

Acupuncture for Early Parkinson's Motor Symptoms: A Multicenter Randomized Controlled Trial Protocol

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Background: Pharmacological treatment of motor disorders in early Parkinson (PD) has reached a bottleneck, and acupuncture as an important component of non-pharmacological therapy has demonstrated therapeutic potential. However, current evidence is limited in both quantity and quality, highlighting the need for further clarification of its efficacy.

Methods: A multi-center, investigator and participant blinded, randomized parallel group design was employed. 136 eligible participants were randomly assigned in a 1:1 ratio to either the acupuncture or sham acupuncture group via a central randomization system, received 12 sessions over 4 weeks. The primary outcome was motor function, assessed using the Unified Parkinson's Disease Rating Scale-III (UPDRS-III). Secondary outcomes were objective gait metrics captured with the Ready system, disease stage assessed by the Hoehn and Yahr scale (HY), and quality of life measured by the Activities of Daily Living scale (ADL) and the Parkinson's Disease Questionnaire 39 (PDQ 39). Levodopa dosage was recorded before and after treatment. Assessments were conducted at four time points (weeks 1, 2, 3, and 4), with 8 weeks follow up. Blood samples were collected before and after treatment for LC-MS/MS untargeted metabolomics and deep proteomics analysis.

Discussion: This study will aim to clarify the efficacy of acupuncture for early PD motor symptoms through an evidence-based randomized controlled trial (RCT), and explore the underlying mechanisms of acupuncture using multi-omics approaches.

Keywords: acupuncture, Parkinson, motor, randomized controlled trial, protocol

Introduction

Since Parkinson's disease (PD) was first described, finding ways to overcome or slow its progression has become a major global health issue.¹ Driven by factors such as aging, the prevalence of PD has increased by 118% over the past 30 years, making it the second most common neurodegenerative disease worldwide.¹⁻³ Furthermore, the burden of PD on healthcare systems is expected to continue to increase, underscoring the need to develop effective health policies to address this challenge.^{1,2} The clinical manifestations of PD are primarily characterized by four core motor symptoms: tremor at rest (T), rigidity (R), akinesia (A), and postural instability (P).^{1,4} Additionally, PD also associated with a range of non-motor symptoms, which contribute to the significant symptom overlap between PD and other diseases.^{4,5} Despite the development of landmark diagnostic criteria by the Movement Disorder Society (MDS), diagnosing PD remains



challenging.^{1,4,6} Moreover, due to the persistent progression of PD, once the disease reaches advanced stages, its core motor symptoms become increasingly difficult to manage, severely compromising patients' quality of life and potentially leading to irreversible disability or even death in later stages.^{7,8} As a result, typical core motor symptoms continue to serve as key evidence for confirming a PD diagnosis and remain the primary focus of treatment.^{4,6,7} In such cases, timely identification of early PD core motor symptoms and intervention are particularly crucial.

Currently, the early core motor symptoms of Parkinson's disease (PD) are primarily treated with dopamine replacement agents, represented by levodopa.^{9–11} However, prolonged use of levodopa leads to the “wearing-off phenomenon” (reduced duration of therapeutic effect) and the “on-off phenomenon” (sudden fluctuations in symptoms due to variations in drug efficacy).¹² Furthermore, complications such as dyskinesia, which are associated with levodopa, may exacerbate the core symptoms of PD. In addition, the risk of adverse effects, including nausea and vomiting, has led some clinicians and patients with PD to hesitate to initiate this therapy in the early stages of the disease.⁹ Other available pharmacological treatments, such as dopamine receptor agonists and monoamine oxidase B inhibitors (MAOBIs), are commonly used as adjuncts to levodopa therapy, where negative consequences are inevitable with levodopa again.^{9,13–15} Against the backdrop of a bottleneck in the progress of pharmacological treatments, the development of non-pharmacological therapies has opened up new possibilities for the management of early motor symptoms in PD,¹⁶ further exploration of various non-pharmacological therapies for managing early PD motor symptoms holds considerable clinical value and is urgent.

