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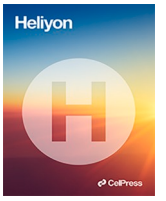

Research article

Intraoperative transcutaneous electroacupoint stimulation on early postoperative fatigue in patients with Parkinson's disease undergoing deep brain stimulation surgery

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ABSTRACT

Background: In this clinical trial, we evaluated the effects of transcutaneous electroacupoint stimulation (TEAS) on postoperative fatigue (POF) in Parkinson disease (PD) patients undergoing deep brain stimulation (DBS) surgery.

Methods: A total 60 PD patients undergoing DBS surgery were enrolled. They were randomized to receive either electrical stimulation [alternative frequency 2/10 Hz, dense and disperse, intensity adjusted to the maximum tolerated by the participants (6–15 mAmp)] via surface electrodes (TEAS group) or surface electrodes only without electrical stimulation (Con group) at bilateral Zusanli and Sanyinjiao acupuncture points. All participants received their assigned intervention (TEAS or Con) during the 1st stage of surgery [(except during microelectrode recording (MER)] and the entire 2nd stage of surgery. Intraoperative anesthetic requirements were adjusted based on bispectral index (BIS) monitor. POF was assessed by Christensen fatigue scales (ChrFS), along with Quality of Recovery-15 (QoR-15) and mini-mental state examination (MMSE) post-operatively over a 7-day-period. We recorded the usage of rescue analgesics and anti-emetics.

Results: Fifty-nine patients' datasets were included for final analyses. Fewer patients in TEAS experienced severe POF (defined as ChrFS $\geq$6) at T_3 than those in the Con group (TEAS vs. Con: 7 vs. 22, $p < 0.001$). During the 1st stage of surgery, more patients in Con group required dexmedetomidine infusion (TEAS vs. Con: 2 vs. 6; $P < 0.01$). Total dosages of propofol and remifanil during the 2nd stage of surgery were TEAS vs. Con: 374.7 ± 61.2 vs 421.5 ± 81.9; $p < 0.001$ and 572.3 ± 82.0 vs. 662 ± 148.2; $P < 0.001$, respectively. Postoperative rescue analgesics (TEAS vs. Con: 2 vs. 6; $P < 0.001$) were used less in the TEAS group. TEAS patients reported better POF, MMSE and QoR15 scores than those in the Con group during most of the assessment period.

Conclusions: Intraoperative TEAS decreased the severity of POF, reduced intraoperative anesthetic requirements and facilitated post-DBS recovery in this group of PD patients.

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1. Background

While high frequency deep brain stimulation in the subthalamic nucleus (STN-DBS) has been a treatment of choice to reduce dyskinesis for many patients with mid-to late stage Parkinson disease (PD) [1],a recent article indicated that about 58 % (43%–73 %) of PD patients still experienced moderate to severe fatigue one year after DBS surgery [2]. Throughout this manuscript, we will use STN-DBS and DBS interchangeably. Postoperative fatigue not only causes delayed postoperative recovery but also worsens the quality of life of PD patients [2].

Even though most PD patients have extensive discussions with their neurosurgeons and are well-informed prior to undergoing DBS surgery, many of them still experience anxiety and pain during the 1st stage of surgery (when headframe and electrodes are positioned because they remain awake) [3]. Pain and anxiety can cause tachycardia and hypertension, increasing the risk of postsurgical complications [4]. Thus, it is critical to alleviate anxiety and pain to stabilize heart rate and blood pressure during the 1st stage of DBS surgery. Pharmacological agents e.g. anxiolytic agents and analgesic medications have been used to alleviate anxiety and pain but they may compromise airway patency and suppress respiration [5]. Thus, anesthesia management for the 1st stage DBS surgery can be a challenge [6]. Non-pharmacological interventions which can provide anxiolysis and analgesia without causing these side effects would be beneficial.

Transcutaneous electroacupoint stimulation (TEAS), is a form of acupuncture stimulating techniques, which has been successfully integrated into perioperative anesthetic management for various surgeries. The integration of TEAS into routine anesthesia management has shown promising advantages over routine anesthesia management alone in preventing and/or minimizing various adverse perioperative events. Beneficial effects of acupuncture and related stimulations documented in the literature to date include: a) decrease in perioperative anxiety [7], b) decrease in the dosage required for intraoperative sedation and narcotics [8], c) decrease in postoperative pain, rescue analgesia, nausea and vomiting (PONV) [9], and d) facilitation of postoperative recovery [10].

While integration of TEAS into routine anesthesia management has been effective in improving postoperative recovery, no study has investigated whether TEAS has any direct effect on POF in PD patients undergoing DBS surgery. We therefore designed the following prospective clinical randomized controlled trial (RCT) to determine whether intraoperative TEAS at bilateral Zusanli (ST36) and Sanyinjiao (SP6) acupoints could serve as an adjunctive therapy for routine anesthetic management for PD patients undergoing DBS surgery, i.e. to evaluate whether intraoperative TEAS could decrease the incidence and severity of POF. We would also evaluate its effects in supplementing intraoperative sedation/analgesia as well as its effect on the incidence of postoperative complications and quality of postoperative recovery.

2. Methods

This is a prospective clinical double-blinded RCT. Its guidelines were consistent with the Declaration of Helsinki. The Medical Research Ethics Committee of the First Hospital of the University of Science and Technology of China approved this study on February 4, 2023. The duration of this study was from March 1, 2023 to June 1, 2023.

