Electroacupuncture for motor dysfunction and constipation in patients with Parkinson's disease: a randomised controlled multi-centre trial

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Summary

Background Motor disturbances and non-motor disturbances such as constipation are the main factors affecting the quality of life in patients with Parkinson's disease (PD). We investigated the efficacy and safety of electroacupuncture combined with conventional pharmacological treatment on motor dysfunction and constipation in PD.

Methods In this multi-centre randomised controlled trial, we enrolled 166 eligible participants between September 19, 2018 and September 25, 2019 in four hospitals in China. Participants were randomly assigned (1:1) to the electroacupuncture (EA) group and the waitlist control group. Each participant in both groups received the conventional pharmacological treatment, EA group received 3 sessions of electroacupuncture per week for 12 weeks. The primary outcome was the change in the Unified Parkinson's Disease Rating Scale (UPDRS) score from baseline to week 12. The secondary outcomes included the evaluation of functional disability in motor symptoms and constipation, the adherence and adverse events were also recorded. Registered with Chictr.org.cn, ChiCTR1800019517.

Findings At week 12, the change in the UPDRS score of the EA group was significantly higher than that of the control group, with a difference of −9.1 points (95% CI, −11.8 to −6.4), and this difference continued into weeks 16 and 24. From baseline to week 12, the 39-item Parkinson Disease Question (PDQ-39) decreased by 10 points (interquartile range, IQR −26.0 to 0.0) in the EA group and 2.5 points (IQR: −11.0 to 4.0) in the control group, the difference was statistically significant. The time and steps for the 20-m walk at week 12, as well as the changes from baseline in the EA group, were comparable with that in the control group. But the EA group had a greater decrease than the control group from baseline in the times for 20-m walks at weeks 16 and 24. From week 4 to week 24, the median values of spontaneous bowel movements (SBMs) per week in the EA group were higher than that in the control group, the differences were all statistically significant. The incidence of EA-related adverse events during treatment was low, and they are mild and transient.

Interpretation The findings of our study suggested that compared with conventional pharmacological treatment, conventional pharmacological treatment combined with electroacupuncture significantly enhances motor function and increased bowel movements in patients with PD, electroacupuncture is a safe and effective treatment for PD.

Abbreviations: **PD**, Parkinson's disease; **UPDRS**, Unified Parkinson's Disease Rating Scale; **PDQ-39**, 39-item Parkinson Disease Question; **SBMs**, Spontaneous bowel movements; **EA**, Electroacupuncture; **MMSE**, Mini-Mental State Examination; **LED**, Levodopa equivalent dose; **VAS**, Visual Analogue Scale; **CCS**, Chronic constipation severity scale; **PAC-QOL**, Patient assessment of constipation quality of life; **ITT**, Intention-to-treat

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Keywords: Electroacupuncture; Parkinson's disease; Motor dysfunction; Constipation

Research in context

Evidence before this study

Using the search terms "acupuncture", "electroacupuncture" or "moxibustion" in combination with "Parkinson's disease", we searched PubMed for studies including clinical trials, randomized controlled trials, systematic reviews, and meta-analyses from the inception of the database to September 31, 2021. Although more than 60 trials report acupuncture-related therapies treatment for Parkinson's disease (PD), the quality of these evidences are not optimal, include inadequate follow-up duration, treatment regimens are complex, and lack of conclusive evidence of electroacupuncture's efficacy in relieving motor and non-motor symptoms. A multi-centre randomised controlled trial is urgently needed to investigate the efficacy of electroacupuncture for treating motor dysfunction and constipation in patients with PD.

Added value of this study

To our knowledge, this is the first multi-centre, randomised, controlled, 12-week follow-up clinical trial that evaluated the efficacy and safety of electroacupuncture for PD. The study provides stronger evidence that 12 weeks of electroacupuncture was safe and effective in enhancing motor function and bowel movements in patients with PD, and that this effect maintained for at least 12 weeks.

Implications of all the available evidence

The effect of current medication for PD gradually diminishes over time, resulting in motor fluctuations and medication side effects. Our study suggested that compared with conventional treatment, electroacupuncture significantly enhances motor function and bowel movements in patients with PD. The conclusions of this study could encourage further investigation into clinical use of electroacupuncture as a safe and effective complementary treatment for motor dysfunction and constipation symptoms in patients with PD.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, behind Alzheimer's disease, affecting approximately 1% of people over 65.[1] According to a research, the anticipated number of patients with PD globally in 2016 was 6.2 million, a 118 percent rise from 1990, indicating that the number of patients with PD will more than double by 2030.[2] As the world's most populated area, Asia is home to a substantial number of patients with PD.[3] PD is characterised by four primary motor symptoms: bradykinesia, rigidity, resting tremor, and postural instability, which are primarily caused by the death of nigrostriatal dopaminergic neurons.[4,5] In addition to motor symptoms, PD can produce a spectrum non-motor symptoms, such as constipation, urine incontinence, cognitive impairment, fatigue, mood disturbances, and sleep, with constipation being the most frequent.[6] Due to inability to fulfil social roles and curtailment of normal social activities and high hospitalization rate, PD had a pro-found negative impact on daily life, physical and high hospitalization rate.[7] It is estimated that the annual economic cost of PD in the United States alone exceeds $23 billion, considerably increasing the social pressure and financial burden on sufferers and their families.[8]

With an increased focus on PD, the objective of patient-centred treatment is to decrease disability while maximizing the patient's quality of life and well-being. Based on this, PD clinics apply the premise of "early detection, prompt diagnosis, and early therapy" to improve patients' symptoms.[9] Levodopa, a dopamine replacement treatment, is cornerstone of symptomatic therapies for PD and is especially useful in the early stages of the disease for alleviating motor symptoms. As the disease progresses and the dosage increases, levodopa has limitations in PD patients' motor symptoms and medication side effects.[10,11] In addition, it is less effective in treating non-motor symptoms, which require further symptomatic medication. Studies indicate that patients with PD have aberrant bowel behavior and intestinal flora, and that constipation can disrupt levodopa absorption and increase PD symptoms.[12] However, the use of probiotics, polyethylene glycol, lubiprostone, beta-blockers, in PD constipation is not

supported by sufficient evidence.[13] Prior to 2013, survey-based research revealed that 26%–76% of people in different countries used treatments to relieve their symptoms.[14] According to recent surveys conducted in the United States, the use of complementary treatments has increased by 50–74.1%.[15–17] Therefore, safe and effective complementary treatments for the motor and non-motor symptoms of PD are required.