Acupuncture therapy plays a critical role in non-pharmacological therapy; it emphasizes exerts therapeutic effects by stimulating specific acupoints to induce the sensation of “de qi”.^{8,17,18} Due to its distinct advantages, including safety, ease of administration, and cost-effectiveness, acupuncture has increased application in PD treatment,^{19,20} and has been recommended (Grade B) by clinical practice guidelines for symptom management of PD, indicating its considerable potential.^{8,16,17,21} Acupuncture has a history of application spanning thousands of years in its country of origin, China, and its global influence is rising.⁵ Therefore, demonstrating the efficacy of acupuncture for early PD core motor symptoms has significant implications for health policies. However, the application of acupuncture in this field still suffers from significant deficiencies in the level of evidence, which primarily stem from methodological flaws in research design. One such issue is randomization bias and the challenges associated with blinding. As a critical initiation procedure in RCTs, randomization bias leads to the infiltration of confounding factors that affect efficacy evaluation, causing issues such as baseline imbalance and weakening causal inference regarding acupuncture's efficacy; it may even lead to the prediction of subject allocation, resulting in erroneous feedback on acupuncture's efficacy. The challenges regarding blinding stem from the inherent difficulty of blinding acupuncturists in clinical research; previous studies have lacked effective blinding devices, causing loopholes regarding intervention bias to be infinitely magnified. Another issue is the questioning of the “placebo effect” caused by the setting of acupuncture control measures. Due to the lack of an ideal inert sham acupuncture control, there remains a prevalent view in the international academic community that the observed efficacy may stem from non-specific factors such as the therapeutic environment or the natural course of the disease. Furthermore, the insufficient feedback on the true efficacy of acupuncture caused by the lack of efficacy assessment tools further exacerbates the challenges regarding the level of evidence for acupuncture treatment. Therefore, establishing high-quality RCT evidence to verify the therapeutic value of acupuncture is crucial for confirming its future clinical relevance.²²

Based on the above, this study will aim to (1) address the issues mentioned above and implement a self-developed randomization system to correct flaws in the randomization process, utilizing a Modular Multichannel Acupuncture Device (MoCAD) to ensure blinding throughout the process, and minimize placebo effects, (2) employ objective measurement tools to accurately assess the treatment effects of acupuncture in a rigorously designed, evidence-based randomized controlled trial (RCT) aimed at preliminarily evaluating the efficacy of acupuncture in treating core motor symptoms in early PD.²³ Additionally, this study also will utilize multi-omics techniques to explore the mechanistic effects of acupuncture at the clinical level. The findings of this study will provide valuable reference for future research and help develop new strategies to improve PD treatment.

Methods

This study adhered to the overall reporting guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 checklist and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).^{24,25} The details of sham acupuncture are in accordance with the latest SHam Acupuncture REporting guidelines and a checklist in clinical trials (SHARE) guidelines.²⁶

Involvement from Patients and the Public

During the protocol design phase, dedicated investigators conducted verbal consultations with patients presenting at the outpatient clinic with motor symptoms of PD to assess their willingness and previous experience with acupuncture therapy, as well as the frequency of treatment they would most readily accept. Additionally, the investigators inquired about their willingness to participate if this study were to be conducted. After completing the survey, the investigators compiled patient feedback, which was used to refine certain aspects of the protocol, including the estimated duration of the study and the number of acupuncture sessions. The planning and details of reporting the study results were not developed with direct involvement from patients or the public.

Study Design

This RCT was designed as a multicenter study with blinding to the principal investigators (study designers, outcome assessors, and statisticians) and participant, no blinding to the acupuncturists, parallel randomization, superiority trial design. A total of 136 eligible participants were randomly assigned in a 1:1 ratio to either the acupuncture group (n=68) or the sham acupuncture group (n=68) following baseline assessments (Table 1 and Figure 1). The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Tianjin University of Chinese Medicine and other

Table 1 Inclusion Criteria

Time Point	-t1	0	t1	t2	t3	t4	t5
		Day 0	Week 1	Week 2	Week 3	Week 4	8-Weeks
Enrolment							
Eligibility screen	X						
Informed consent	X						
Baseline information	X						
Random Allocation		X					
Interventions							
MA			←————→				
Sham MA			←————→				
Assessments							
UPDRS III	X		X	X	X	X	X
ReadyGo		X	X	X	X	X	X
HY	X		X	X	X	X	X
ADL		X	X	X	X	X	X
PDQ-39		X	X	X	X	X	X

(Continued)

Table I (Continued).

Time Point	-t1	0	t1	t2	t3	t4	t5
		Day 0	Week 1	Week 2	Week 3	Week 4	8-Weeks
LEDD		X	X	X	X	X	X
Blood sample		X				X	
Adverse events			X	X	X	X	X

Notes: "X": indicates collection of the corresponding data or information at this time point; "↔": indicates that the corresponding intervention is performed during this time period.

Abbreviations: MA, manual acupuncture; Sham MA, Sham acupuncture; UPDRS III, Unified Parkinson's Disease Rating Scale III; HY, Hoehn-Yahr Scale; ADL, Activity of Daily Living Scale; PDQ-39, The Parkinson's Disease Questionnaire-39; LEDD, levodopa equivalent daily dose.

participating centers (TYLL2025[K]) and registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR2025001351).

Trial Setting

This trial was conducted at five centers in China: the First Affiliated Hospital of Tianjin University of Chinese Medicine, Tianjin Huanhu Hospital, Tianjin Beichen District Chinese Medicine Hospital, Tianjin Medical University General Hospital, and Guangdong Provincial Hospital of Chinese Medicine. During the study period, acupuncture was administered in dedicated acupuncture rooms established in the outpatient or inpatient departments of each center. Each acupuncture bed was separated by curtains, ensuring privacy and independence of each subject during the acupuncture treatment, unaffected by the research environment.