2.1. Patient population

All potential PD patients undergoing STN-DBS at Anhui Provincial Hospital were identified in the operating room schedule. The inclusion criteria were: PD patients scheduled to have elective DBS surgery; middle and late stage of PD; age 40–80 years old; BMI = 18.5 to 29.9; American Society of Anesthesiologists (ASA) physical status II-III; and able to read and write at a 6th grade educational level. The exclusion criteria were: PD patients scheduled for elective surgical procedures other than DBS surgery; BMI $\leq$18.5 or $\geq$30; not able to read or write; ASA physical status IV (i.e. suffering from multiple medical comorbidities); hearing loss or difficulty in communication; a history of acupuncture treatments within the past 6 months; nerve injury or infection at the site(s) selected for electrode placement; allergies to adhesive/electrode; or refusal to participate in the study. F. K. met with potential subjects, provided verbal description of the procedure, and obtained their written consents. All participants were informed that he/she might not be able to sense the stimulation/vibration when the intervention started.

2.2. Randomization and blinding

Once participants consented to this clinical trial, he/she was randomized by another investigator (M.M.H) using a computer-generated randomization table (SPSS 25.0 software) into either the TEAS or Con group. Each random number was concealed in a sealed envelope. Only the acupuncturist (T.F.) could open the sealed envelope on the day of intervention and perform the intervention determined by the random number assigned and then follow a strict script [1]when interacting with each participant to ensure all participants were blinded to the intervention they received. In addition, the neurosurgeons, operating room (OR) anesthesia team, perioperative supporting staffs (nurses in PACU & hospital floor) and assessors (B.Q.Z and B.F.K) were also blinded to the group assignments.

2.3. Acupoints selection

According to the traditional Chinese medical (TCM) prospective, PD patients suffer from a mixture of deficiencies in the liver,

spleen and stomach [11]. Similarly, POF is caused by multiple factors such as stress in the perioperative period leading to *qi* stagnation, blood stasis and/or blood/*Qi* deficiency caused by surgical trauma [12]. Zusanli (ST36) acupoint is one of the acupoints of the Zu Yang Ming Wei Jing (Stomach meridian), which has the function of strengthening as well as eliminating stagnation of the spleen and stomach meridians by regulating "*qi*" flow [13]. Sanyinjiao (SP6) acupoint is one of the Zu Tai Yin Pi Jing (Spleen meridian) and it is the meeting point of the three Yin meridians of the foot (spleen, liver, and kidney). This point has the function of nourishing the essence of the liver, kidney, spleen and blood. Stimulations applied to a combination of these two acupoints can provide sedation and analgesia and promote cognitive recovery [14]. Therefore, both ST36 and SP6 were chosen for this study.

2.4. TEAS and control (Con) protocol

All participants received a total of 4 percutaneous electrodes at bilateral ST36 and SP6 acupoints (Fig. 1). Once all surface electrodes were placed (T.F. followed the script as described in footnote[2] regardless the group assignment). The difference was that the participants in the TEAS group received electrical stimulation [frequency 2/10 Hz, dense and disperse, intensity adjusted to the maximum tolerated by the participants (6–15 mAmp)] using a Hwato electronic stimulator (model SDZ-V, Suzhou Medical Appliances Co. Ltd, Suzhou, China). Participants in the Con group received the same placement of electrodes except their electrodes were connected to a disabled electrical stimulator.

2.5. Anesthesia and perioperative management

On the day of surgery, the patient was brought into the OR. After he/she was situated in a wheel chair, an intravenous (IV) line was placed. Using a local anesthetic, the neurosurgeon placed a Leksell® stereotactic headframe over the patient's head. Once the headframe was placed, the patient was wheeled to the magnetic resonance imaging suite for fluid-attenuated inversion recovery scanning. Once scanning was complete, the patient was returned to the operating room (OR).

*The 1*st *stage of DBS surgery-electrode placement & multichannel microelectrode recording:* Soon after the patient returned to the operating room, the OR anesthesia team placed all ASA monitors, and a bispectral (BIS) index monitor on the patient. Each patient received supplemental oxygen (4 l/min) via nasal cannula and an arterial line was placed in the patient's radial artery. After arterial line placement, the first blood sample was collected, processed and stored for inflammatory biomarker [tumor necrosis factor-alpha (TNF- α) and C-reactive protein (CRP)] analyses. While the OR anesthesia team applied monitors and performed procedures, the acupuncturist (F.T.) executed the assigned intervention and initiated the appropriate stimulations. Subsequently, the neurosurgeon infiltrated the scalp with additional local anesthetic and established a burr hole to place the electrode into the target location in the brain. The assigned intervention continued throughout the 1st stage of the DBS surgery except during MER. If the patient had pain/anxiety and/or uncontrollable tremor which interfered with the placement of electrodes, IV dexmedetomidine 0.5 μg/kg loading over 15 min followed by 0.3 $\mu g\text{-}kg^{-1}\text{-}h^{-1}$ was administered. Both IV dexmedetomidine infusion and the assigned intervention (TEAS or control) were stopped during MER. Once MER was completed, TEAS/control intervention was resumed and continued throughout the 2nd stage of DBS.