Acupuncture is an essential part of Traditional Chinese Medicine, which has been used for thousands of years. Electroacupuncture may be viewed as a modern extension of acupuncture, which was brought about by the introduction of electronics in acupuncture. We have demonstrated previously that acupuncture can promoted the autophagic clearance of α-synuclein (a well-known aggregation-prone protein closely related to PD), improved the activity of dopaminergic neurons in SNpc, and improved the motor function at the behavior level of PD mice.[18] A recent meta-analyses have noted the positive effects of acupuncture combined with conventional treatment in reducing motor symptoms in PD (as measured by UPDRS II, III, IV and total score).[19] Another trial reported that acupuncture helped patients with PD with their quality of life and non-motor symptoms, such as fatigue, pain, sleep, and depression.[20,21] Although there has been a quantitative explosion of research into various forms of acupuncture treatment, the evidence for acupuncture's efficacy in the treatment of PD is limited. Inadequate follow-up duration, lack of standardization of acupuncture technique assessment, and lack of conclusive evidence of acupuncture's efficacy in relieving motor and non-motor symptoms are the major flaws of past research. Furthermore, the efficacy of constipation, a prevalent non-motor symptom in patients with PD and a significant cause of aggravation, has not been demonstrated. Therefore, this multi-centre randomised controlled trial was conducted to seek accurate conclusions about the role of electroacupuncture (EA) in a large sample size of PD motor and more well-established non-motor symptoms. We hypothesised that EA combined with conventional pharmacological treatment would be an effective treatment for motor and non-motor symptoms of patients with PD.

Methods

Study design

This was a multi-centre, randomised, assessor-blinded trial conducted between September 19, 2018 and September 25, 2019 in four tertiary hospitals in China (Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Longhua Hospital, Shanghai Municipal Hospital of Traditional Chinese Medicine, and Shuguang Hospital, all of which are affiliated with Shanghai University of Traditional Chinese Medicine). The purpose of the study was to compare EA with usual care in PD with motor dysfunction and constipation. The ethics committees of all four hospitals approved the study protocol (2018-049; 2018LCSY065; 2018SHL-KY-01; 2018-607-36-01). This trial was registered with Chinese Clinical Trial Registry (ChiCTR1800019517). All patients signed informed consent before participation. The study adheres to the Consolidated Standards of Reporting Trials (CONSORT)[22] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines[23] for reporting randomised trials. The trial protocol can be found in the Supplementary Material.

Participants

From September 19, 2018, to September 25, 2019, Patients with PD were recruit and screened in four hospitals and recruited by publishing recruitment announcements in newspapers or on the information platform of the official website and the bulletin boards of various research and recruitment websites. The acupuncture treatment is done by the outpatient clinic of each hospital. All participants pro-vided written consent before the study started. Patients were included if they met the inclusion criteria as follows: (1) had a diagnosis of idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[24]; (2) met the diagnostic criteria of Roman IV diagnostic criteria for functional constipation if the patients accompanied with constipation[25]; (3) were aged between 40 and 80 years; (4) had PD for ≥6 months; (5) were in stages 1–4 of the Hoehn and Yahr (H&Y) scale; (6) If the patient is accompanied with constipation, the course of disease is more than 3 months, and the number of spontaneous bowel movements (SBMs) is less than 3 times per week; (7) voluntarily provided written informed consent prior to randomization. The exclusion criteria are as follows: (1) serious cardiovascular and cerebrovascular diseases, hematopoietic diseases, malignant tumors, or other serious life-threatening diseases; (2) diagnosis of schizophrenia, major depression, or cognitive impairment (Cognitive impairment is defined based on the Mini-Mental State Examination [MMSE], which categorises cognitive impairment based on different educational levels. The definition of these criteria are as follows: people who are illiterate, have only received primary school education, or have formal education higher than primary education will be classified as having cognitive impairment if they score less than 14, 20, or 24 respectively on the MMSE); (3) EA could not be performed on acupuncture points due to skin diseases, limb defects, or other conditions; (4) involvement in other clinical trials or having undergone acupuncture treatment within 30 days before participation, which might affect the results of this study; (5) took antidepressants, analgesics, and antihistamines that affected the symptoms of PD within 2 weeks before treatment; and (6) pregnancy or lactation. (7) Patients with constipation were excluded if they had any other identifiable cause of constipation,

including history of laparotomy or anorectal surgery (except for haemorrhoid surgery, appendectomy in the last year, or inguinal hernia repair), acute gastrointestinal disease diagnosed within two weeks before treatment, or anal tumors, malformations, suspected intestinal obstruction, or other organic diseases leading to constipation.

Randomisation and masking

Using stratified randomization, patients were assigned at random (1:1) to either the EA or the usual care waitlist control group. The stratification was based on two variables: (1) patients with constipation or not; (2) the site of the trial. Independent statisticians used the entire randomization feature of SAS (SAS Institute, Cary, NC) to construct computer-generated random sequences, and each stratum was generated from a unique random sequence. The printed random numbers were placed in a light-resistant envelope and managed by a third party (not the investigators). When a participant was eligible, the clinical research coordinator required to call the third party to get the person's random number and group assignment. The acupuncturist will give the corresponding intervention to the participant. Due to the nature of EA and the necessity of this study, neither the patients nor the acupuncturists were blinded to the treatment allocation. During the trial period, the outcome assessors, data collectors, and statistician responsible for performing the statistical analysis were unaware of the group assignments to prevent bias. The site of data gathering was separate from the treatment room. Patients and acupuncturists were instructed not to disclose the patient's group assignment to the trial's data collectors at any time.

Intervention and control

Waitlist control (control group)

In this trial, PD treatment was strictly restricted due to the complexity of the clinical presentation of PD and the principle of personalised treatment in PD clinical guidelines. However, if the participant was taking medication prior to enrollment, the dose cannot be modified at will. To solve this issue, the dosages of the different drugs will be converted to a total daily levodopa equivalent dose (LED).[26]

Based on the constipation symptoms of the patient, the following medication proposals have been made. If patients have no bowel movements for three or more consecutive days, the researchers allowed them to utilise an emergency therapy. Several options were available to patients. Patients with no urge to defecate were advised to consume oral lactulose solutions according to the following protocol. 15 mL of oral lactulose solutions taken at 12-h intervals; if ineffective, 30 mL of oral lactulose solutions taken at 12-h intervals on the second day. It was recommended to provide 20 mL of glycerine enemas through rectal injection to individuals who had the urge to defecate but were unable to pass stool. Patients who do not respond to emergency treatment after two days were advised to take a combination of the two treatments. The patients were instructed not to use any additional emergency treatments. In the stool diary, each usage of emergency therapy was noted. If any other emergency treatment medication was used, this was also recorded in the stool diary. After 24 weeks, all patients in the waitlist control group could receive the same EA treatment as the EA group.