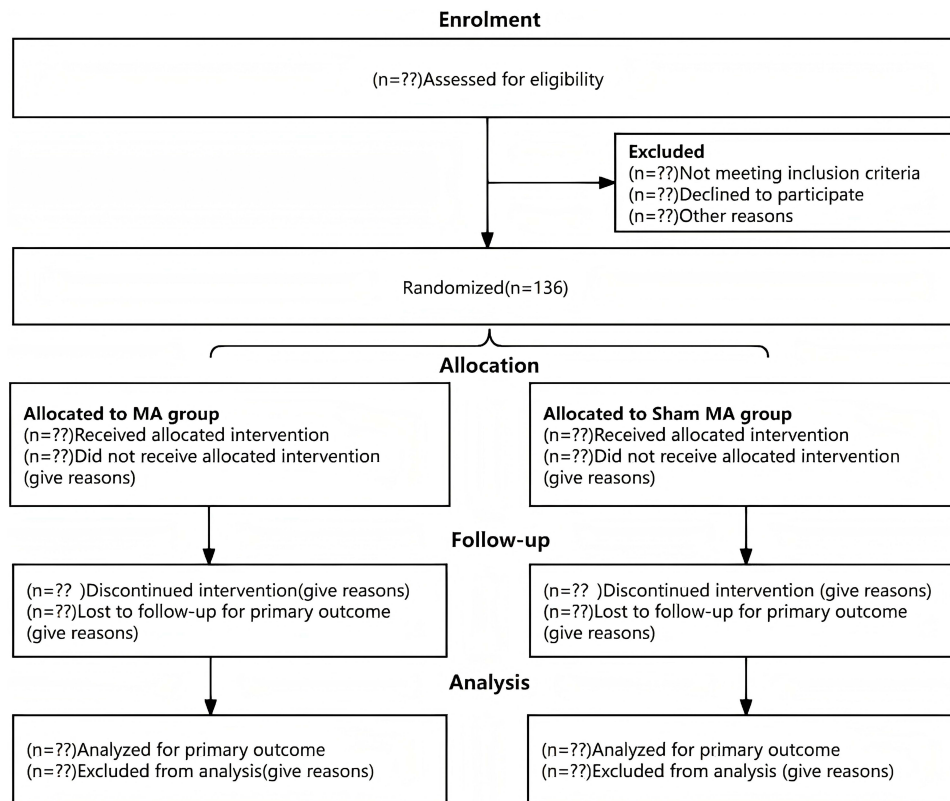


Figure 1 Study flow (The "??" symbol indicates the number of subjects who met this item).

Participant Recruitment and Consent

Participant recruitment will be conducted through multiple channels at each trial center, including outpatient clinics, recruitment posters, and official WeChat accounts. For individuals who meet the eligibility criteria determined by clinical physicians, the researchers will provide a thorough explanation of the trial objectives, procedures, content, and relevant details. After ensuring complete understanding, the participants or their legally authorized representatives will provide informed consent before proceeding to the next phase.

Eligibility Criteria

Diagnostic Criteria

Diagnostic criteria for PD were based on the 2015 MDS Diagnostic Criteria. These diagnostic criteria have been validated in the population with PD in China and demonstrate higher sensitivity and specificity than alternative criteria.^{6,27}

Inclusion Criteria

- (1) Meeting the above diagnostic criteria.
- (2) Aged 30–75.
- (3) Hoehn & Yahr stage ≤ 2 .
- (4) The presence of one or more TRAP core motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS).
- (5) Clear consciousness, normal cognition, and the ability to understand and cooperate with relevant assessments and examinations.
- (6) Having been using a stable dose of levodopa for the past 30 days.
- (7) Voluntarily signing and providing informed consent.
- (8) Have not received acupuncture treatment within the past six months.

Exclusion Criteria

- (1) Having motor symptoms attributable to other diseases.
- (2) Having uncorrectable coagulopathy or bleeding tendency, leading to the inability to receive acupuncture.
- (3) Previously underwent DBS or other surgery related to PD treatment.
- (4) With a history of psychiatric disorders, substance-use disorders, or epilepsy, or current use of antipsychotics or antidepressants.
- (5) Severe primary diseases of the circulatory or respiratory system (or other serious primary diseases).
- (6) Currently participating in other clinical studies.

Dropout Criteria

Participants will be considered to drop out of the trial due to the following reasons:

- (1) The participants withdrew their informed consent or were lost to follow-up owing to lack of treatment efficacy or other reasons.
- (2) Participants were unable to continue participating in the study owing to adverse events (AEs), disease progression, or other uncontrollable factors.

Elimination Criteria

Participants will be eliminated from the trial due to the following reasons:

- (1) A diagnosis error.
- (2) Assignment to an incorrect group for any reason.
- (3) Poor compliance and failure to cooperate in completing the acupuncture treatment course during the trial.
- (4) The established protocol was violated during the study period, and other therapies that compromised the evaluation of the overall therapeutic effect were arbitrarily used.

