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Efficacy of transcranial direct current stimulation on postoperative delirium in elderly patients undergoing lower limb major arthroplasty: A randomized controlled trial

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ABSTRACT

Background: Postoperative delirium (POD) is a common and severe postoperative complication in elderly patients undergoing major surgery linked to increased morbidity and mortality. It is reported that transcranial direct current stimulation (tDCS) effectively enhances cognitive function and improves impaired consciousness.
Objective: This study aimed to evaluate the efficacy of tDCS on POD in elderly patients undergoing lower limb major arthroplasty, including total hip arthroplasty (THA) or total knee arthroplasty (TKA).
Methods: Patients aged ≥65 years scheduled for THA or TKA were randomly assigned to receive 2 mA tDCS for 20 min active-tDCS (n = 61) or sham-tDCS (n = 61). The primary outcome was the incidence of POD during the first 3 postoperative days.
Results: All 122 patients (median age, 70 years; 80 women [65.6%]) completed the trial. The incident delirium risk was 4.9% (n = 3) *vs.* 19.7% (n = 12) in active-tDCS and sham-tDCS groups, respectively (relative risk, 0.250; 95% CI, 0.074 to 0.842; $P = 0.013$). Compared to the sham-tDCS group, the anxiety and depression scores of patients in the active-tDCS group were lower at 2 h and one day after surgery ($P < 0.001$ for each), and pain scores of patients in the active-tDCS group were lower during the first three days after surgery ($P < 0.05$).
Conclusion: One session of anodal tDCS over the left dorsolateral prefrontal cortex may decrease the incidence of POD in elderly patients undergoing lower limb major arthroplasty.

1. Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are common and effective treatments for advanced degenerative hip and knee diseases. However, Postoperative delirium (POD), one of the dominant complications usually occurs in elderly patients after major surgery, results in delayed recovery, extended hospital stays, and even related mortality [1,2].

The underlying mechanisms of POD are multifactorial, including severe pain, high doses of opioids, stress, and inflammation

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associated with the procedure [3,4]. The primary approach to delirium management is prevention through controlling or eliminating modifiable risk factors. The American Society of Anesthesiologists (ASA) proposed six approaches to reduce the incidence of perioperative neurocognitive disorders by performing multidisciplinary education, cognitive assessment, delirium screening, non-pharmacologic interventions, pain management, and avoidance of anti-psychotics and stated that non-pharmacologic interventions are the most effective measures [5]. Although it is crucial for patients with the potential risks of developing POD to receive specific interventions, multi-component and targeted interventions are still under investigation [1,6,7].

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that regulates the excitability and spontaneous neural activity of cortical neurons [8] and can enhance the functional connectivity strength of key nodes in the sensorimotor network, the left frontoparietal network, and the default network associated with the level of consciousness [9]. Evidence suggests that tDCS enhances cognitive abilities, including memory, attention, and perception [10,11]. tDCS can also affect brain-derived neurotrophic factor (BDNF) [12] and inflammatory cytokines IL-6 and IL-10 [13].

Therefore, we hypothesized that tDCS may reduce the incidence of POD among patients at high risk of delirium. The primary objective of our randomized sham-controlled study was to assess the efficacy of tDCS on the incidence of POD in elderly patients undergoing lower limb major arthroplasty, including THA or TKA.

2. Material and methods

2.1. Study design

This is a prospective, single-center, randomized, double-blind, controlled clinical trial conducted in the department of Anesthesiology and the department of Orthopedic Surgery at the Affiliated Hospital of Xuzhou Medical University from February to August 2022. The research protocol was approved by the Ethics Committee of the affiliated hospital of Xuzhou Medical University (Ethics identifier: XYFY2022-KL001-01; Chairperson Prof: Tie Xu) in Jiangsu, China, on January 25, 2022. The trial was registered at the China Clinical Trial Center (http://www.chictr.org.cn/) with the registration identifier ChiCTR2200057024 on February 26, 2022. All procedures performed in the study involving humans followed the ethical standards of the institutional and national research committee. Written informed consent was obtained from either participants or legal surrogates before enrolment in this trial.

2.2. Study population

All patients who participated in the trial received detailed information about the study protocol before enrolling. Patients aged $\geq$65 with ASA $\leq$3 and scheduled for THA or TKA were eligible for trial inclusion.

Patients who refused to sign the consent form, Mini-Mental State Examination (MMSE) score <15, neuropsychiatric disorders and history of previous neurological or psychiatric disorders, cranial or scalp injuries, drug or alcohol abuse, visual or hearing impairments, communication difficulties, metal implants in the body, history of severe cardiovascular disease, or severe liver or renal dysfunction were excluded from the study. In addition, participants were eliminated for the following reasons: voluntary withdrawal or poor compliance, violation of the protocol, use of other drugs or methods that affected the trial's outcome indicators, or failure of the subject's follow-up.