Electroacupuncture (EA groups)

The EA group received 30-min sessions of electroacupuncture treatment on the basis of conventional pharmacological treatment, 3 times each week for 12 weeks, for a total of 36 sessions. The acupoints were selected with reference to data mining studies on acupuncture for PD[27] and combined with the results of our previous studies,[28] included the bilateral connection of Qianding (GV21) to Xuanlu (GB5), Connect Qianshencong (EX-HN1) to Xuanli (GB6), Quchi (LI11), Hegu (LI4),Yanglingquan (GB34), Zusanli (ST36), Sanyinjiao (SP6), Taixi (KI3) and Taichong (LR3). Patients with constipation add Tianshu (ST25), Fujie (SP14), Shangjuxu (ST37). All EA treatments were performed by senior acupuncturists (≥2 years of service), who used the same standardised protocol. Patients were treated in a prone position, after confirming the acupuncture points of ST25, SP14 and RN2, sterile acupuncture needles (length 50 mm, diameter Φ30 mm or length 70 mm, diameter Φ30 mm; Hwato, Suzhou Medical Appliance Factory, China, depending on the patient's size) were inserted vertically for approximately 45 mm–65 mm until the muscle layer of the abdominal wall was pierced. Using sterile acupuncture needles (length 25 mm, diameter Φ25 mm), needles were inserted bilaterally from the GV21 to GB5, bilaterally from the EX-HN1 to GB6 (two needles in each line), LI4, KI3and LR3, at a depth of approximately 10–20 mm. Deqi (a sensation of aching, soreness, swelling, heaviness, or numbness[29])was then obtained by manipulation. The paired electrodes of the electro-acupuncture instrument (SDZ-III EA device, Huatuo, Suzhou Medical Equipment) were connected to GV21 to GB5 (tremor type) or EX-HN1 to GB6 (stiff type). Either pairing can be chosen according to the clinical presentation of the patient's motor symptoms (left acupoint to left acupoint and right acupoint to right acupoint). Finally, depending on the constipation symptoms, the bilateral ST25 and SP14 were connected laterally to the EA instrument. Electroacupuncture instrument lasted 30 min with a dilatation wave of 10/50 Hz and an output pulse width of 0.2 ms ± 30%. The current intensity was adjusted between 1 mA and 10 mA until the skin around the acupuncture point trembled slightly without pain.

Outcomes

Our primary outcome was the group difference in the change in total score on the Unified Parkinson's Disease Rating Scale (UPDRS) from baseline to weeks 12. UPDRS includes 42 items in 4 categories: mental, behavioral, and emotional (4 items); activities of daily living (13 items); exercise (12 items); and complications of treatment (10 items).[30] This scale is mainly aimed at scoring the overall sleep quality, insomnia, sleep disruption, motor symptoms, nightmares, hallucinations, and other problems of patients with PD, which can evaluate the status of patients with PD in a more comprehensive way.

The secondary outcomes included adherence (assessed via acupuncture sessions and the completion of treatment course), adverse events, and the evaluation of PD motor dysfunction and constipation with the following protocol: (1) Assessment of PD symptoms: total score of UPDRS (other time points except week 12), UPDRS I, UPDRS II, UPDRS III, UPDRS IV, a total daily levodopa equivalent dose (LED), walking time for 20 m and step distance were observed at week 4, 8, 12, 16 and 24. And 39-item Parkinson Disease Question[31] (PDQ-39) were observed at week 8 and week 12. If the patients appeared "on/off", the status of the patients in the "on" stage was assessed. (2) Assessment of constipation: Average weekly spontaneous bowel movements (SBMs), Visual Analogue Scale (VAS) were observed at week 4, 8, 12, 16 and 24. We assessed constipation with chronic constipation severity scale[32] (CSS) at week 12, and patient assessment of constipation quality of life[33] (PAC-QOL) were observed at week 8 and week 12.

Statistical analysis

The sample size was calculated based on the results of our pilot study which as conducted to observe the effects of EA on patients with PD.[28] Finds in previous pilot study indicated that the mean UPDRS score was 27.20 with a standard deviation (SD) of 13.51 in the EA group and was 38.00 with a SD of 13.06 in the control group. In this study, PASS 15.0 software was applied for sample size calculation, we assumed that the SD for UPDRS score in week 12 was 13.51, sample size calculation showed that at least 57 patients in each group would be required to have 90% power to detect a difference in the UPDRS score of 7.4 between groups at a significant level of 0.05. Considering a 20% dropout rate, we enrolled 144 qualified patients with PD in this study. To compensate for variation among sites and the prespecified subgroup analysis, the sample size was increased to 166 participants. In this study, the intention-to-treat (ITT) analysis population, consisting of all participants who passed the randomization phase, was the primary population for efficacy and safety analyses. Missing data on the primary outcome were assumed to be missing at random and imputed using the multiple imputation method. In this study, sensitivity analysis was conducted based on patients with complete outcome data (per-protocol, PP), and subgroup analysis was implemented to explore the differences of change of UPDRS score from baseline to week 12 between EA group and control group by sex and age (≤60 years and >60 years). And statistical analysis was performed by applying SAS 9.4 software with a two-tailed P value of less than 0.05 was considered as statistically significant.

In this study, normality distribution of quantitative variables were assessed based on the "Shapiro–Wilk" results, with a P value >0.05 indicated that the quantitative variable was normally distributed. We described the data as means and standard deviations (SD) or as median and interquartile range (IQR) for quantitative variables. And we described the data by frequency counts and proportions (rate) for qualitative variables. The same statistical methods used for the primary outcome will be used to analyse mean weekly bowel movements, mean weekly stool consistency, mean weekly straining score, step speed and average step distance, and UPDRS scores. In addition, Levodopa equivalent daily dose was compared between the two groups using an independent samples t-test or Wilcoxon rank-sum test. VAS for stool symptoms will be compared between the two groups using Wilcoxon rank-sum test. The results will be presented by P value and 95% confidence interval. Adverse events (AEs) and serious adverse events (SAEs) will be compared between the two groups using a Chi-square test or Fisher's exact test. And we used a generalised linear model adjusted baseline confounders as appropriate to analyse the effect of treatment on the primary and all secondary outcomes on a continuous scale.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Between 19 September 2018 and 25 September 2019, there were 195 patients screened in 4 study sites. After 29 patients were excluded, the intention-to-treat analysis included 166 patients with PD (83 in the EA group and 83 in the control group). A total of 25 (15.0%) patients dropped out during this study, including 13 (15.7%) in the EA group and 12 (14.5%) in the control group (Fig. 1). The baseline features of patients are shown in Table 1. There were no significant differences between