Discontinuation Criteria

If a participant experiences a serious adverse events (SAEs) or other significant incident during the study, the clinical investigator will report it, and the Clinical Events Committee (CEC) will jointly determine whether continuation of the trial is inappropriate; if this were the case, the study would be discontinued.

Dropout, Discontinuation, and Exclusion Handling Procedures

In the event of a dropout, elimination, or discontinuation, the responsible investigator must document the reasons in detail, file them in the study records, and report them to the Data Monitoring Committee (DMC). For participants who experience special circumstances but are not lost to follow-up, the responsible investigator should encourage and provide multiple means, such as phone calls, to facilitate completion the follow-up and data collection. If a participant experiences special circumstances due to a AEs/SAE, the responsible investigator will implement appropriate measures based on the situation to ensure the safety of the participant.

Termination Criteria

Considering that the safety of acupuncture has been widely recognized, in consultation with the research team and DMC, pre-specified stopping criteria triggered by AEs related to acupuncture were not established. However, if any center commits a significant error, resulting in the full disclosure of blind information, the termination criteria for this trial will be activated. Only the DMC had the authority to terminate the entire study.

Randomization

A third party (responsible only for randomization) personnel will use a centralized randomization system developed by the research team, specifically for evidence-based acupuncture research, to randomly allocate 136 eligible participants according to a 1:1 ratio using stratified (by center) block randomization (block size set as four or six modules according to center sample size). The detailed randomization procedure involved randomization staff collecting the necessary participant information and entering it into a central randomization system. Upon receiving the data, the system automatically assigns groups. The randomized personnel then forwarded the group assignment to the designated acupuncturist via the backend of the system.

Blinding and Allocation Concealment

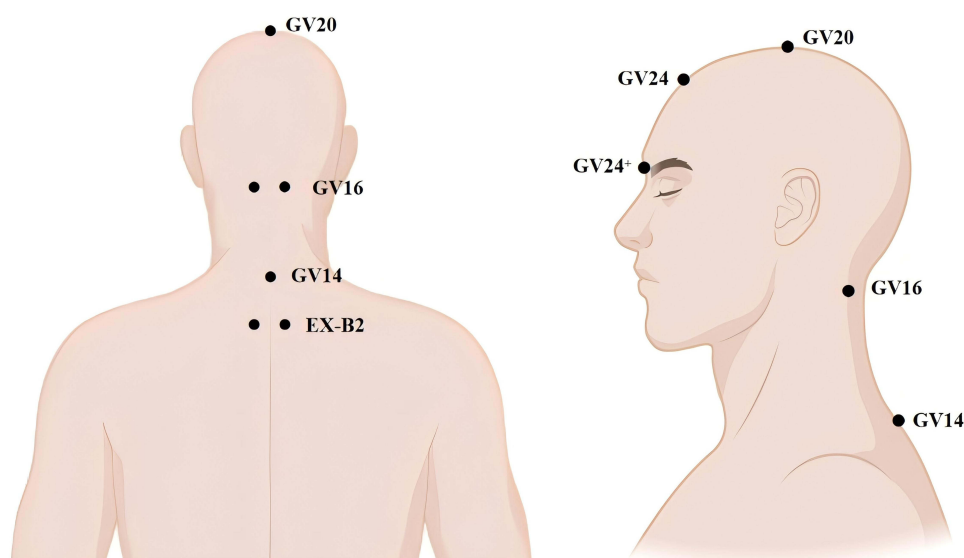
The trial employed a double-blind design for both the principal investigators (study designers, outcome assessors, and statisticians) and participants. Due to the specific nature of acupuncture clinical trials, the acupuncturists performing the treatments were not blinded in this study. Randomization was performed by independent personnel using a central randomization system. The allocation sequence was unpredictable and concealed prior to assignment, and the results were communicated to acupuncturists through the backend of the system, ensuring the rigor of allocation concealment. The principal investigators independently worked under rigorous allocation concealment to ensure that blinding was maintained throughout the study. Furthermore, owing to the lack of reliable tools in most previous acupuncture clinical trials, achieving complete blinding of the participants during the entire acupuncture procedure has been challenging. For this purpose, we developed MoCAD. The overall MoCAD enclosure is hemispherical, featuring five channels on the device shell: one at the top, two at a 45-degree angle, and two near the bottom, which can meet the diverse requirements of perpendicular, oblique, and horizontal acupuncture techniques in clinical practice. Meanwhile, the MoCAD includes two type, MoCAD-A and MoCAD-B. Among them, MoCAD-A's base is hollow and is used for the acupuncture group, while the MoCAD-B's base is impermeable and equipped with a disposable blunt acupuncture needle is used for the sham acupuncture group. When acupuncturist used the MoCAD-B to manipulate, simulates the sensation of needle insertion on the skin's surface without penetrating the skin or acupuncture points to evoke the "de qi" sensation, thereby ensuring that subjects remain blinded during the acupuncture procedure. The details of the MoCAD have been documented in previous studies.²³ Additionally, blinded study information will be stored in duplicate by independent randomization personnel and a central system. Should emergency unblinding be necessary during the study, it will be conducted in accordance with established protocols.