2.6. The 2nd stage of DBS surgery - pulse generator implantation

This stage of DBS was performed under standardized general anesthesia. General anesthesia was induced with IV sufentanil 0.2–0.3 μg/kg, propofol 1–2 mg/kg, and rocuronium 0.3 mg/kg; once the patient became unconscious, an I-gel laryngeal mask airway (LMA) was inserted. The patient was placed on mechanical ventilation (tidal volume 8–10 ml/kg, rate 10–12/min). Intraoperative anesthesia was maintained with sevoflurane minimum alveolar concentration of 0.7–1.0; target control infusions of propofol and remifentanil were titrated to maintain intraoperative BIS index between 40 and 60. At the end of surgery, IV palonosetron 0.1 mg and flurbiprofen ester 100 mg were administered to prevent PONV and postoperative pain, respectively. When the patient emerged from general anesthesia, the second blood sample was collected, processed and stored for later TNF-α and CRP analyses. After LMA removal, the patient was transported to the post-anesthesia care unit (PACU). Once the patient fulfilled the PACU discharge criteria, he/she was transported to the hospital floor. If the patient complained of pain (as assessed by a visual analog score >4) either in PACU or on the floor, a dose of tramadol 50 mg IV was administered. Similarly, any episodes of nausea and vomiting was treated with IV ondansetron 4 mg during the PACU stay or on the floor.

2.7. Tools for outcomes assessment (please refer to Table 1 for outcomes assessment schedule)

a. **Christensen Fatigue Scale (ChrFS):** The ChrFS [15] is a unidimensional measure for fatigue, numeric rating scale (1–10) with four verbal anchors (see appendix A). The cutoff point of clinically significant fatigue is ≥ 6 [16].
b. **Visual Analog Scale-pain (VAS-p):** The VAS-p scale [17] is a unidimensional measure of pain intensity. It consists of a line with left side "0" represents "no pain" and right side "10" representing "extreme pain."

[2] "Now, the electrodes are in place. I will start adjusting the intensity gradually. As I increase the intensity, please let me know whether it is tolerable. I will adjust the intensity to the maximum as you can tolerate."

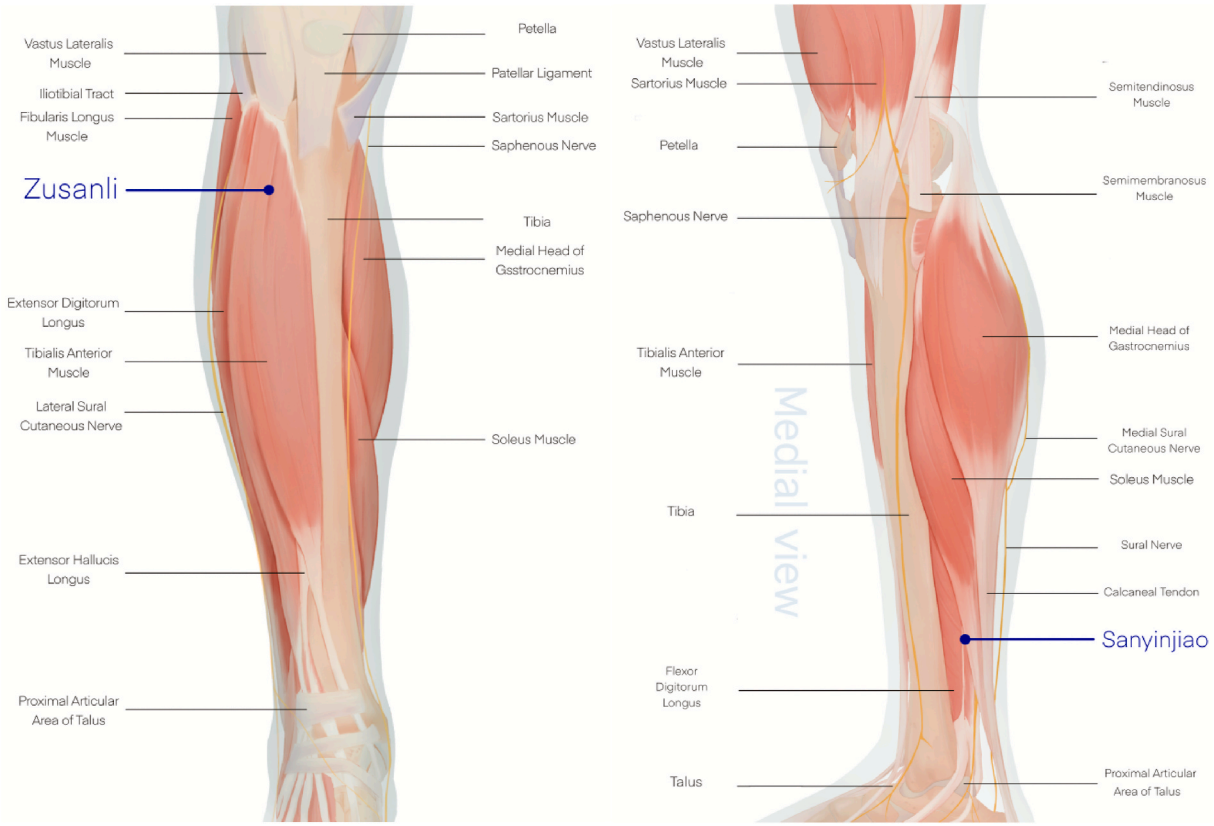

Fig. 1. Schematic diagram of acupuncture points.

c. **Mini-mental State Examination (MMSE):** The MMSE [18] is a 30-point questionnaire commonly used in clinical settings to measure cognitive impairment. A score of 24 or more indicates a normal cognition, scores between 19 and 23 indicate mild impairment, scores between 10 and 18 indicate moderate impairment, and scores $\leq$9 indicate a severe degree of cognitive impairment.
d. **Quality of Recovery-15 (QoR-15):** The QoR-15 [19] ranges from 0 to 150. It is a validated multidimensional questionnaire that measure postoperative quality of recovery. The QoR-15 scores for excellent, good, moderate, and poor recovery are 136–150, 122–135, 90–121, and 0–89, respectively.