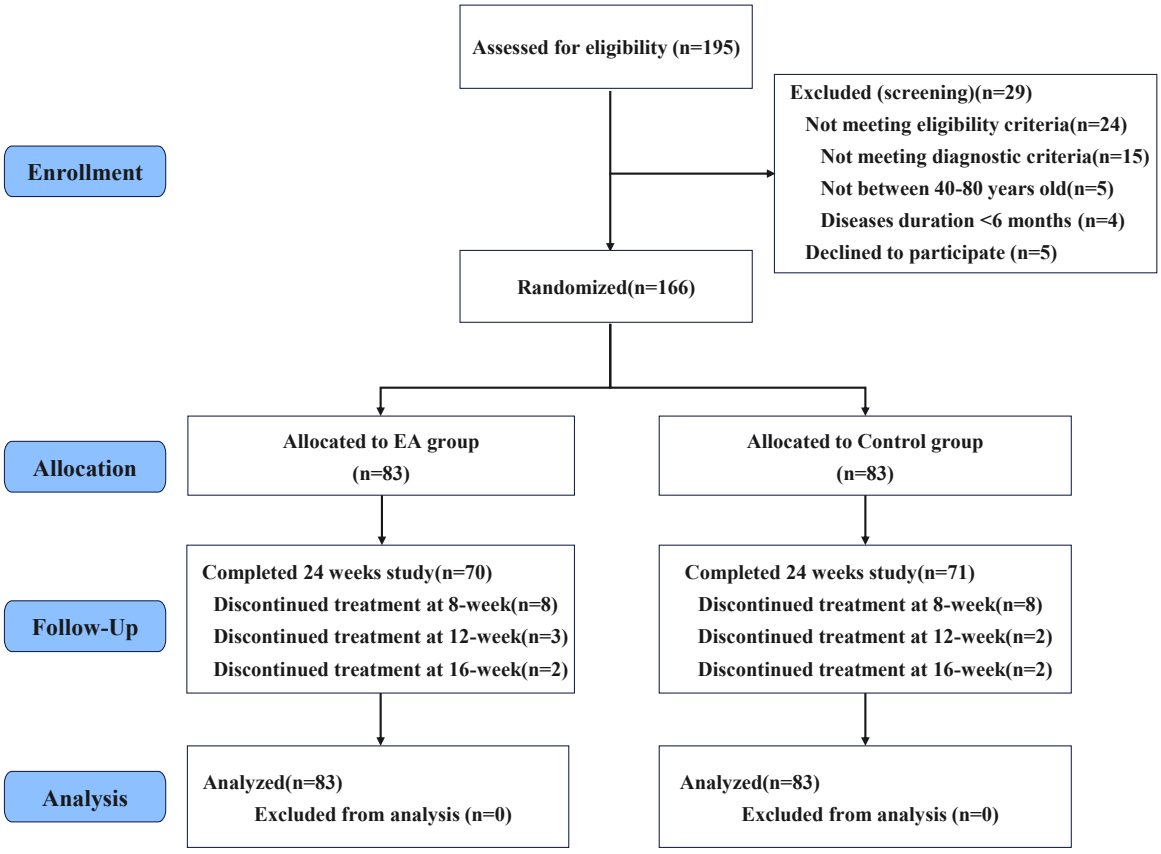

Fig. 1: **Flow of Participants Randomised to Receive EA group (electroacupuncture plus drug treatment) or Control group (drug treatment).**

the EA group and control group in any demographic features, the general health condition only except for UPDRS III score and PDQ 30 for life quality and CCS for constipation severity. The mean UPDRS score in EA group and control group was 36.1 points (SD = 16.6) and 32.2 points (SD = 16.5), respectively. The per-protocol analysis included 141 patients with PD (70 in the EA group and 71 in the control group), the differences of baseline features between EA group and control group were similar to the outcomes in the intention-to-treat analysis (Table S1 in Supplementary Data).

Primary outcome

In Table 2, the mean UPDRS score was 30.9 (95% CI, 27.3–34.4) at week 12 in the EA group and 36.1 (95% CI, 32.2–39.9) in the control group (between-group difference, –5.2 [95% CI, –10.4 to –0.01]). The median UPDRS score was 36.0 (IQR, 23.0–46.0) at baseline and 26 (IQR, 20–41) at week 12 in the EA group and 30.0 (IQR, 21.0–42.0) at baseline and 35 (IQR, 25–47) at week 12 in the control group (between-group difference, $P = 0.035$). The change of UPDRS score from baseline to week 12 in the EA group was –5.3 (adjusted mean 95% CI, –6.9 to –3.6) and 3.9 (adjusted mean 95% CI, 1.7–6.1) in the control group (between group difference, –9.1 [95% CI, –11.8 to –6.4]).

Secondary outcomes

Similar results of change UPDRS score were observed at week 4, 8, 16 and 24 (Table 2). The change of UPDRS II and UPDRS III score were similar to the UPDRS score result, at week 4, 8, 16 and 24, the reduction was greater in the EA group than in the control group (Fig. 2). Compared with the control group, the EA group had a greater decrease from baseline in the times for 20-m walk at week 16, 24 ($P < 0.01$) (Table 2). Change of steps for 20-m walk from baseline was greater in the EA group than the control group at week 16 ($P < 0.05$). The EA group reduced more in change of PDQ-39 score at week 12 ($P < 0.001$). Related results for the constipation section include SBMs, VAS, CCS, and PAC-QOL 4 sections. Compared with the control group, the number of SBMs in the EA group was significantly improved at week 4, 8, 12, 16, 24 ($P < 0.05$) (Fig. 3). No differences were found between the 2 groups in VAS score. Compared with the control group, the EA group had a