Table 2 Acupoints Detail

Acupoints	Location	Angle	Depth
GV20	In the head, 5 cun directly above the midpoint of the anterior hairline, or at the midpoint of the line connecting the tips of the ears.	The needle is inserted at a 15° angle to the body surface.	12.5–20mm
GV24	In the head, 0.5 cun directly above the midpoint of the anterior hairline.	The needle is inserted at a 15° angle to the body surface.	12.5–20mm
GV24+	In the head, the depression at the midpoint of the inner ends of both eyebrows.	The needle is inserted at a 15° angle to the body surface.	7.5–12.5mm
GV14	In the spinal region, in the depression below the spinous process of the 7th cervical vertebra, along the posterior midline.	The needle is inserted perpendicularly at a 90° angle to the body surface.	12.5–25mm
GV16	In the nape, 1 cun directly above the midpoint of the posterior hairline, in the depression between the trapezius muscles, just below the external occipital protuberance.	The needle is inserted at a 15° angle to the body surface.	12.5–25mm
EX-B2	In the spinal region, on both sides of the spinous processes from the 1st thoracic to the 5th lumbar vertebra, 0.5 cun lateral to the posterior midline.	The needle is inserted at a 15° angle to the body surface.	12.5–25mm

Treatment Protocol

All the participants underwent foundational treatment administered by clinicians in accordance with the American Academy of Neurology’s Clinical Practice guidelines for early PD and the 2020 Chinese “Parkinson’s Disease Treatment (4th edition)”. Foundational treatment included medications, such as levodopa and levodopa combination therapies, to alleviate PD symptoms.²⁸ The responsible personnel record the initial dose of the medication and information on any changes, documenting these details in the Case Report Form (CRF). Furthermore, manual acupuncture (MA) will be used as the acupuncture type in this trial, given its demonstrated effectiveness in previous research.^{8,17} Both MA and sham MA procedures will be administered by licensed acupuncturists with at least five years of experience at each center, with no more than two practitioners involved to reduce operator bias. Acupoint selection was based on the clinical practice of the research team and related evidence, utilizing Yintang (GV24⁺), Shenting (GV24), Baihui (GV20), Dazhui (GV14), bilateral Fengfu (GV16), and Jiaji (EX-B2), among them, the EX-B2 points include all the EX-B2 acupoints on both sides of the spinous processes from the 1st thoracic to the 5th lumbar vertebra. All acupoint localizations were referred to the 2021 Chinese publication of “Nomenclature and Location of Meridian Points” (Table 2 and Figure 2).

**Figure 2** Detail of acupoints.

Acupuncture Group

The responsible acupuncturist performed acupuncture treatment daily at 10:00 AM \pm 30 min in the dedicated acupuncture room at each center. Patients were instructed to relax and assume a sitting position while avoiding unnecessary communication. The total acupuncture treatment cycle lasted four weeks, with three sessions per week, and the needle retention time was 30 min per session. Specific details are listed as follows. The acupuncturist performed routine disinfection using alcohol swabs to disinfect areas at the GV24⁺, GV24, GV14, GV16, and EX-B2 acupoints. The adhesive pad at the bottom of MoCAD-A was peeled off and applied to the selected acupuncture points on the skin. The corresponding needle catheter was inserted depending on the insertion angle for each acupoint. It should be noted that the MoCAD-A device covers insertion angles from 0° to 180° and has a circular hollow design at the bottom, which does not interfere with the acupuncturist's needle insertion technique. The acupuncturist then selected a disposable stainless steel acupuncture needle (0.25 mm \times 40 mm or 0.25 mm \times 25 mm, Suzhou Medical Supplies Factory, Huatuo brand), placed it into the catheter, and used the Flick-finger needle insertion technique to insert the needle into the acupoints. The depth was adjusted to locally induce the sensation of “de qi”. Specific details of the insertion direction, angle, and depth are listed in [Table 2](#).

Sham Acupuncture Group

Given that the efficacy of acupuncture has been questioned due to the “placebo” effect, we established a sham acupuncture group in this study. To maximize the demonstration of the specific therapeutic effects of acupuncture, the duration of treatment, communication information, course of treatment, and detailed procedures in the sham acupuncture group were kept consistent with those in the acupuncture group, and the same was applied to acupoint selection. The only difference was that the sham acupuncture group used MoCAD-B and 0.25 mm \times 40 mm or 0.25 mm \times 25 mm sterile stainless steel blunt-tip needles (Suzhou Medical Supplies Factory, China) in the specific acupuncture procedures. The functions of MoCAD-B have been previously described. In brief, it does not induce the sensation of “de qi” and prevents unblinding.

Outcomes

Primary Outcome

The primary outcome was assessed using the UPDRS-III, evaluated by clinical physicians. The UPDRS-III includes 16 items, each item with professional guidelines for standardizing the assessment process and offers five response options: 0 (normal, no disability), 1 (mild, symptoms noticeable but without impact on physical function), 2 (moderate, affecting independent activities), 3 (moderate, affecting normal life), and 4 (severe, unable to perform normal activities), with lower scores indicating better functioning. Additionally, the UPDRS-III includes supplementary items for recording medication and “on-off” phase information. The validity and reliability of the UPDRS-III have been extensively validated, and the minimum clinically important difference (MCID) is 3.25 points.^{29–31} Currently, the UPDRS-III has become the core tool for assessing motor symptoms of PD and, therefore, served as the primary outcome in this study.

Secondary Outcomes

- (1) ReadyGo Motion Function Quantitative Evaluation System: The ReadyGo system (Beijing Zhongke Ruiyi Information Technology Co., China) was equipped with independent capture cameras and time-of-flight sensors. It incorporates tracking and recognition algorithms into the system and a deep neural network algorithm based on long short-term memory (LSTM) for enhanced analysis.³² Based on these characteristics, without requiring participants to wear any devices, ReadyGo can precisely identify and capture the spatiotemporal characteristics of up to 32 joint points in three-dimensional space in patients with PD, and further extract frame-by-frame motion sequences of each joint point during the walking process from tracking images. Spatiotemporal and kinematic parameters are input into the algorithm and iteratively calculated to derive refined gait outcomes, such as stride length, gait speed, and swing velocity.^{32,33}
- (2) Hoehn and Yahr (HY) Scale: The HY scale is a clinician-assessed tool primarily designed to evaluate motor dysfunction and deficits in patients with PD, aiming to reflect the overall severity of PD.³⁴ The HY scale has been validated for its effectiveness in assessing motor function and has the characteristics of simple operation, making it a widely accepted and authoritative tool internationally. The scale includes eight stages ranging from Stage 0 (no symptoms) to Stage 5 (requiring a wheelchair or being bedridden), with higher stages indicating more severe disabilities.

- (3) Activities of Daily Living Scale (ADL): The ADL scale includes 10 items designed to assess the ability to perform daily activities, such as dressing, washing, and other seven dimensions of normal living. The total score ranged from 0 to 100, with higher scores indicating greater independence in daily activities.
- (4) Parkinson's Disease Questionnaire-39 (PDQ-39): The PDQ-39 is a patient-reported outcome (PRO) tool specifically designed to assess the quality of life of patients with PD. It is currently the most widely used tool in the field of PD and has been proven to effectively focus on issues that are most important to patients in clinical settings. Its reliability and validity have been well-established.^{35,36} The PDQ-39 consists of 39 items that reflect eight major areas of life, including motor function, social situations, and communication. It uses a four-point scoring system with a total score ranging from 0 to 48, with higher scores indicating poorer quality of life.^{35,36}
- (5) Levodopa Equivalent Daily Dose (LEDD): A change in LEDD was observed before and after treatment. LEDD was calculated by recording the daily doses of anti-Parkinsonian medications throughout the study period, converting each dose to its levodopa equivalent dose (LED), and summing the daily LEDs to obtain the LEDD.³⁷
- (6) Bang's Blinding Index (BBI): A BBI assessment was conducted after treatment to evaluate the success of participant masking. Participants were asked to report whether they believed they had received real acupuncture, sham acupuncture, or were uncertain. BBI was calculated according to the participants' treatment guesses to quantify the degree of blinding, with values close to 0 indicating random guessing and successful blinding.

Outcome Assessments

All outcome assessments were performed by independent qualified, assessors at weeks 1, 2, 3, and 4, with a total of four assessment points. The assessors were blinded to participants group. Primary outcomes were followed up until 8 weeks post-treatment.

Additional Outcome-Omics Sample Collection and Analysis

Peripheral blood samples were drawn from participants by a nurse at baseline and after treatment completion at 6:30 AM and were collected in EDTA anticoagulant tubes. A third-party technician separated the serum samples by centrifugation at 4000 rpm, 4°C for 15 min, aliquoted 200 µL of the supernatant into each cryovial tube, and stored the samples at -80°C. Upon completion of the study, serum samples were sent to the Shanghai OuYi Biological Company for LC-MS/MS full-spectrum metabolomics and deep blood proteomics analyses, with specific testing procedures described in previous studies.^{38,39}

AEs and Safety Assessment

Common AEs with acupuncture include hematoma, bruising, and pain. AEs were reported by the participants or discovered by acupuncturists and researchers. Once an AE occurs, the acupuncturist or researcher must immediately manage it to ensure it does not progress and inform the subject of potential impacts that may result from the AE. Meanwhile, it will be reported to the CEC for causality assessment according to the World Health Organization Uppsala Monitoring Centre standard (WHO-UMC).⁴⁰ The CEC will be composed of acupuncturists selected by each center independently of the research. Additionally, AEs will be documented in detail by researchers in the CRF, including the name, onset and resolution time, management approach, causality assessment, and severity classification. SAEs were defined as death, hospitalization, prolonged hospitalization, or any other severe impairment of function or life-threatening condition during the study period. The handling process for SAEs was the same as that for AEs. The DMC reviewed both AEs and SAEs every 6 months.