2.8. End points

The primary endpoint was the number of PD patients experiencing POF in the TEAS group compared to the Con groups. Secondary endpoints were the differences between the TEAS and Con group intraoperative anesthesia requirements, postoperative anesthesia-related complications, e.g. pain and PONV as assessed by the VAS-P, postoperative rescue analgesics and antiemetics usage as well as other recovery profiles as assessed by MMSE and QoR-15. We also collected blood specimens at pre and post-DBS to determine serum levels of TNF-alpha and CRF using enzyme linked immunosorbent assays (ELISA).

2.9. Sample size calculation

As there is a paucity of data available in the current literature regarding the effect of TEAS on the incidence and/or severity of POF following DBS, sample size was calculated based on published data related to the efficacy of acupuncture in relieving chronic fatigue syndrome. The incidence of POF was about 58 % in PD patients after DBS surgery [2] and acupuncture treatment was effective in decreasing 60 % of the severity of fatigue in patients with chronic fatigue syndrome [20]. Using PASS 15.0 software, 24 patients in each group were required to detect a 50 % difference between the groups, assuming a two-sided type I error $\alpha = 0.05$ and power of 80 %. To account for potential loss to follow up and enable greater statistical power for secondary analysis, sample size was increased to 60 patients (30 per group).

2.10. Statistical analyses

SPSS 26.0 statistical software was used to process the collected data. Data were expressed as: normal distribution, mean ± standard deviation (±*s*); for skewed distribution data, median (interquartile range) [*M*(*IQR*)]. The *t*-test was used to compare data differences between groups. ANOVA for repeated measures was used for intra-group comparison. The *Chi-square* test or Fisher's exact test was used to compare the distribution of categorical variables. $P < 0.05$ was considered a statistically significant difference.

3. Results

This report adhered to the guidelines of Consolidated Standards of Reporting Trials (CONSORT) [21] and obeyed Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [22].

3.1. Patient characteristics and perioperative events

From March 2023 to June 2023, a total of 60 PD patients undergoing STN-DBS surgery at Anhui Provincial Hospital agreed to participate in this study. One patient withdrew from the study because of personal reason (Fig. 2). Only 59 patients' datasets were included into the final data analyses. There were no differences between the two groups in age, ASA status, duration of anesthesia and duration of surgery. However, patients in the TEAS group had shorter average time [minute (min.)] to emergence from general anesthesia [TEAS vs. Con: 6 min (3–14) vs. 15 min. (10–25); P = 0.048], shorter average time to removal of LMA [TEAS vs. Con: 12 min (5–24) vs. 20 min. (15–35); P = 0.017], and fewer incidences of agitation than those in the Con group [TEAS vs. Con: 3 (10 %) vs. 11 (37.9 %); P < 0.001]. Please refer to Table 2.

Primary outcome (please refer to Table 3)

3.2. ***Scores of ChrFS*** *{express by median [interquartile (IQR)]}*

At one day before surgery (T_0), both groups of patients reported having significant fatigue i.e. 20 of 30 (66.7 %) patients in TEAS group and 19 of 29 (65.5 %) patients in the control group reported having ChrFS scores ≥6. There were no differences in the level of