2.3. Randomization and blinding

Using a computer-generated random number table, patients were centrally randomized in a 1:1 ratio into either active-tDCS or sham-tDCS group by an investigator (LRG). The allocation information was concealed in opaque envelopes and revealed by investigators (LCY and WQ) who performed the tDCS stimulation session upon patients' arrival at the post-anesthesia care unit (PACU). The researchers who assessed the outcomes and collected and processed data were blinded to the treatment allocation. The surgeons, anesthesiologists, and nurses were also blinded to the intervention protocol.

2.4. tDCS procedure

The tDCS was applied in the patients after surgery when the tracheal catheter was removed at PACU. The electrostimulation was delivered through two electrodes placed in saline-soaked sponges. The electrodes were fixed by a stretchy hat, with the anode over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the right orbitofrontal area. The apparatus (machine manufacturer: Jiangxi Huaheng Jingxing Medical Technology Co.; machine specification model: MBM-I) used in this trial and the electrode locations are described in detail in Fig. 1(B and C) and Fig. A.3. Immediately after catheter removal, patients in the active-tDCS group received one session of tDCS for 20 min of 2 mA with a 30-s ramp-up phase at the beginning and a 30-s ramp-down phase at the end. While patients in the sham-tDCS group only received a 30-s ramp-up phase at the beginning and a 30-s ramp-down phase at the end without a constant current of 2 mA for 20 min. The researchers (LCY and WQ) who implemented the intervention closely monitored the participants' symptoms and asked if the patients were experiencing any discomfort. If the patients complained of unbearable local discomfort, the stimulation would be terminated immediately, and the event was recorded.

2.5. Anesthesia procedures

Standard monitoring procedures included electrocardiography, invasive arterial blood pressure, and pulse oximetry. General anesthesia was induced using 0.05 mg/kg midazolam, 0.5 μg/kg sufentanil, 0.3 mg/kg etomidate, and 1 mg/kg rocuronium. The tracheal catheter was inserted after the patient losing consciousness. The end-expiratory carbon dioxide partial pressure was maintained between 35 and 45 mmHg. Propofol 4–6 mg/kg/h and remifentanil 0.1–0.3 μg/kg/min were intravenously infused, and 1% sevoflurane was continuously inhaled to maintain BIS values between 40 and 60. Blood pressure fluctuations were maintained within 20% of the baseline by vasoactive drugs. Patients were administered femoral nerve block under ultrasound guidance with 20 ml of 0.5% ropivacaine. All participants were transferred to the PACU after surgery, and the neostigmine and flumazenil were given. The tracheal catheter was extubated on the wakefulness of the patients from anesthesia with the ideal tidal volume, and hemodynamic parameters returned to the normal level, Patient-controlled intravenous analgesia with 1.5 μg/kg sufentanil, 6 mg tropisetron, and saline to 100 ml was applied for postoperative analgesia. The continuous infusion rate of the patient-controlled pump was set at 2 ml/h, the self-controlled analgesic dose was 0.5 ml, and the occlusion interval was 15 min.

2.6. Clinical outcomes and assessments

The primary outcome was the incidence of POD during the first 3 postoperative days. POD was assessed with the Confusion

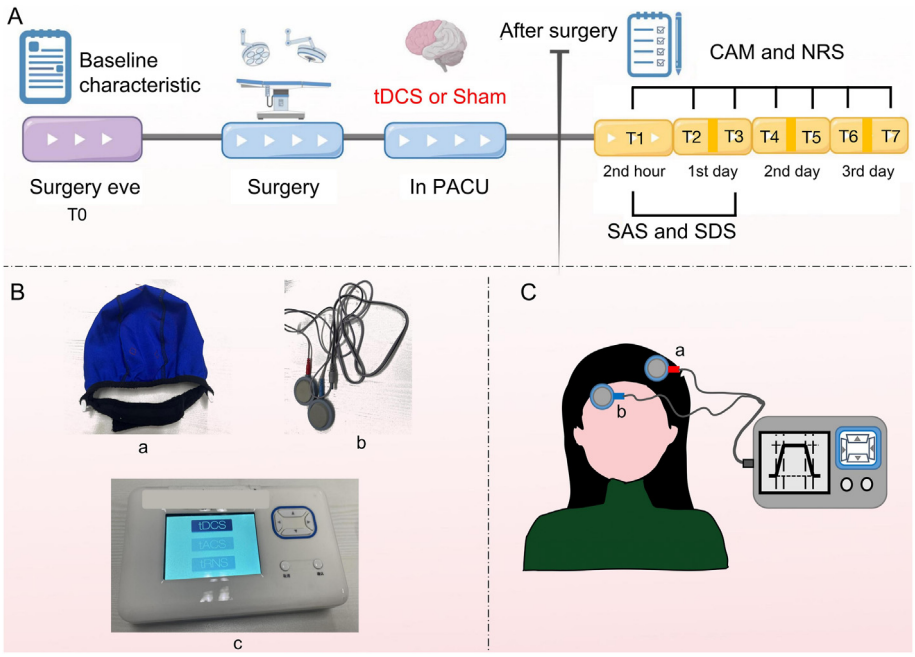

Fig. 1. The timeline of the trial and apparatus used in this test.
A: the experimental design and timeline of the two experimental sessions (active-tDCS and sham-tDCS). B: the apparatus used in this test; a: stretchy hat used to fix the electrodes; b: electrodes; c: the mainframe of the apparatus. C: the electrode locations; a: the anode over the left dorsolateral prefrontal cortex, which corresponds to the F3 region of the 10–20 electroencephalogram (EEG) system; b: the cathode over the right orbitofrontal area, which corresponds to the Fp2 region of the 10–20 EEG system. tDCS, transcranial direct current stimulation; PACU, postanesthesia care unit; CAM, Confusion Assessment Method; NRS, Numeric Rating Scale; SAS, Self-Rating Anxiety Scale; SDS, Self-Rating Depression Scale.