Data Entry and Management

Data assessors and entry personnel used both paper forms and an Electronic Data Capture (EDC) system for CRF data entry. To ensure the accuracy and completeness of data evaluation and entry, an independent monitoring assistant oversaw the process throughout the assessment and data entry phases. All CRF data were stored at the Clinical Quality Management (GCP) center during the study period and uniformly archived at the GCP Center of the First Affiliated Hospital of Tianjin University of Chinese Medicine upon completion of the trial. The DMC will review the completeness and accuracy of the data every six months to ensure compliance with the study requirements and relevant regulations.

Quality Assurance

All established procedures in this trial, including informed consent communication and signing by the responsible investigators, randomization steps performed by independent personnel, and communication and treatment processes conducted by acupuncturists underwent standardized training in accordance with Standard Operating Procedures (SOPs).

Sample Size

The sample size was calculated using the Power Analysis and Sample Size (PASS) version 15 superiority module based on the primary outcome of the UPDRS III. The parameters were set as follows: significance level (α) = 0.05 and power (β) = 0.9. According to previous research, the mean difference (MD) and standard deviation (SD) between the acupuncture group and the control group were 16.4 ± 20 . The superiority margin was determined to be five points based on the MCID of the UPDRS III, combined with consensus opinions from the research team.^{31,41} Considering a 20% dropout rate, 68 participants per group (136 participants in total) provided 90% of the statistical power, meeting the requirements of this trial.

Statistical Analysis

Data analysis for this study was performed using R, Version 4.3.3, with α set to 0.05. The analysis sets in the data analysis plan include the modified intention-to-treat (mITT) and per-protocol set (PPS). The mITT group was defined as participants who were randomized and received at least one treatment, and the PPS group was defined as participants who successfully completed the treatment protocol. Baseline characteristics were analyzed descriptively. Continuous variables were tested for normal distribution; normally distributed data were presented as $MD \pm SD$, while non-normally distributed data were expressed as median and interquartile range (M[P25, P75]). Categorical variables were analyzed using the chi-square test and reported as counts (percentages). The primary outcome was analyzed using the Linear Mixed-Effects Model (LMM) according to a predefined analysis plan. The dependent variable was the UPDRS III score, with fixed effects including group-time interaction, age, sex. Random effects included individual random intercepts and study center effects. Under the assumption of missing completely at random (MCAR) or missing at random (MAR), the LMM provides a valid statistical inference without the need for the imputation of missing values.⁴² For nonrandom missing data (MNAR), appropriate imputation methods were applied depending on the extent of missingness. The primary outcome analysis results were reported as least squares means (MD) and 95% confidence intervals (95% CI). Secondary outcomes were analyzed using the same model as the primary outcomes, and the results were presented in an identical format. Sensitivity analysis was performed by comparing the outcomes of the mITT and PPS analysis sets to verify the reliability of the results.

Discussion

PD is a common progressive neurodegenerative disorder that severely affects patients' quality of life and daily functioning, and early intervention is of great significance for delaying disease progression, maintaining motor function, and improving long-term outcomes. Currently, although acupuncture therapy has been confirmed to have potential clinical value in ameliorating early motor and non-motor symptoms of PD and improving quality of life. However, current clinical evidence for acupuncture in treating PD remains inconsistent; previous studies generally suffer from issues such as flaws in research design and methodology, high heterogeneity in acupuncture protocols, and insufficient reporting of efficacy outcomes, limiting the reliability and generalizability of the research results. Furthermore, although some studies have revealed the potential mechanisms of acupuncture in treating PD, most have focused on basic research and lack clinical data for more direct verification of their therapeutic mechanisms. Therefore, addressing the problems generally existing in current research, this study adopted a more rigorous research design. It aims to clarify the efficacy of acupuncture on motor symptoms in early PD through an evidence-based RCT, providing high-quality evidence for the management of motor symptoms in early PD using acupuncture, while further utilizing multi-omics approaches to investigate the potential mechanisms of acupuncture in treating PD.