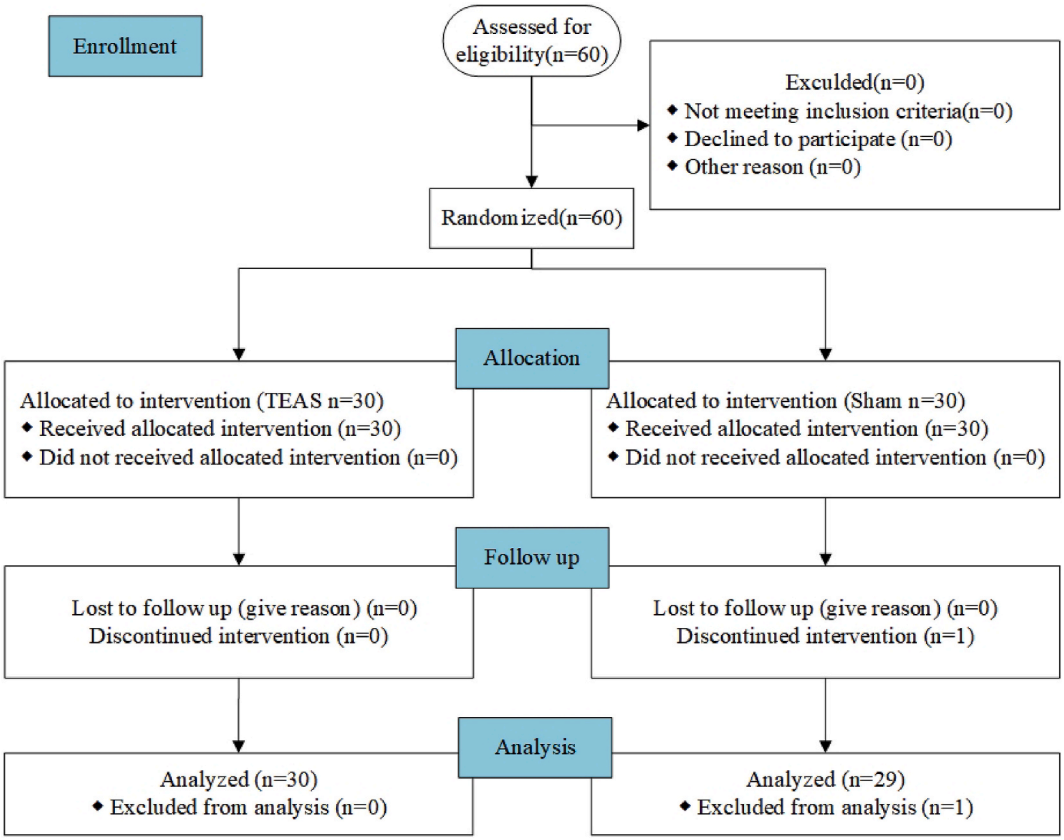

Fig. 2. Study flow diagram.

Table 1
The outcomes assessment schedule.

Assessment Schedule	T_0	T_1	T_2	T_3
Christensen fatigue score (ChrFS)	x	x	x	x
Mini-mental State Examination (MMSE)	x	x	x	x
Visual Analogue Scale for Pain (VAS-P)	x	x	x	x
The Quality of Recovery – 15 (QoR-15)	x	x	x	x

T_0- One day before surgery, T_1- Postoperative day 1, T_2- Postoperative day 3, T_3- Postoperative day 7.

Table 2
Data of demographic indicators and perioperative events.

Parameter	TEAS group (N = 30)	Control group (N = 29)	*P*-value
Age [yr; mean (SD)]	61.4 (7.3)	62.2 (8.0)	0.606
Body mass index [kg m^{-2}; mean ($_{SD}$)]	23.7 (3.2)	22.9 (2.9)	0.317
Sex [n (%)]			0.486
Male	17 (56.7)	19 (65.5)	
Female	13 (43.3)	10 (34.5)	
ASA physical status [n (%)]			0.701
II	24 (80.0)	22 (75.9)	
III	6 (20.0)	7 (23.3)	
Duration of surgery (min)	186.3 (23.5)	183.1 (28.7)	0.364
Duration of anesthesia (min)	82.0 (24.6)	80.0 (29.4)	0.463
Time to emergence from anesthesia (min)	6 (3–14)*	15 (10–25)	0.048
Removal time of LMA (min)	12 (5–24)*	20 (15–35)	0.017
Incidence of Postoperative agitation n (%)	3 (10.0)*	11 (37.9)	<0.001
Incidence of severe POF at T_3, n (%)	7 (23.3)*	22 (75.9)	< 0.001

Notes: Values are presented as means (SD), n (%), median (IQR).
Abbreviations: ASA physical status: American Society of Anesthesiologist's physical status; SD: standard deviation; IQR: interquartile range; LMA: Laryngeal mask airway; DBS: deep brain stimulation; POF: postoperative fatigue; T_3: postoperative day 7.
$^{\#}P < 0.05$, compared within the group, $^{*}P < 0.05$, compared between the groups.

Table 3
Primary outcomes and recovery profiles.

Measurements	TEAS Group (n = 30)	Control group (n = 29)	*P*-value
ChrFS [scores, median, (IQR)]			
T_0	6.0 (4.0,8.0)	6.0 (4.0,8.0)	0.803
T_1	9.0 (7.0,10.0)$^{\#}$	9.0 (8.0,10.0)$^{\#}$	0.001
T_2	5.0 (3.0,7.0)$^{*\#}$	7.0 (5.0,9.0)$^{\#}$	<0.001
T_3	3.0 (2.0,5.0)$^{*\#}$	5.0 (2.0,7.0)	<0.001
VAS-p [scores;median, (IQR)]			
T_0	1.0 (0.0,1.0)	1.0 (0.0,1.0)	0.894
T_1	5.0 (4.0,6.0)$^{*\#}$	6.0 (5.0,7.0)$^{\#}$	<0.001
T_2	3.0 (2.0,3.0)$^{*\#}$	4.0 (3.0,4.0)$^{\#}$	0.001
T_3	1.0 (1.0,2.0)	1.0 (1.0,2.0)	0.319
MMSE [scores, median, (IQR)]			
T_0	27.0 (21.0, 29.0)	27.0 (18.0, 30.0)	0.957
T_1	24.0 (18.0, 29.0)$^{*\#}$	21.0 (9.0, 26.0)$^{\#}$	0.005
T_2	25.0 (20.0, 30.0)$^{*\#}$	23.0 (15.0, 29.0)$^{\#}$	0.010
T_3	26.5 (21.0, 32.0)	25.0 (19.0, 31.0)$^{\#}$	0.075
QOR-15 [scores;mean ± (SD)]			
T_0	116.4 ± 5.3	116.2 ± 4.9	0.761
T_1	118.4 ± 3.5$^{*\#}$	112 ± 4.8$^{\#}$	0.004
T_2	125.5 ± 4.9$^{*\#}$	119.1 ± 4.6$^{\#}$	0.008
T_3	134.9 ± 6.1$^{*\#}$	125.8 ± 4.5$^{\#}$	0.020

Note: Values are presented as means ± SD, median (IQR).
Abbreviations: SD: standard deviation; IQR: interquartile range; ChrFS: Christensen fatigue score; MMSE: Mini-mental State Examination; QoR-15: quality of recovery-15; SD: standard deviation; T_0: one day before surgery; T_1: postoperative day 1; T_2: postoperative day 3; T_3: postoperative day 7.
$^{\#}P < 0.05$, compared within the group; $^{*}P < 0.05$, compared between the groups.

