPFC are considered a useful tool that could offer enhancing postoperative analgesia and has a potential role to decrease the amount of narcotic consumption in patients undergoing spine surgery. However, these findings are clinically mild because a minimum reduction of 10 mg of morphine at 24 h is needed to have a clinical impact on reducing morphine side effects (Marret et al., 2005). More studies are needed to better establish the clinical significance of tDCS in postoperative pain relief.

5.1 | Study limitations and recommendations

The main limitation of the current study is the small sample size, which made the sensitivity analyses difficult. The second limitation is that we only considered the effects of tDCS on subjective measure using static and dynamic VAS. However, neuroimaging and neurophysiological assessment are objective measures that could help to understand the mechanism of pain reduction after TDCS. Despite these limitations, a mild to moderate effect-size was observed for tDCS in postoperative pain relief after spine surgery suggesting that more work is needed. Several novel tDCS techniques like high definition tDCS are beginning to demonstrate more promising effect for pain reduction could be useful for postoperative patient-controlled analgesia (Kold & Graven-Nielsen, 2021).

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