Characteristics	Electroacupuncture group (n = 83)	Control group (n = 83)
Age, mean (SD)	67.3 (8.1)	66.9 (7.1)
Gender, (n, %)		
Male	45 (54.2)	43 (51.8)
Female	38 (45.8)	40 (48.2)
Race, (n,%)		
Han	82 (98.8)	82 (98.8)
Minorities	1 (0.2)	1 (0.2)
BMI[b], mean (SD)	23.2 (3.4)	22.93 (2.9)
Educational level, (n,%)		
Junior high or lower	16 (19.3)	22 (26.5)
Senior high	38 (25.8)	30 (36.1)
College and above	29 (34.9)	31 (37.4)
Comorbidities, (n,%)	42 (50.6)	41 (49.4)
Types of comorbidities, (n,%)		
Hypertension	19 (22.9)	18 (21.7)
Diabetes	10 (12.1)	11 (13.3)
Cardiovascular diseases	4 (4.8)	6 (7.2)
Cerebroinfarction	3 (3.6)	3 (3.6)
Cancer	2 (2.4)	3 (3.6)
Others	6 (7.2)	4 (4.8)
Hoehn-Yahr classification[c], (n, %)		
Level 1	9 (10.8)	18 (21.7)
Level 1.5	21 (25.3)	17 (20.5)
Level 2	15 (18.1)	20 (24.1)
Level 2.5	19 (22.9)	13 (15.7)
Level 3	13 (15.7)	13 (15.7)
Level 4	6 (7.3)	2 (2.4)
Sub-type of Parkinson's disease		
Tremors	11 (13.3)	7 (8.4)
Forced inactivity	18 (21.7)	18 (21.7)
Mixed	54 (65.1)	58 (69.9)
UPDRS[d] score		
Mean (SD)	36.1 (16.6)	32.2 (16.5)
Median (IQR)	36.0 (23.0–46.0)	30.0 (21.0–42.0)
UPDRS I score, median (IQR)	3 (1–4)	3 (2–4)
UPDRS II score, median (IQR)	11 (8–15)	10 (8–13)
UPDRS III score[g], median (IQR)	18 (11–26)	13 (8–21)
UPDRS IV score, median (IQR)	1 (0–3)	1 (0–3)
PDQ39 for life quality[g], median (IQR)	39 (24–58)	29 (15–50)
Time for 20 m walk, median (IQR)	17.2 (14.5–20.2)	16.3 (15.2–19.3)
Steps for 20 m walk, median (IQR)	32 (29–36)	33 (30–37)
VAS[e] score, median (IQR)	0 (0–3)	0 (0–3)
Constipation, (n, %)	30 (36.1)	29 (34.9)
CCS[f,g] for constipation severity, median (IQR)	10.5 (9.0–12.0)	11.0 (9.0–12.0)
Number of SBMs in 1 week[h], median (IQR)	2.5 (0.5–2.8)	2.0 (0.0–3.0)
Percentage of SBMs in 1 week (%)[h], mean (SD)	27.5 (21.2)	21.4 (18.1)
LED, median (IQR)	400.0 (300.0–550.0)	412.0 (200.0–662.5)

Abbreviations: BMI, body mass index; CCS, constipation scoring system; IQR, Interquartile range; LEDD, Alpha-dopa equivalent daily dose; PDQ-39, 39 item Parkinson's disease question; SBMs, spontaneous bowel movement; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, visual analogue scale. [a]Data represented as Mean (standard deviation), Median (Interquartile range) or frequency (%) as appropriate. [b]BMI was calculated as weight in kilograms divided by height in meters squared. [c]Hoehn-Yahr classification level indicated the severity of Parkinson's diseases, with a higher value of Hoeln-Yahr represents a more severe condition (1, 1.5, 2, 2.5, 3, 4, 5). [d]UPDRS was composed by UPDRS I (psychology, behavior and emotion), UPDRS II (daily activity), UPDRS III (physical activity), and UPDRS IV (complications after treatment), the score of UPDRS was additive (0 [better]–147 [worse] outcomes). [e]VAS was additive (0 [better]–10 [worse] outcomes). [f]CCS was additive (0 [better]–32 [worse] outcomes). [g]The difference between groups as statistically significant (Wilcoxon rank-sum test, P value < 0.05). [h]Number of participants: 27, electroacupuncture group and 26, control group.

Table 1: **Participant baseline characteristics[a].**

Variable	Electroacupuncture group (n = 83)	Control group (n = 83)	Difference (95% CI)	*P* value[a]
Primary outcome[b]				
UPDRS score at week 12, Mean (95% CI)	30.9 (27.3–34.4)	36.1 (32.2–39.9)	−5.2 (−10.4 to −0.01)	0.049
UPDRS score at week 12, Median (IQR)	26 (20–41)	35 (25–47)	NA	0.035
Change at week 12, adjusted mean (95% CI)[c]	−5.3 (−6.9 to −3.6)	3.9 (1.7–6.1)	−9.1 (−11.8 to −6.4)	<0.001
Secondary outcomes[d]				
PDQ-39 for life quality at week 12[e]				
PDQ-39 score, median (IQR)	20 (9–42)	25 (10–47)	NA	0.556
Change at week 12, adjusted median (IQR)	−10.0 (−26.0 to 0.0)	−2.5 (−11.0 to 4.0)	NA	<0.001
Time for 20 m walk at week 12[f]				
Times (min), median (IQR)	16.6 (15.4–18.6)	17.3 (15.4–19.2)	NA	0.321
Change of times at week 12, adjusted median (IQR)	−0.2 (−1.8 to 1.0)	0.2 (−1.1 to 1.2)	NA	0.054
Steps for 20 m walk at week 12[f]				
Steps, median (IQR)	33.0 (30.0–34.0)	32.0 (30.0–37.0)	NA	0.519
Change of steps at week 12, adjusted median (IQR)	0 (−2.0 to 2.0)	1 (−1.0 to 2.0)	NA	0.113
Change UPDRS score, adjusted mean (95% CI)[g]				
Week 4	−2.4 (−3.9 to −1.0)	0.5 (−1.2 to 2.2)	−2.9 (−5.1 to −0.7)	0.001
Week 8	−2.1 (−5.1 to 0.9)	2.4 (0.2–4.6)	−4.5 (−8.2 to −0.8)	0.017
Week 16	−3.7 (−5.5 to −1.9)	8.9 (6.2–11.8)	−12.7 (−15.9 to −9.4)	<0.001
Week 24	−1.4 (−3.9 to 1.1)	11.4 (8.3–14.4)	−12.7 (−16.6 to −8.9)	<0.001
PDQ-39 for life quality at week 8[h]				
PDQ-39 score, median (IQR)	34 (18–63)	28 (13–56)	NA	0.196
Change at week 8, adjusted median (IQR)	−3 (−14 to 3)	−1 (−5 to 3)	NA	0.208
Change of times for 20 m walk, adjusted median (IQR)[i]				
Week 4	0.1 (−1.0 to 0.8)	0.1 (−1.0 to 1.0)	NA	0.513
Week 8	0.0 (−1.3 to 1.1)	0.1 (−1.1 to 1.2)	NA	0.702
Week 16	−0.5 (−2.1 to 1.1)	0.5 (−0.6 to 2.2)	NA	0.004
Week 24	0.1 (−1.6 to 1.3)	1.2 (−0.4 to 3.1)	NA	0.002
Change of steps for 20 m walk, adjusted median (IQR)[i]				
Week 4	0.0 (−1.0 to 2.0)	1.0 (−1.0 to 2.0)	NA	0.988
Week 8	0.0 (−2.0 to 2.0)	0.0 (−2.0 to 2.0)	NA	0.816
Week 16	0.0 (−2.0 to 2.0)	2.0 (−1.0 to 4.0)	NA	0.025
Week 24	1.0 (−1.0 to 4.0)	2.0 (−1.0 to 5.0)	NA	0.138
Change of VAS score, adjusted median (IQR)[j]				
Week 4	0 (0–0)	0 (0–0)	NA	0.269
Week 8	0 (0–0)	0 (0–0)	NA	0.210
Week 12	0 (0–0)	0 (0–0)	NA	0.086
Week 16	0 (0–0)	0 (0–0)	NA	0.501
Week 24	0 (0–0)	0 (0–0)	NA	0.148
CCS for constipation severity at week 12[k]				
Score at week 12, mean (95% CI)	8.0 (6.8–9.2)	10.3 (9.0–11.6)	−2.3 (−4.0 to −0.6)	0.008
Change of CCS score, adjusted mean (95% CI)	−2.1 (−2.9 to −1.3)	−1.9 (−3.2 to −0.6)	−1.9 (−3.2 to −0.6)	0.004
PAC-QOL score for life quality, mean (95% CI)[l]				
Week 8	25.4 (21.5–29.3)	36.5 (29.5–43.4)	−11.1 (−18.9 to −3.2)	0.007
Week 12	24.0 (20.0–27.9)	37.0 (30.6–43.5)	−13.0 (−20.7 to −5.4)	0.001
Difference between week 12 and week 8	−1.7 (−4.1 to 0.7)	1.4 (−1.6 to 4.3)	−3.1 (−6.8 to 0.6)	0.098
Number of SBMs in 1 week, median (IQR)[m]				
Week 4	2.5 (2.0–3.0)	1.5 (0.3–3.0)	NA	0.025
Week 8	3.0 (2.5–3.5)	0.5 (0.0–2.0)	NA	0.001
Week 12	3.0 (2.5–4.0)	0.5 (0.0–2.3)	NA	0.001
Week 16	2.5 (2.5–3.5)	0.5 (0.0–2.0)	NA	<0.001
Week 24	2.5 (2.0–3.0)	1.0 (0.0–1.8)	NA	0.009
Percentage of SBMs in 1 week (%), median (IQR)[m]				
Week 4	35.7 (28.6–42.9)	21.4 (3.6–28.6)	NA	0.025
Week 8	42.9 (35.7–50.0)	7.1 (0.0–28.6)	NA	0.001

(Table 2 continues on next page)

Variable	Electroacupuncture group (n = 83)	Control group (n = 83)	Difference (95% CI)	P value[a]
(Continued from previous page)				
Week 12	42.9 (35.7–57.1)	7.1 (0.0–32.1)	NA	0.001
Week 16	38.5 (35.7–53.9)	7.7 (0.0–30.8)	NA	<0.001
Week 24	38.5 (30.8–46.2)	15.4 (0.0–26.9)	NA	0.009
Change of LED, adjusted median (IQR)[n]				
Week 4	0 (0–0)	0 (0–0)	NA	0.659
Week 8	0 (0–0)	0 (0–0)	NA	0.329
Week 12	0 (0–0)	0 (0–0)	NA	0.294
Week 16	0 (0–0)	0 (0–0)	NA	0.646
Week 24	0 (0–0)	0 (0–0)	NA	0.208

Abbreviations: CCS, constipation scoring system; CI, confidence interval; IQR, Interquartile range; LEDD, Alpha-dopa equivalent daily dose; PAC-QOL, patient assessment of constipation quality of life; PDQ-39, 39 item parkinson's disease question; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, visual analogue scale. [a]All tests were 2-sided. *P* value of less than 0.05 was considered significant. [b]Number of participants with imputed data: 11 (13.3%), electroacupuncture group and 9 (10.8%), control group. [c]Generalised linear model adjusted baseline values. [d]Missing data not imputed for secondary outcomes analyses. [e]Number of participants: 82, electroacupuncture group; 82, control group. [f]Number of participants: 82, electroacupuncture group; 83, control group. [g]Number of participants: electroacupuncture group: 83, week 4; 83, week 8; 70, week 16; 70, week 24 and control group: 83, week 4; 83, week 8; 71, week 16; 71, week 24. Generalised linear model adjusted baseline values. [h]Number of participants: 75, electroacupuncture group; 75, control group. [i]Number of participants: electroacupuncture group: 83, week 4; 82, week 8; 69, week 16; 69, week 24 and control group: 83, week 4; 83, week 8; 71, week 16; 71, week 24. Wilcoxon rank-sum test is applied. Between-group differences were not provided, adjusted for baseline values (week 0). [j]Number of participants: electroacupuncture group: 83, week 4; 83, week 8; 82, week 12; 70, week 16; 70, week 24 and control group: 83, week 4; 83, week 8; 82, week 12; 71, week 16; 71, week 24. Wilcoxon rank-sum test is applied. Between-group differences were not provided. [k]Number of participants: 30, electroacupuncture group; 29, control group. [l]Number of participants: electroacupuncture group: 27, week 8; 26, week 12 and control group: 28, week 8; 29, week 12. Generalised linear model adjusted baseline values. [m]Number of participants: electroacupuncture group: 27, week 4; 23, week 8; 25, week 12; 21, week 16; 25, week 24 and control group: 26, week 4; 26, week 8; 26, week 12; 23, week 16; 23, week 24. Wilcoxon rank-sum test is applied. Between-group differences were not provided. [n]Number of participants: electroacupuncture group: 82, week 4; 74, week 8; 72, week 12; 70, week 16; 70, week 24 and control group: 83, week 4; 75, week 8; 74, week 12; 70, week 16; 69, week 24. Wilcoxon rank-sum test is applied. Between-group differences were not provided, adjusted baseline values.

Table 2: **Primary and secondary outcomes[a].**

greater decrease from baseline in the CCS at week 12, and PAC-QOL between week 8 and week 12 ($P < 0.01$).

AE, SAE, and concomitant medication

In this study, there was no difference in the proportion of concomitant medication, which refers to the drugs except PD drugs, between the EA and control groups (between-group difference, 4.8 [95% CI, −9.4 to 19.1] $P = 0.508$) (Table 3). Adverse effects occurred in 13.3% of participants in the EA group and 7.2% in the control group. The most reported acupuncture-related adverse effects were local ecchymosis, abdominal pain, dizziness, and local hematoma. Non–acupuncture-related adverse effects occurred mainly in the control group, including headache, dizziness, fever, and diarrhea. One patient had a non–acupuncture-related AEs of herpes zoster adverse in the EA group. No patients withdrew from the study due to adverse effects and no serious adverse event occurred in the trial. No differences were found between the 2 groups in the proportion of compliance with treatment and complete treatment course ($P > 0.05$).

Sensitivity analysis

In per-protocol analysis, 70 patients in the EA group and 71 patients in the control group were included. The change of UPDRS score from baseline to week 12 was −6.4 (adjusted mean 95% CI, −8.1 to −4.6) in the EA group and 3.7 (adjusted mean 95% CI, 1.2–6.3) in the control group (between group difference, −10.1 [95% CI, −13.2 to −7.0]). For secondary outcomes, except for the EA group had a greater decrease from baseline in the times for 20-m walk at week 12 than patients in the control group ($P < 0.05$), the other outcomes (change of UPDAS score at week 4, 8, 16, 24, change of PDQ-39 at week 12, decrease of times for 20-m walk at week 16, 24, and SBMs, VAS, CCS, and PAC-QOL 4 sections) were in line with the outcomes in intention-to-treat analysis (Table S2 in Supplementary Data).

In this study, we also implemented sub-group analysis for the change of UPDRS score from baseline to week 12. Both of male and female patients with PD in EA group had great reduction of UPDRS score than control group, and the outcomes were similar in patients aged equal or under 60 years, as well as patients aged over 60 years (Fig. S1 in Supplementary Data).

Discussion

In this study, most patients with PD had Hoehn and Yahr scale scores of 2.5 or above. During a 12-week treatment period, the EA group received PD medication, and EA treatment was associated with a higher reduction in the change from baseline of UPDRS score than the control group, which got PD medication alone. The effects lasted for 12 weeks following treatment. There were no differences in LED between the two groups, indicating that both received equivalent amounts of PD medicine. The incidence of adverse events was modest, and no participant dropped out of the study due to acupuncture-related ill effects. The

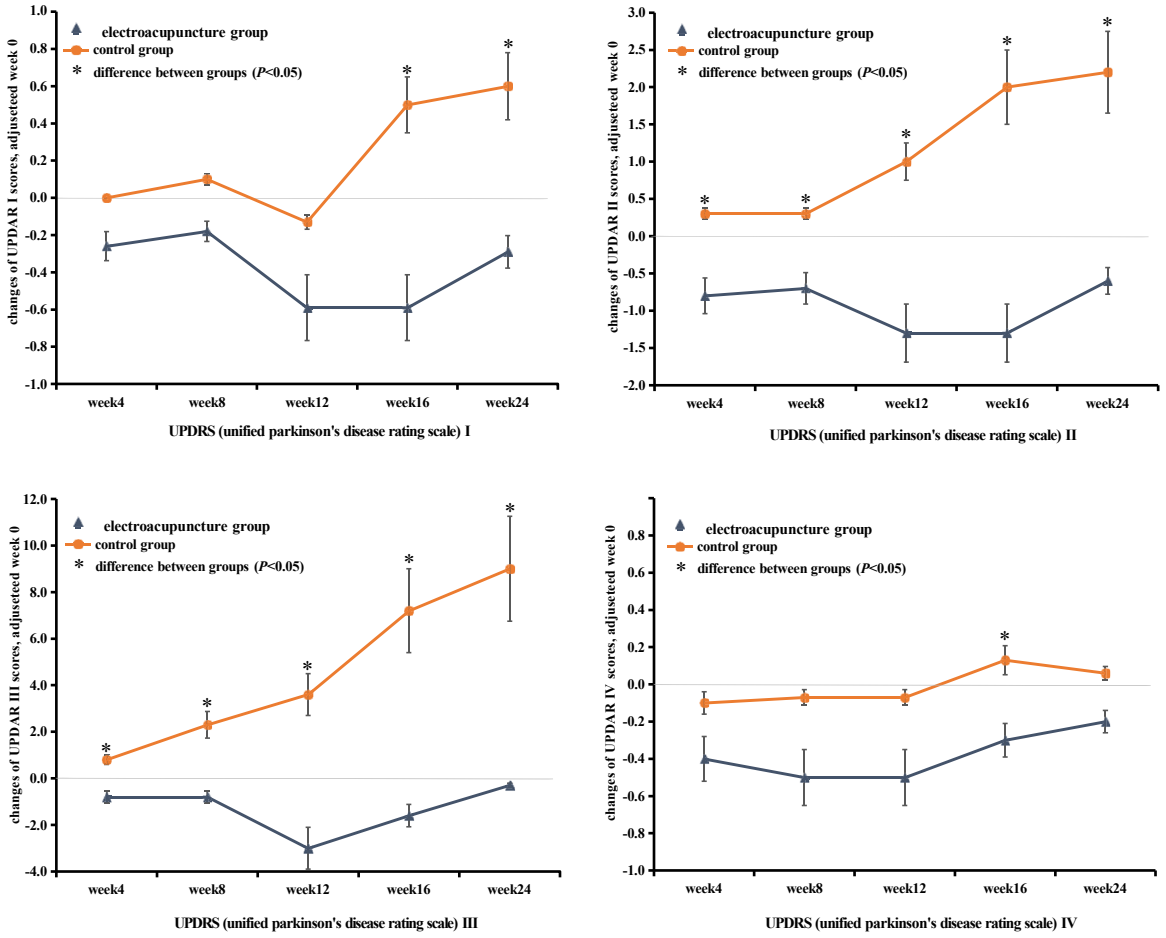

Fig. 2: **Change of UPDRS score in four components (I, II, III and IV) in week 4, week 8 week 12, week 16 and week 24 between EA group (electroacupuncture plus drug treatment) or Control group (drug treatment).**

findings were consistent in the intention-to treat analysis and the per-protocol analysis. In this study, acupoints for PD were chosen based on the results of a pilot trial that demonstrated the effectiveness of these points in reducing the UPDRS score.[28]

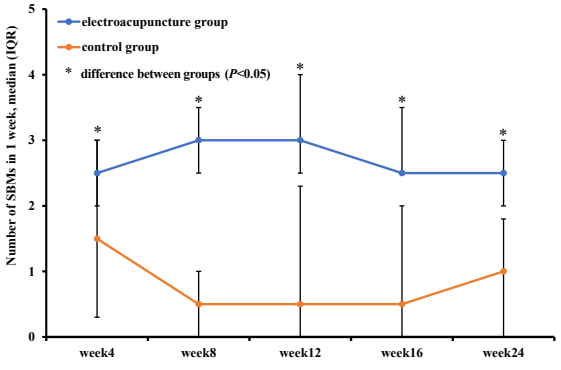

Fig. 3: **Number of SBMs in 1 week between EA group (electroacupuncture plus drug treatment) or Control group (drug treatment).**

The UPDRS is a standard scale for assessing PD that consists of 4 sections,[34–36] EA treatment primarily decreased scores on the UPDRS II and UPDRS III. UPDRS II is concerned with activities of daily living, whereas UPDRS III is concerned with motor examination. The results of this study indicate that EA improved PD patients' activities of daily living and motor examination. UPDRS I is used to evaluate the non-motor symptoms of PD, including mental, behavioral, and emotional symptoms. Long-term exposure to the disease's symptoms causes patients to lose initiative and even suffer depression. Intellectual impairment and thought disorder are related to a protracted course of PD or long-term medication use. During therapy, EA did not significantly enhance UPDRS I score. UPDRS IV is concerned with therapy-related consequences, which consist primarily of dyskinesias and clinical fluctuations. Intermediate and advanced patients are more likely to experience dyskinesia and clinical fluctuations.

Items	Electroacupuncture group (n = 83)	Control group (n = 83)	Difference (95% CI)	*P* value[a]
Concomitant medication, n (%)				0.508
Yes	29 (34.9)	25 (30.1)	4.8 (−9.4 to 19.1)	
No	54 (65.1)	58 (69.9)		
Adverse effect, n (%)[b]				0.201
Yes	11 (13.3)	6 (7.2)	6.0 (−3.2 to 15.2)	
No	72 (86.8)	77 (92.8)		
Severe adverse effect, n (%)				1.000
Yes	0 (0.0)	0 (0.0)	0 (0–0)	
No	83 (100.0)	83 (100.0)		
Compliance with treatment, n (%)				0.129
Yes	79 (95.2)	83 (100.0)	−4.8 (−9.4 to −0.2)	
No	4 (4.8)	0 (0.0)		
Complete treatment course, n (%)				0.828
Yes	70 (84.3)	71 (85.5)	−1.2 (−12.1 to 9.7)	
No	13 (15.7)	12 (14.5)		

[a]Calculated using the chi square test. [b]Adverse effect: Electroacupuncture group: local ecchymosis (6), abdominal pain (2), dizziness (1), local hematoma (1), herpes zoster (1) and control group: headache (2), dizziness (1), fever (2), diarrhea (1).

Table 3: **Adverse effect, severe adverse effect, concomitant medication and therapy obedience condition during 12 weeks of treatment among patients with Parkinson's diseases.**

Dyskinesia is a side effect of Levodopa, the drug of choice for the clinical treatment of PD.[37] EA showed no obvious therapeutic impact on UPDRS IV compared to the control group. Similar to the results of UPDRS III, we also observed a significant reduction in walking time of 20 m in the EA group in this study, and these results suggest that electroacupuncture enhanced motor function in patients with PD.

PDQ-39 are used to evaluate the clinical change in health-related quality of life in patients with PD.[38] At week 12, the change in PDQ-39 was different between the two groups, indicating that EA may improve the quality of life of patients with PD. The results of this study revealed that the change in 20-m walk times at weeks 12 (PP analysis), 16, 24, and the change in 20-m walk steps were fewer in the EA group than in the control group. We hypothesised that this outcome could be attributable to the fact that PD is a progressive disease, and that the treatment impact shows as the disease progresses.

Constipation is prevalent in PD and has a negative impact on the quality of life for many individuals.[39] Constipation tends to become more common as the condition advances.[11] This study revealed that the incidence of constipation in patients with PD was approximately 36.1% in the EA group and 34.4% in the control group, which was comparable to findings from other studies in this field.[40] According to research published in Annals of Internal Medicine, EA at ST25, SP14, and ST37 is a good treatment for Chronic Severe Functional Constipation.[41] Consequentially, a similar treatment technique was utilised in this investigation to treat constipation in PD. The average number of SBMs per week is an objective measure of constipation. During treatment and follow-up, the average SBMs per week in the EA group were significantly higher than in the control group. PAC-QOL is often used to assess the quality of life in patients with constipation. It contains four dimensions: physical and psychological discomfort, worries/concerns, and satisfaction level.[32] The results of this study showed that EA intervention may improve the quality of life of patients with PD with constipation. These results suggest that electroacupuncture significantly improves constipation symptoms and enhances patient satisfaction with bowel movements in patients with PD.

This study used usual care as the control group instead of sham acupuncture to increase participant adherence. Due to their motor impairment, advanced age, and lack of significant symptom improvement, many patients with PD were unable to adhere to a 12-week, three-times-per-week course of sham electroacupuncture (EA) in our pilot trial. After a period of treatment, they frequently refused to continue sham EA, resulting in a greater loss rate than the EA group.

In our study, the proportions of participants having AEs in the EA and control groups were low, some of them may be related to their normal PD medication. The specific EA-related AEs were mild and transient, including hematoma, ecchymosis, dizziness, and abdominal pain. If local hematoma, ecchymosis occurred, patients were advised to ice compress within 24 h, hot compress after 24 h, generally will dissipate after a few days.

This study has the following deficiencies. Firstly, the follow-up period is not long enough to observe the long-term impact of EA treatment on patients with PD. For example, the EA group stills showed sustained effects on the change of times for 20-m walk, and SBMs at week 24, and an appropriate extension of the follow-up period may observe the duration of sustained effects of electroacupuncture in these indicators. Several index scores such as UPDRS III rebounded during the follow-up period, reflecting that the effect of electro-acupuncture on UPDRS III in patients with PD is mainly applied to short-term changes. In clinical practice, we usually use continuous acupuncture for efficacy consolidation, and providing a longer course of treatment may improve long-term efficacy. Still, this hypothesis needs to be tested by further clinical studies. Secondly, due to the long duration of the efficacy evaluation point from September 2018 to March 2020, evaluators in some sub-centres were forced to make some adjustments, although they are all trained. This may affect the UPDRS score. The last, patients were not blinded in this study, and the results of the EA group may contain some placebo effect.

In conclusion, this study presents evidence that EA is a safe and effective treatment to enhances motor function and increased bowel movements in patients with PD. Further studies are needed to understand the long-term efficacy and mechanism of EA interventions on PD.

Contributors

H.W. and L.W. conceived and designed the study; K.L., Z.W., S.X., X.L., M.D. and J.L. recruited and followed up patients; H.L., Y.C. and G.L. analysed and interpreted the data; Y.W. and Q.Y. were responsible for study monitoring; R.W., H.W., Z.W., and K.L. accessed and were responsible for the raw data associated with the study, and R.W., H.W. is responsible for data verification; R.W., X.Z. and C.H. performed the statistical analysis; K.L. and Z.W. drafted the manuscript; C.F., C.Y. and X.M. critically revised the important intellectual content of the manuscript. All authors had full access to the data in the study and gave the final approval of the manuscript and agree to be accountable for all aspects of work.

Data sharing statement

De-identified individual clinical data will be made available to others upon request to the corresponding authors, only for research, non-commercial purposes to individuals affiliated with academic or public health institutions. These data will be available for a period of 6 months to 3 years after publication. Data requests require a methodologically sound proposal as well as a data access agreement and approval by the local ethics committee.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101814.

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