fatigue between patients in the TEAS group and Con group [6.0 (4.0,8.0) vs. 6.0 (4.0,8.0), P = 0.803] prior to DBS surgery. At postoperative day 1 (T_1) both groups of PD patients reported a worsening of fatigue compared to T_0. As the days progressed, however, both groups of patients reported improvement of fatigue (P < 0.05). When the ChrFS scores at T_1, T_2 (postoperative day 3) and T_3 (postoperative day 7) were compared between the two groups, patients in the TEAS had a significant improvement in fatigue compared to those in the Con group [T_1- TEAS vs. Con: (9.0 (7.0,10.0) vs. 9.0 (8.0,10.0), P = 0.001; T2-TEAS vs. Con: 5.0 (3.0,7.0) vs. 7.0

(5.0,9.0), P < 0.001; T_3-TEAS vs. Con: 3.0 (2.0,5.0) vs. 5.0 (2.0,7.0), P < 0.001]. At postoperative day 7 (T_3), the number of patients who reported still having significant fatigue were TEAS vs. Con: 7 vs. 22; P < 0.001.

3.3. Secondary outcomes

A. Requirement for intraoperative anesthetics

During the 1st stage of surgery, 2 patients in the TEAS group and 6 patients in the Con group required IV dexmedetomidine (P < 0.001). For 2nd stage of surgery, the total consumptions of IV propofol (TEAS vs. Con: 374.7 ± 61.2 vs. 421.5 ± 81.9, P < 0.001) and IV remifentanil (TEAS vs. Con: 572.3 ± 82.0 vs. 662 ± 148.2, P < 0.001) were greater in the Con group compared to the TEAS group; please refer to Table 4.

B. Postoperative pain and anesthesia related complications

a. **Score of VAS-P:** [express as median (IQR)] (please refer to Table 3)

Preoperatively, there were no differences in pain between patients in the TEAS and Con group (TEAS vs. Con: 1.0 (0.0,1.0) vs. 1.0 (0.0,1.0, P = 0.894). Postoperative day 1, both groups reported worsening of pain compared to their preoperative assessment but gradually improved over the 7-day postoperative period (P < 0.05). However, postoperative pain experienced by patients in the TEAS was less than those in the Con group at T_1, and T_2 but no different at T_3 [T_1- TEAS vs. Con: 5.0 (4.0,6.0) vs. 6.0 (5.0,7.0), P < 0.001; T2-TEAS vs. Con: 3.0 (2.0,3.0) vs. 4.0 (3.0,4.0), P = 0.001; T3- TEAS vs. Con: 1.0 (1.0,2.0) vs. 1.0 (1.0,2.0) P = 0.319].

b. Postoperative rescue analgesics and rescue anti-emetic requirements:

Two patients in the TEAS group and 6 patients in the Con group required rescue analgesics (P < 0.001). No patient required rescue anti-emetics in either group (P = 1). Please refer to Table 4 for detail.

a. **Score of MMSE** [expressed as median (IQR)] **and QoR-15** [expressed as mean ± standard deviation (SD)]**:** please refer to Table 3 for detail.

The scores of MMSE were not different between the two groups at T_0. Both groups of patients had worsening of MMSE immediately following surgery (compared to T_0) (p < 0.05). As the postoperative period progressed, the MMSE scores of both groups improved. (Please refer to Table 3). Postoperative MMSE scores were better in the TEAS group compared to the Con group at T_1, and T_2 but not at T_3 [T_1- TEAS vs. Con: 24.0 (18.0, 29.0) vs. 21.0 (9.0, 26.0), P = 0.005; T_2-TEAS vs. Con: 25.0 (20.0, 30.0) vs. 23.0 (15.0, 29.0), P = 0.01; T_3- TEAS vs. Con: 26.5 (21.0, 32.0) vs. 25.0 (19.0, 31.0), P = 0.075)]. QoR-15 scores indicated that both groups were not different statistically at baseline (P = 0.76). Postoperatively, patients in the TEAS group reported not only immediate improvement statistically compared to preoperative values but also had their fatigue status range from moderate (score between 91 and 121) to good (score between 122 and 135) at T_2 and T_3 during the postoperative 7 day assessment period. QoR15 scores of patients in the Con group indicated that the TEAS group patients were significantly better at T_1, T_2 and T_3 [T_1- TEAS vs. Con: 118.4 ± 3.5 vs. 112 ± 4.8, P = 0.004; T_2-TEAS vs. Con: 125.5 ± 4.9 vs. 119.1 ± 4.6, P = 0.008; T_3- TEAS vs. Con: 134.9 ± 6.1 vs. 125.8 ± 4.5, P = 0.02)]. Intra-group comparison for the Con group also showed improvement as the days progressed (P = 0.02).

C. **ELISA results for Pre- and Post- DBS Serum levels of Inflammatory Biomarkers:** Even though compare to pre-DBS serum TNF-α and CRP levels, both groups had

elevations of serum TNF-α and CRP levels at the conclusion of surgery. Intraoperative TEAS attenuated postoperative elevations of serum TNF-α and CRP levels when compared to pre- and post-DBS serum TNF-α and CRP levels between the two groups (TEAS vs. Con: 69.72 ± 12.41 vs. 77.61 ± 10.11, P = 0.018), (TEAS vs. Con: 10.27 ± 1.58 vs. 11.31 ± 1.67, P = 0.020), respectively (Fig. 3).