Assessment Method (CAM) or Confusion Assessment Method-intensive care unit (CAM-ICU) for intubated patients by trained investigators who were masked to the group assignment [14]. The CAM (sensitivity, 94%–100%; specificity, 90%–95%) is used for the identification of delirium through a diagnostic algorithm based on 4 cardinal features of delirium, namely acute onset and fluctuating course, disorganized thinking, inattention, and either disorganized thinking or altered level of consciousness. The CAM-ICU includes the CAM algorithm to determine the presence or absence of delirium and brief cognitive testing. Delirium was assessed at least 2 h after the end of the surgery (T1) and twice daily during the first 3 postoperative days with at least 6 h elapsing between assessments, including the morning of the first day (T2), the afternoon of the first day (T3), the morning of the second day (T4), the afternoon of the second day (T5), the morning of the third day (T6), and the afternoon of the third day (T7). If the patient developed delirium, the delirium assessment was performed daily until the symptoms disappeared.

Secondary outcomes included delirium subtypes (hyperactive delirium featured behavior ranging from simple restlessness to constant movement and agitation; hypoactive delirium characterized by one or more of the following characteristics: slowing or lack of movement, paucity of speech with or without prompting, and unresponsiveness; and mixed delirium manifesting quickly switch back and forth from hypoactive to hyperactive signs and symptoms), delirium severity (assessed by Delirium Rating Scale Revised 98 [15]) and delirium duration; pain scores (assessed by the Numeric Rating Scale (NRS) [16] both at rest and motion within the first three postoperative days); anxiety scores (assessed by the Self-Rating Anxiety Scale (SAS) [17] at T1 and T3); depression scores (assessed by the Self-Rating Depression Scale (SDS) [17] at T1 and T3); neutrophil-lymphocyte ratio (NLR); length of hospitalization; nausea and vomiting; 30-day all-cause mortality; and complications within postoperative 30 days. Delirium was classified using the Richmond Agitation Sedation Scale (RASS) [18]. The subtypes of delirium were the hypoactive type with a RASS of −3 to 0, the hyperactive type with a RASS of +1 to +4, and the mixed type with alternative positive and negative. Patients with a RASS of −4 (responsive to the physical stimulus only) or −5 (completely unresponsive) were considered comatose. Outcome assessments were performed by the investigators (YJ, FJX, and CDX) in the ward. Due to the fluctuating nature of delirium, investigators also asked family members and caregivers about the patient's symptoms.

The timeline of this trial is shown in Fig. 1(A).

2.7. Sample size

The sample size was determined *a priori* using PASS 15.0. The preliminary data showed that the incidence of postoperative delirium was 23.9% in older patients for major surgery [19]. We assumed that the incidence of postoperative delirium would be reduced from 23.9% in the control group to 5% in the intervention group. We chose a study power of 0.80 and a significance level of 0.05, and used a two-sided significance level to show a significant difference in the incidence of POD; we then derived that 51 patients per group were required. Considering a 20% loss of follow-up, the sample size was increased to 61 per group.

2.8. Statistical analysis

Since there were no missing data for the primary outcome, and missing data for all secondary outcomes were less than 5%. We did not perform an imputation of missing data. All analyses were conducted with the intention-to-treat principle.

Categorical data were presented as frequencies and proportions and analyzed using the chi-squared test or Fisher exact test. Continuous data were presented as median and interquartile range (IQR) or mean and standard deviation (SD) depending on the

variable distribution. The Shapiro-Wilk test was used to assess normality. Normally distributed data were analyzed with independent sample t-tests, and non-normally distributed data were analyzed with Mann–Whitney U tests. Data collected at multiple points in time were analyzed using repeated-measures analysis of variance (ANOVA). Nonnormally distributed data collected at multiple points in time were analyzed using the generalized estimated equation (GEE). The treatment-by-time interaction term was tested first. If significant, the between-group differences at each time point were tested, and the analyses were adjusted for multiple comparisons using the Bonferroni Test. Otherwise, the main effect of treatment was tested next, and no Bonferroni correction was made for assessing the treatment effect at each time point. The difference and 95% confidence interval (CI) between medians were calculated with Hodges–Lehmann estimator. The relative risk (RR) and 95% CI were used to describe the differences in dichotomous outcomes. The cumulative incidence of POD was analyzed with Kaplan–Meier survival analyses and the between-group difference of incidence was compared with the Log-rank test.

Exploratory analyses were conducted to assess differences of the primary outcome in predefined subgroups. Logistic regression was used to account for potential confounding by first pre-determining adjustment for age, education, and cognition score, and second, adjusting for additional variables associated with delirium in bivariate analysis. We examined four subgroups identified based on differences in bivariate analyses, and the RRs within each subgroup were calculated. The mediation model was analyzed using Model 4 in the PROCESS Marco. For the best test of the mediation effect, the bootstrapping procedure to measure the indirect effect was carried out and 95% CI was estimated. If the confidence interval includes zero, it means that there is no significant mediating (indirect) effect at the significance level of 5%. SPSS 26.0 (IBM Corp, Armonk NY) was used for statistical analyses, with 2-sided and $P < 0.05$ considered statistically significant.

3. Results

3.1. Flowchart of the study

A total of 187 patients were screened for inclusion from February 27, 2022, to August 25, 2022, 9 patients were excluded for MMSE score of less than 15 (n = 4) or < 65 years (n = 5), 56 patients declined to participate in the trial, finally, 122 patients were enrolled and randomly assigned to either active-tDCS group (n = 61) or sham-tDCS group (n = 61), and they all completed the trial. The participant flow diagram is shown in Fig. 2.

3.2. Baseline demographics and clinical characteristics

The baseline and clinical characteristics were randomized evenly among the two groups, excluding fewer female patients in the active-tDCS group (Table 1). The majority of intraoperative characteristics were also similar between the two groups (Table 2). Overall, the majority of participants were female (80 [65.6%]), and had a median age of 70 (IQR, 66.8–75.0) years. The baseline comorbidities, Age-adjusted Charlson Comorbidity Index [20] scores, and FRAIL [21] scores were well-matched between the groups. The median (IQR) MMSE score for all participants was 29 (28.0–29.0). There were 76 cases (62.3%) of TKA and 46 cases (37.7%) of THA. Patients rated their preoperative pain scores as a median of 4 (IQR, 1–4) at motion and 2 (IQR, 0–3) at rest. The median (IQR) of preoperative depression scores and anxiety scores for all participants were 26 (25.0–28.8) and 29 (27.5–31.3).

3.3. Primary outcome

The incidence of POD at any time during the first postoperative 3 days was significantly lower in the active-tDCS group (3 [4.9%] of 61 patients) than that in the sham-tDCS group (12 [19.7%] of 61 patients; relative risk, 0.250; 95% CI, 0.074 to 0.842; $P = 0.013$; Fig. 3). The overall incidence of POD was 12.3% (15 of 122 patients).

3.4. Secondary outcomes

Total delirium-positive days and onset were represented in Fig. A.1. An intention-to-treat analysis showed there was no statistical difference in delirium duration (overall: median, 2 [IQR, 2–3] days; $P = 0.365$) and the worst delirium severity score (overall: median, 25 [IQR, 24–27]; $P = 0.295$) of delirium patients between the active-tDCS and sham-tDCS groups (3 patients and 12 patients, respectively). All three subtypes of delirium were less common in the active-tDCS group ($P = 0.538$; Table 2).

There was an interaction between time and group for the depression scores, anxiety scores, and pain scores. Compared to the sham-tDCS group, the depression scores in the active-tDCS group were significantly lower at T1 ($P < 0.001$) and T3 ($P = 0.007$), and the anxiety scores in the active-tDCS group were significantly lower at T1 ($P < 0.001$) and T3 ($P = 0.003$, Table 2). The active-tDCS group had lower pain scores at rest and motion than the sham-tDCS group both in the morning and afternoon of three days after surgery (Table 2). The summary distribution of pain degrees between the two groups at different times is presented in Fig. A.2. There were no significant differences in the duration of hospital stay (10 [IQR, 8.0–11.5] days *vs.* 9 [IQR, 8.0–12.0] days; $P = 0.401$), and ICU admission after surgery (1 [1.6%] *vs.* 5 [8.2%]; $P = 0.209$) between the active-tDCS group and sham-tDCS group. There was no difference in NLR and other complications within 30 days after surgery between the two groups. One patient in the active group died from respiratory failure, a complication that was considered unrelated to the study intervention. Mixed delirium occurred in this dead patient, which was not excluded from data processing because the cause of death was not related to this intervention of the trial. Two patients in the active group felt a slight skin tingling. No one has dropped out due to adverse events with the use of tDCS.

Single factor logistic regression analysis showed that the *P*-values of tDCS, age, education, ICU admission, type of surgery, and preoperative MMSE score are less than 0.1 (Table A.1). Incorporating these factors into the multivariate logistic regression analysis, we found that active-tDCS intervention showed significant statistical differences (Odds ratio, 5.619; 95% CI, 1.23–25.62; $P = 0.026$) (Table A.2). The subgroup analyses of the primary outcome is shown in Fig. 4.

To further investigate whether tDCS indirectly affects postoperative delirium by relieving pain, anxiety, or depression, we performed a mediation analysis of the data. First, the postoperative anxiety and depression scores were averaged separately, and the median pain scores at rest and motion were taken separately. The mediation analysis was performed using one independent variable (tDCS), one dependent variable (POD), and one mediator. Each of the above four values is treated as a mediator value and brought into the mediational model for calculation. There was no significant difference in the mediating effect of all four variables, including anxiety and depression, pain at rest, and motion (Table A.3; Fig. A.4).

4. Discussion

This prospective randomized trial indicates one session of anodal tDCS over the left DLPFC immediately after catheter removal

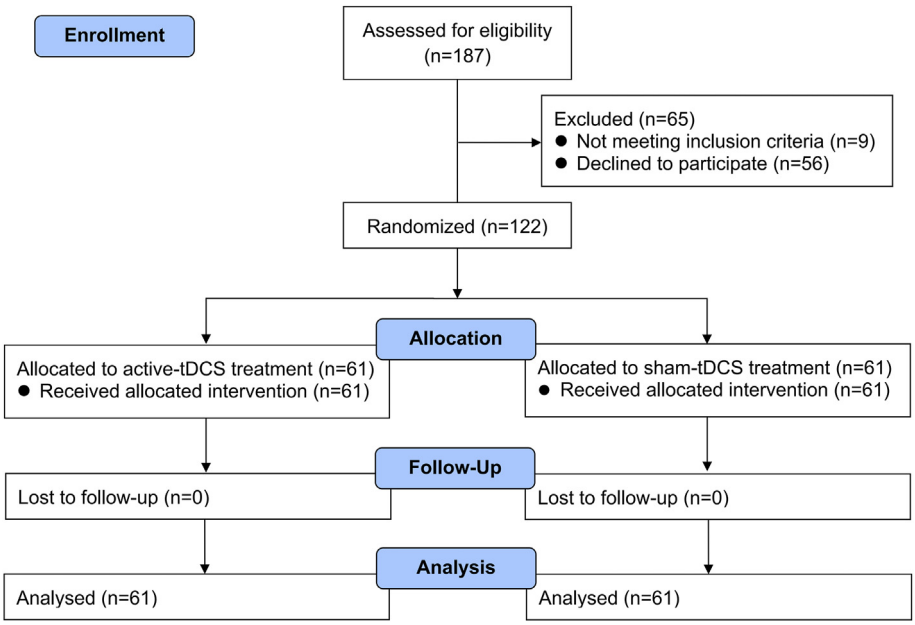

Fig. 2. Consolidated Standards of Reporting Trials flow study diagram describing patient progress through the study.
tDCS, transcranial direct current stimulation.

Table 1
Baseline characteristics of study participants by treatment group.

Characteristic	Active-tDCS (n = 61)	Sham-tDCS (n = 61)	*P* value
Age, median (IQR), year	70 (66–75)	72 (68–75)	0.137
Sex, No. (%)			0.057
Male	26 (42.6)	16 (26.2)	
Female	35 (57.4)	45 (73.8)	
Weight, median (IQR), kg	65 (60–70)	62 (55–71)	0.374
Height, median (IQR), cm	160 (157–168)	158 (155–165)	0.094
Body mass index, mean (SD), kg m^{-2}	24.8 (3.2)	24.6 (3.8)	0.718
Education level, No. (%)			0.326
Illiteracy	18 (29.5)	25 (41.0)	
Elementary school	23 (37.7)	13 (21.3)	
Middle school	10 (16.4)	11 (18.0)	
Technical secondary school	4 (6.6)	4 (6.6)	
High school	6 (9.8)	6 (9.8)	
College graduate	0 (0.0)	2 (3.3)	
Type of operation, No. (%)			0.709
TKA	39 (63.9)	37 (60.7)	
THA	22 (36.1)	24 (39.3)	
American Society of Anesthesiologist rating, No. (%)			0.203
II	31 (50.8)	24 (39.3)	
III	30 (49.2)	37 (60.7)	
Age-adjusted Charlson Comorbidity Index, median (IQR)	3 (2.0–4.0)	3 (3.0–4.0)	0.169
FRAIL, No. (%)			0.210
Robust	5 (8.2)	11 (18.0)	
Prefrail	17 (27.9)	12 (19.7)	
Frail	39 (63.9)	38 (62.3)	
Numeric Rating Scale score at motion, median (IQR)	4 (1.0–4.0)	4 (1.0–4.0)	0.872
Numeric Rating Scale score at rest, median (IQR)	2 (0.0–3.0)	2 (0.0–3.0)	1.000
Mini-Mental State Examination score, median (IQR)	29 (28.0–29.0)	29 (28.0–29.0)	0.878
Self-Rating Depression Scale score, median (IQR)	26 (25.0–28.8)	26 (25.0–28.8)	0.617
Self-Rating Anxiety Scale score, median (IQR)	29 (26.3–31.3)	29 (27.5–31.3)	0.975
Comorbidities, No. (%)			0.064
Diabetes	7 (11.5)	15 (24.6)	
Hypertension	22 (36.0)	24 (39.3)	
Stroke	12 (19.7)	6 (9.8)	
Coronary artery disease	5 (8.2)	13 (21.3)	
Neutrophil-lymphocyte ratio, median (IQR)	2.1 (1.5–2.8)	2.2 (1.8–3.3)	0.335
History of anesthesia, No. (%)	13 (21.3)	15 (24.6)	0.667

tDCS, Transcranial direct current stimulation; TKA, total knee arthroplasty; THA, total hip arthroplasty; IQR, interquartile range; SD, standard deviation.

Table 2
Intraoperative and postoperative data by treatment Group.

Characteristic	Active-tDCS (n = 61)	Sham-tDCS (n = 61)	*P* value
Intraoperative			
Duration of surgery, median (IQR), min	100 (82.5–130.0)	100 (82.5–110.0)	0.319
Duration of anesthesia, median (IQR), min	125 (107.5–147.5)	120 (105.0–147.5)	0.770
Infusion quantity, median (IQR), ml	1250 (1000.0–1500.0)	1000 (1000.0–1375.0)	0.601
Estimated blood loss, median (IQR), ml	100 (50.0–135.0)	100 (50.0–175.0)	0.724
Femoral nerve block, No. (%)	44 (72.1)	37 (60.7)	0.180
Postoperative			
In-hospital delirium, No. (%)	3 (4.9)	12 (19.7)	0.013
Days with delirium, median, d	2	2	0.365
Worst delirium severity, median	27	25	0.295
Type of delirium, No. (%)			0.538
Hypoactive	1 (1.6)	6 (9.8)	
Hyperactive	0 (0.0)	3 (4.9)	
Mixed	2 (3.3)	3 (4.9)	
Self-Rating Depression Scale score, median (IQR)			
T1	26 (25.0–26.3)	28 (26.3–31.3)	<0.001
T3	25 (25.0–27.5)	28 (26.3–30.7)	0.007
Self-Rating Anxiety Scale score, median (IQR)			
T1	26 (25.0–27.5)	29 (26.3–31.9)	<0.001
T3	26 (25.0–28.8)	29 (26.3–31.3)	0.003
Numeric Rating Scale score at motion, median (IQR)			
T1	1 (0.0–1.0)	1 (1.0–4.0)	<0.001
T2	1 (1.0–3.5)	4 (1.0–5.0)	0.001
T3	2 (1.0–4.0)	4 (1.0–5.0)	<0.001
T4	1 (1.0–3.0)	3 (1.0–4.0)	<0.001
T5	1 (1.0–2.0)	3 (1.0–4.0)	<0.001
T6	1 (1.0–1.0)	1 (1.0–4.0)	<0.001
T7	1 (1.0–1.0)	1 (1.0–3.0)	<0.001
Numeric Rating Scale score at rest, median (IQR)			
T1	0 (0.0–0.0)	1 (0.0–3.0)	<0.001
T2	1 (0.0–2.0)	3 (0.0–3.0)	0.001
T3	1 (0.0–2.5)	3 (0.0–3.0)	0.001
T4	0 (0.0–1.0)	2 (0.0–3.0)	<0.001
T5	0 (0.0–1.0)	2 (0.0–3.0)	<0.001
T6	0 (0.0–0.0)	0 (0.0–3.0)	<0.001
T7	0 (0.0–0.0)	1 (0.0–3.0)	<0.001
Patient control analgesia, No. (%)	36 (59.0)	39 (63.9)	0.577
ICU admission after surgery, No. (%)	1 (1.6)	5 (8.2)	0.209
Duration of hospitalization, median (IQR), d	10 (8.0–11.5)	9 (8.0–12.0)	0.401
All-cause 3-day mortality, No. (%)	1 (1.6)	0 (0.0)	1.000
Neutrophil-lymphocyte ratio	8.1 (4.9–11.3)	7.5 (4.9–10.9)	0.859
Adverse event, No. (%)			1.000
Nausea and vomiting	20 (32.7)	20 (32.7)	
Urinary retention	2 (3.3)	3 (4.9)	
Diarrhea	1 (1.6)	0 (0.0)	
Arrhythmia	1 (1.6)	0 (0.0)	
Acute left heart failure	0 (0.0)	1 (1.6)	
Acute respiratory failure	1 (1.6)	0 (0.0)	
Headache and dizziness	5 (8.2)	6 (9.8)	
Hospitalization costs, median (IQR), yuan	50,884 (44,977–55,729)	52,387 (50,240–55,306)	0.248

tDCS, Transcranial direct current stimulation; IQR, interquartile range; SD, standard deviation.

has prophylactic efficacy on POD in elderly patients undergoing THA or TKA. This study also highlighted that the active-tDCS could alleviate pain, decrease anxiety scores, and improve depressive symptoms in these elderly patients. To our knowledge, this is the first sham-controlled study evaluating the prophylactic efficacy in the incidence of POD using active-tDCS over the left DLPFC in elderly patients undergoing THA or TKA.

With its advantages of safety, efficiency, and portability, tDCS has been widely used in the field of brain function regulation such as neuropsychiatric diseases, but it has been less studied in the field of perioperative medicine [22]. POD is primarily a result of acute postoperative changes in brain function [1], and tDCS affects patients' consciousness and cognitive function more directly than traditional measures. The use of tDCS for DLPFC in healthy individuals and patients with neuropsychiatric disorders can enhance cognitive abilities, including memory, attention, and perception [10,11]. In addition, a single session of tDCS over DLPFC can lead to a significant behavioral improvement in the minimally conscious state (MCS) [23] and result in post-anodal tDCS-related signs of consciousness [24]. Oh J et al. found that tDCS over the right frontal cortex has the potential to modulate aberrant neural activity and connectivity in animal models of POD [25]. However, although the stimulation site is not the same as that in this animal model, the left DLPFC was chosen as the target for anodal tDCS in this study because of its central integrated function in motor control and behavior, and it is the key component of the decision-making network [26]. POD is primarily the acute postoperative changes in brain function, and acute neurobiological changes associated with postoperative psychosis may occur in the short-term critical period after surgery [27], so we chose to perform stimulation immediately after extubation to modulate aberrant neural activity and connectivity.

Pain is the most common complication after surgery. Studies have found that higher postoperative pain scores are associated

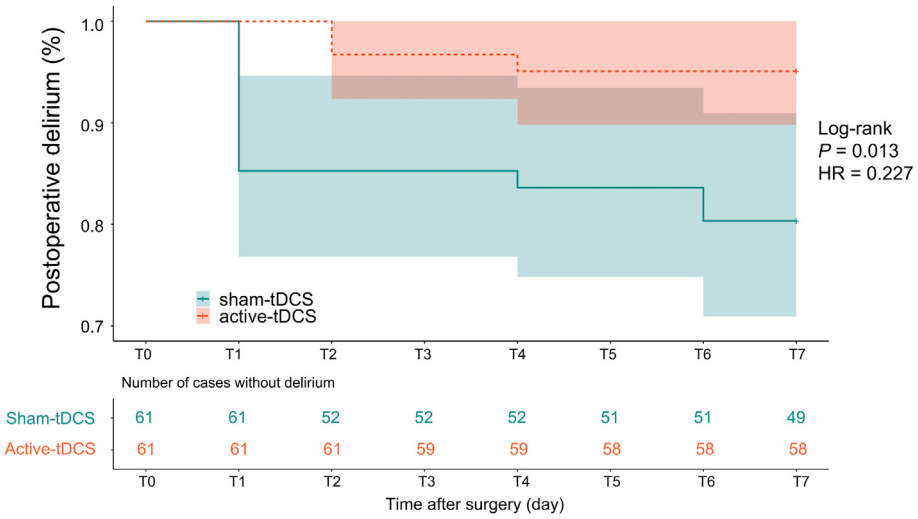

Fig. 3. Kaplan-Meier curve showing intention-to-treat analysis of the cumulative incidence of postoperative delirium during postoperative days 1 to 3 in the active-tDCS and sham-tDCS groups.
tDCS, transcranial direct current stimulation; HR, hazard ratio.

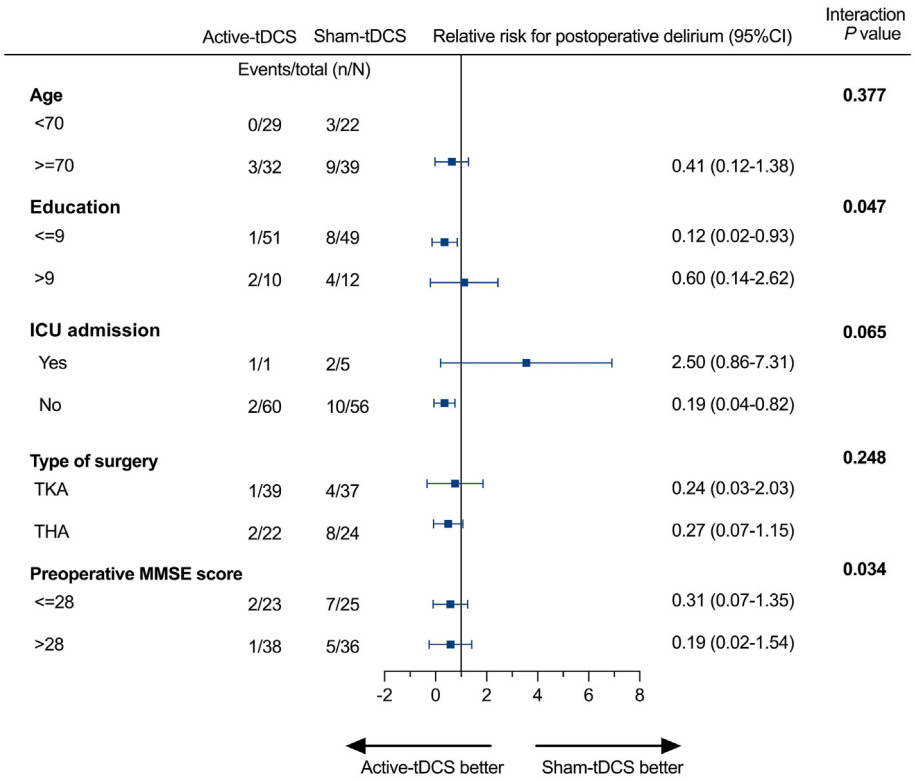

Fig. 4. Forest plot of the subgroup analysis for the primary outcome.
Prespecified subgroup analyses were conducted based on stratification by age (<70 *vs.* ≥ 70), education (≤9 *vs.* > 9), Intensive care unit admission (yes *vs.* no), type of surgery (total knee arthroplasty *vs.* total hip arthroplasty), and preoperative Mini-Mental State Examination score (≤28 *vs.* > 28). *Post hoc*, four subgroups were identified based on differences in bivariate analysis. To determine the effect of the intervention in that particular subgroup, the effect of the intervention method (relative risk [95% CI (confidence interval)]) is presented separately in each subgroup. The interaction term is a test of whether the effect of the experimental intervention is statistically different in significance between subgroups.