Firstly, regarding the methodological rigor of the study design, particularly in terms of randomization and blinding, this study employs a self-developed randomization system and a MoCAD device to address these issues. Regarding randomization, it is a key process for initiating high-quality RCTs and a crucial link for inferring the causal strength of acupuncture efficacy; flaws in randomization will lead to between-group differences in confounding factors that affect efficacy evaluation, thereby reducing the credibility of the study results.^{43,44} Based on this, this study adopts a self-developed randomization system, in which the built-in stratified block randomization method can compensate for randomization flaws. Regarding blinding, due to the inherent specificities of acupuncture clinical research, it is difficult to blind acupuncturists, making blinding setup long regarded as a formidable challenge.⁴⁵ Analysis of existing high-quality evidence-based acupuncture research indicates that the most appropriate method for blinding is to ensure that principal investigators and participants remain blinded throughout the process.^{8,17} In this trial, we not only use the self-developed randomization system to ensure allocation concealment, but also developed a MoCAD device capable of simulating the sensation of acupuncture stimulation, making it difficult for the sham acupuncture group to guess their group assignment, thereby reducing the risk of subject bias to ensure the rigor of blinding.⁴⁵ Sham acupuncture devices such as MoCAD, currently widely used in research, face problems such as limited needle insertion angles that restrict clinical practice operations and invasive procedures that amplify the placebo effect; the self-developed MoCAD device used in this study addresses the aforementioned two problems,^{23,46} further enhancing the rigor of the study design.

Secondly, addressing the issue of high heterogeneity in acupuncture protocols, this study adopted a standardized acupuncture intervention protocol to enhance the consistency and reproducibility of the intervention. Integrating traditional Chinese medicine theory with modern clinical practice, this study used the acupoints such as GV24 and GV14; existing evidence indicates that acupuncture at GV24, GV14, and related points can improve UPDRS scores by approximately 40% compared to baseline, while also reducing the risk of falls.^{22,47} Furthermore, the study standardized the qualifications of acupuncturists while implementing standardized training to minimize operator bias. Through the standardization of acupoint selection, acupuncturist qualifications, and procedures, the therapeutic effects were maximized.

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Additionally, addressing the issue of insufficient feedback on therapeutic efficacy, this study introduced the Ready system. Although current research primarily relies on the subjective assessment tool UPDRS III to evaluate therapeutic outcomes, it remains susceptible to factors such as rater bias, leading to variability in efficacy.^{29,31} Previous studies have confirmed that acupuncture treatment can ameliorate balance symptoms among typical core motor symptoms of Parkinson's disease, such as gait speed and stride length.⁴⁸ Therefore, we introduced the Ready system to quantify gait-related outcomes in balance and combined it with UPDRS III, thereby combining subjective and objective assessment tools to provide more comprehensive feedback on the efficacy of acupuncture. Ultimately, through a rigorous design, comprehensive feedback, and study implementation, this study aims to strengthen the evidence chain for acupuncture treatment of early PD motor symptoms.

It is worth noting that regarding that the pathogenesis of motor symptoms in PD involves microglial polarization and the dysregulation of apoptosis-related proteins. And existed studies have shown that acupuncture at the chorea control area near GV24 can, on one hand, inhibit the polarization of the M1 microglial subtype by mediating glucose metabolic pathways,⁴⁹ and on the other hand, regulate the ratio of apoptosis-related proteins Bax/Bcl-2 by inhibiting the SIRT1/AMPK signaling pathway,⁵⁰ thereby ameliorating PD-related symptoms through multiple pathways. However, most existing studies on the metabolic and protein-related mechanisms of acupuncture for PD motor symptoms are basic research, and studies providing direct evidence in a clinical setting are still lacking. Against this background, this study

intends to further employ full-spectrum metabolomics and deep proteomics, and apply high-throughput sequencing methods to fill this gap.

Overall, this study addressed the limitations regarding the rigor of randomization and blinding in previous studies and further utilized the validated subjective assessment tool UPDRS III, combined with objectively quantified gait results from the Ready system, to comprehensively and clearly elucidate the efficacy of acupuncture in treating motor symptoms of early PD. Moreover, multi-omics approaches will be used to provide neurobiological evidence at the metabolic and protein levels regarding the clinical dimensions of acupuncture in treating motor symptoms of early PD. However, this study has limitations; most participants will come from fixed regions, such as Tianjin and Guangdong Province, and due to budget constraints, the sample size is relatively small, which may affect the generalizability of the study results.

Reporting Checklist

The authors have completed the SPIRIT reporting checklist.

Data Sharing Statement

The CRFs will be preserved in a locked cabinet at the participating hospitals and can be accessed by the research team only. Patient identifiable data will be used to provide clinical care and follow-up merely, and the trial database will be anonymized. The aggregated research findings will be submitted for publication in a peer-reviewed clinical journal to have widespread dissemination. The original paper files and electronic data will be preserved for at least 5 years after publication, which can be accessible from the corresponding author, Lin wang, with appropriate reasons.

Ethical Approval and Consent to Participate

The study followed the ethical standards established in the 1961 Declaration of Helsinki. This protocol has been registered in International Traditional Medicine Clinical Trial Registry (ITMCTR2025001351) and approved by the Ethics Committee of the First Affiliated Hospital of Tianjin University of Chinese Medicine and other participating centers. Written informed consent will be obtained from all participants.

Author Contributions

Jiewen Zhang and Yici Xie are the co-first authors. Nenggui Xu and Lin Wang are corresponding authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

No potential conflict of interest was reported by the author(s).

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