Table 4
Intraoperative and postoperative medications requirement.

Parameter	TEAS group (N = 30)	Control group (N = 29)	*P*-value
Incidence of Dexmedetomidine usage n (%)	2 (6.7)*	6 (20.7)	< 0.001
Propofol dosage (mg)	374.7 ± 61.2*	421.5 ± 81.9	<0.001
Remifentanil dosage (μg)	572.3 ± 82.0*	662 ± 148.2	<0.001
Incidence of Rescue Analgesic n (%)	2 (6.7)*	6 (20.7)	<0.001
Incidence of rescue anti-emetic n (%)	0 (0)	0 (0)	1.00

Note: Values are presented as means ± SD.
*$P < 0.05$ compared between the groups.

4. Discussion

It is well-known that POF has a significant negative impact on the well-being of surgical patients and yet this topic receives little attention [23]. Our study result indicated that greater than 60 % of PD patients experienced significant fatigue (i.e. ChrFS score ≥6) prior to DBS surgery which is similar to a previous review study [24]. As mentioned above, Kluger and colleagues found that approximate 50 % of PD patients still experienced POF one year after DBS surgery [2]. Preoperative fatigue combined with POF will definitely decrease the quality of life in these PD patients. Therefore, it is important to search for an intervention which can improve recovery of these patients.

Although TEAS has been well-received by many patients who underwent various surgeries to prevent or minimize the development of perioperative complications, it has not yet been determined if TEAS or other acupuncture-related techniques may have a beneficial effect for POF.

This is the first study that has utilized intraoperative TEAS to evaluate its effect on POF. We found that intraoperative TEAS significantly decrease the severity of POF in PD patients undergoing DBS surgery. This is evidenced by only 7 PD patients in the TEAS group reporting complaints of significant fatigue compared to 22 PD patient in the Con group (ChrFS scores ≥6) ($P < 0.001$) at postoperative day 7 (T_3). The beneficial effects of intraoperative TEAS also include better and more rapid recovery of cognition (MMSE scores) recovery and higher overall quality of recovery (QoR-15 scores) than patients in the Con group. At postoperative day 7 (T_3), the scores of MMSE were not significantly different between both groups ($P = 0.075$) and yet patients in the Con group still had not returned to their baseline cognition (MMSE scores at T_0 vs. T_3: 27.0 (18.0, 30.0) vs. 25.0 (19.0, 31.0), $P < 0.05$). In contrast, MMSE scores reported by patients who received TEAS were not significantly different from their baseline values (MMSE scores at T_0 vs. T_3: 27.0 (21.0, 29.0) vs. 26.5 (21.0, 32.0), P═NS) at postoperative day 7. Our findings are supported by previous studies [25,26] found that TEAS facilitated the recovery of cognition to preoperative levels. Moreover, patients in the TEAS group reported significant better QoR-15 scores than those of the Con group during the entire 7-day postoperative period (QoR-15 scores: T_1-TEAS vs. Con: 118.4 ± 3.5 vs. 112 ± 4.8, $P = 0.004$; T_2- TEAS vs. Con: 125.5 ± 4.9 vs. 119.1 ± 4.6, $P = 0.008$; T_3 TEAS vs. Con: 134.9 ± 6.1 vs. 125.8 ± 4.5, $P = 0.02$) which is similar to previous studies in the literature [27,28]. Our results also showed that intraoperative TEAS reduced total consumption of intraoperative sedation/analgesics which had also been documented in previous publications [29]. Furthermore, patients who received intraoperative TEAS had a lower incidence of agitation after emerging from anesthesia [30,31]. Our finding is also supported by a previous meta-analysis that TEAS reduced postoperative delirium in elderly surgical patients [30]. In spite of many previous studies [32,33] that indicate perioperative TEAS reduces the incidence of PONV, we did not observe any differences in the usage of postoperative rescue anti-emetics between the TEAS and Con groups in PD patients who underwent STN-DBS surgery. This may be because we did not assess the incidence of PONV directly but used a surrogate end point assessment, i.e. usage of rescue anti-emetics. Lastly, the etiology of POF remains unclear but several studies have suggested that anxiety, systemic inflammatory response, endocrine-metabolic responses to surgery, impaired nutritional intake, immobilization, etc. could contribute the development of POF [23]. Several studies have suggested that circulating inflammatory markers (cytokines) might be the biomarkers of Parkinson's fatigues but the results were inconclusive. Yet, a recent review article indicated that stress and anesthesia caused the imbalance between pro-and anti-inflammatory cytokines which may exacerbate the neuroinflammatory response in PD patients [34]. Shan et al., using Drosophila PD model found that once exposed to sevoflurane, Drosophila PD displayed worsening locomotor abilities [35]. PD patients having high plasma level of TNF-α had a faster rate of motor decline [36]. Furthermore, C-reactive protein (CRP) levels were found to be closely related to the development of fatigue [37]. We therefore employed inflammatory serum biomarkers (TNF-α and CRP) to explore the potential connection between systemic inflammation and POF in PD patients who underwent STN-DBS