with an increased risk of delirium [28]. Published data suggest that tDCS can reduce pain scores and pain medication use when used for postoperative analgesia [29,30], and enhance the function of the descending pain modulatory system [31], which is consistent with the reduction in postoperative pain scores found in this study. tDCS was also found to reduce postoperative anxiety and depression scores in the participants of the trial, although none of these patients reached a clinical diagnosis of anxiety and depression. Adverse emotions such as anxiety and depressive symptoms can promote a psychological stress response that affects patient prognosis, and stress has been associated with POD [4]. Exploratory analysis of the mediating effect of all four variables, including

anxiety and depression, pain at rest, and motion, showed that tDCS directly led to the lower incidence of POD in patients in this trial, not due to indirect causes for pain relief or alleviation of anxiety and depression.

The treatment effects of tDCS on POD may be related to changes in brain function [32–34] and reduced inflammation [12,13,35]. The transient behavioral improvement after tDCS may be related to the preservation of grey matter on structural magnetic resonance imaging (MRI) analysis and residual metabolism in cortical and subcortical brain areas involved in attention and working memory (of which the left DLPFC) on fluorodeoxyglucose positron emission tomography (FDG-PET) examination [36]. Resting-state functional MRI (fMRI) suggested that high prior connectivity with areas of the executive control network could facilitate recovery of transient consciousness in MCS responders to tDCS [32]. Unfortunately, this trial did not use imaging techniques to explore the effect of tDCS on patients due to limited conditions.

Anesthetics weaken the blood-brain barrier (BBB), which is further deteriorated by surgically induced inflammation leading to the damaged BBB, resulting in elevated biomarkers of neuronal damage and perhaps some long-term side effects of delirium [37]. Suchting R et al. found that active (relative to sham) tDCS was associated with lower levels of stress and inflammation in older adults with knee osteoarthritis, such as lower IL-6, IL-10, TNF-α, β-endorphin and BDNF levels [12,13]. In this study, NLR was selected as a marker of inflammation, but no difference in NLR was found between the two groups. It may be that the true meaning of NLR in these conditions may be misunderstood because of individual differences in the patients undergoing the procedure and multiple sources of stress. It may also be related to the fact that multiple repeated sessions of tDCS were not used in this trial and NLR primarily reflects the homeostasis of the immune system [38].

This study has several limitations. First, this is a single-center study, and the trial population was elderly patients undergoing lower limb major arthroplasty, including THA or TKA. The therapeutic measures and clinical practice in different medical centers may influence the external validity and generalisability of the results. Second, the sample size was relatively small and the incidence of POD was lower in this trial compared to the study used to calculate capacity. Inferences should be interpreted with caution due to the small sample size. Additional prospective, large sample, and multicentre clinical trials are required to further validate the findings of this trial. Third, the trial was only followed up to 3 days postoperatively. Although delirium occurred mainly on the 1 to 3 postoperative days [39], the bias development due to the short follow-up period could not be ruled out. Fourth, this trial did not use objective indicators such as imaging techniques (e.g. structural MRI, FDG-PET, and resting state-fMRI) and biological markers to explore the impact of tDCS on patients. It is possible to combine tDCS with neurophysiological or neuroimaging approaches to determine how tDCS alters structural and functional changes in the brain, which may further facilitate the understanding of the neural mechanisms of delirium and the development of individualized treatment strategies.

5. Conclusions

Under the present study conditions, our results show a possible prophylactic effect of one session of anodal tDCS over the left DLPFC on the incidence of POD in elderly patients undergoing lower limb major arthroplasty. We suggest that this neuromodulatory approach may be part of the prophylactic alternatives available for POD. It is needed to validate our findings in future studies with multi-site randomized controlled trials.

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CRediT authorship contribution statement

Mingshu Tao: Conceptualization, Formal analysis, Data curation, Writing – original draft, Visualization. **Song Zhang:** Conceptualization, Data curation, Writing – review & editing, Project administration, Funding acquisition. **Yuan Han:** Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Chunyan Li:** Investigation. **Qi Wei:** Investigation. **Dexian Chen:** Investigation. **Qiu Zhao:** Conceptualization, Methodology. **Jie Yang:** Investigation. **Rongguang Liu:** Investigation. **Jiaxing Fang:** Investigation. **Xiang Li:** Methodology. **Hongxing Zhang:** Validation, Funding acquisition. **He Liu:** Conceptualization, Methodology, Formal analysis, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Jun-Li Cao:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition.

Declarations of competing interest

All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.01.839.

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