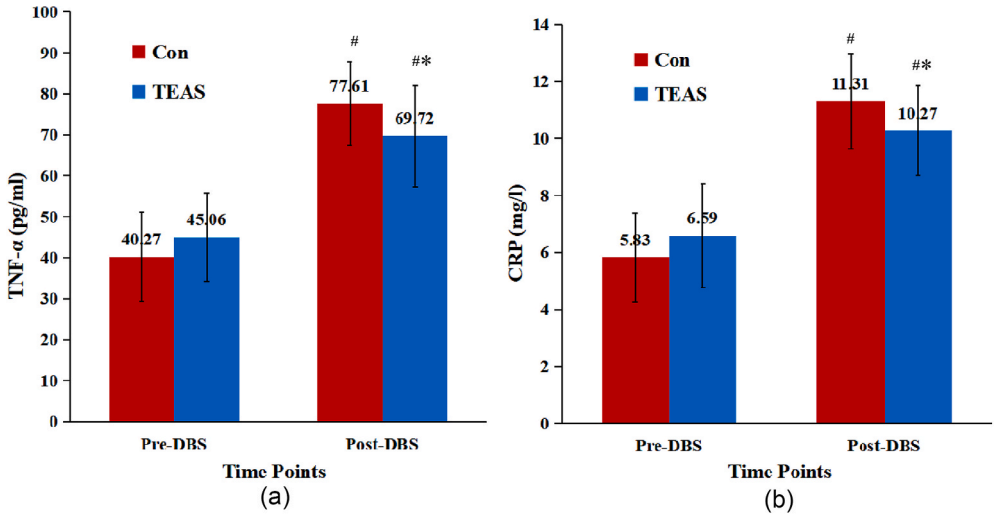

Fig. 3. Serum levels of TNF-α and CRP.

surgery. Our results indicated that the elevation of serum levels of TNF-α and CRP were attenuated by intraoperative TEAS immediately at the completion of surgery compared to those of Con group; however, we did not continue collecting blood samples during the entire postoperative period. Therefore, we could not establish an association between inflammatory responses and the progression of POF during the 7 days postoperative period. Also, we did not perform additional tests to determine the mechanism of intraoperative TEAS in decreasing POF. Thus, we could not determine whether anti-POF effect of TEAS was central or peripheral. Interestingly, a recent study also found that plasma TNF-α was one of the cytokines closely associated with fatigue in PD patients [38]. Because of these encouraging results, future studies will focus on exploring the correlation between inflammatory responses and the development/progression of POF as well as the underlying mechanism of TEAS. Some additional drawbacks of this study are: it is a single center study, it has a relatively small sample size, and it lacks a control group receiving only standard care. We would like to address the reason "Why a standard care control group was not included in this study?" It was to prevent potential disappointment (a negative psychological effect) on this group of patients and potentially unblind members involved in DBS surgery, e.g. neurosurgeon, OR anesthesia team, etc. For above reasons, we deliberately omitted a control group that would receive only standard care. Finally, T.F. adhered to the strict script to ensure each participant was blinded to his/her intervention but we failed to administer a post-study survey to access the effects of potential unblinding of the participants with the interventions received.

5. Conclusions

In conclusion, this double-blinded RCT showed that intraoperative TEAS provided a beneficial effect by decreasing the incidence and severity of POF in a group of PD patients who underwent STN-DBS surgery. TEAS is a non-invasive acupuncture-related stimulating technique which is well received by patients [35]. Additional benefits of intraoperative TEAS in DBS surgery include decreased intraoperative total dosages of analgesics and sedation medications as well as the need for postoperative rescue analgesics. More importantly, it facilitated the recovery of postoperative cognition and improved overall recovery profiles.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Please refer to method section.

The study was conducted consistent with the Declaration of Helsinki. The Medical Research Ethics Committee of the First Hospital of the University of Science and Technology of China approved it on February 4, 2023.

Consent for publication

All authors consented for this manuscript to be published in the Heliyon, once it is accepted after review process. Please see the attached filled consent form.

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CRediT authorship contribution statement

Tong Fu: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fang Kang:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Conceptualization. **Mingming Han:** Validation, Supervision, Methodology, Investigation, Data curation. **Xiang Huang:** Validation, Supervision, Project administration, Methodology. **Bing-qing Zhu:** Validation, Supervision, Methodology. **Bu-Fan Kan:** Formal analysis, Data curation. **Shu-Ming Wang:** Writing – review & editing, Visualization, Supervision, Project administration, Conceptualization. **Juan Li:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Christensen Fatigue Scale (ChrFS)

10	Fatigued	Cannot cope with daily chores or short walks, pronounced need of sleep
9	Tired	Particularly doing house work, gardening or walking stairs, increased need of sleep
8	Slightly tired	Can manage daily chores occasionally more strenous tasks
7	Fit	Tired only by violent excertion, normal need of sleep
6		
5		
4		
3		
2		
1		

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List of abbreviations

TEAS: Transcutaneous electroacupoint stimulation
POF: Postoperative fatigue
DBS: deep brain stimulation
PD: Parkinson disease
STN-DBS: deep brain stimulation in the subthalamic nucleus
PONV: postoperative nausea and vomiting
Con: Control
ChrFS: Christensen fatigue scales
VAS-P:: Visual Analog Scale-pain
QoR-15: Quality of recovery-15
MMSE: mini-mental state examination
RCT: randomized controlled trial
ASA: American Society of Anesthesiologists
IV: intravenous
BIS: bispectral index
TNF-α:: tumor necrosis factor-alpha
CRP: C-reactive protein
MER: microelectrode recording
LMA: laryngeal mask airway
MAC: minimum alveolar concentration
PACU: post-anesthesia care unit
ELISA: enzyme linked immunosorbent assay
Min: Minute
$\overline{x}\pm s$: mean ± standard deviation
M(IQR): median (interquartile range)
CONSORT: Consolidated Standards of Reporting Trials
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture