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Research paper

Acupuncture for improving gait disturbance in Parkinson's disease: A study protocol for a pilot randomized controlled trial

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ABSTRACT

Introduction: Parkinson's disease (PD) is the progressive neurodegenerative disorder, characterized by bradykinesia, resting tremor, and muscle rigidity. Levodopa constitutes the preferred treatment for PD, but is limited by attenuated drug effect and dyskinesia. Therefore, alternative approaches may be useful to enhance levodopa treatment. Acupuncture may relieve PD symptoms, but there is little evidence to support its efficacy. We will assess whether acupuncture improves mobility, and will identify acupuncture-related changes in hemodynamic parameters and neurotransmitter levels, in PD patients with gait disturbance.

Methods: An assessor-blinded, randomized, controlled parallel trial will be conducted in 26 patients diagnosed with PD and gait disturbance. Patients will be randomly allocated to control (n = 13) or intervention groups (n = 13). Intervention will consist of acupuncture for 4 weeks and follow-up for 4 weeks. Control patients will not receive acupuncture and will be followed for 8 weeks. Conventional treatment will be allowed for both groups.

Results: Primary outcome measure is gait speed using GAITRite analysis. Secondary outcome measures are fNIRS-measured hemodynamic changes in motor and prefrontal cortices, along with neurotransmitter alterations, mobility parameters, and immediate, cumulative, and sustained effects of acupuncture.

Discussion/Conclusions: This trial will evaluate clinical effects of acupuncture in PD patients, and will confirm whether acupuncture alters neurotransmitter levels and associated activities. We expect improvement in gait parameters, changes in motor and prefrontal cortex activity, and changes in neurotransmitter activity, thereby providing insight into the therapeutic mechanism of acupuncture in PD and supporting further studies of whether acupuncture may improve motor symptoms in PD.

1. Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder [1]. PD is a complex disease and includes both motor and non-motor symptoms. Representative symptoms include bradykinesia, resting tremor, and muscle rigidity, which occur due to striatal dopamine depletion [2,3]. The gold standard pharmacological treatment for PD is levodopa (L-DOPA), however L-DOPA is limited by its effectiveness which decreases over time and has well known side effects including motor response oscillations and dyskinesia [2,4]. New treatment strategies that overcome these limitations are required.

Acupuncture has been widely used as a complementary and alternative medicine to relieve the symptoms of PD in Asia, Europe, and the United States, but its therapeutic effect remains controversial [5,6]. Many studies have demonstrated the beneficial effects of acupuncture in patients with PD, including improvement of motor symptoms (gait disorder and balance) and non-motor symptoms (psychiatric disorders, sleep problems, and gastrointestinal symptoms) [5,7–11]. In addition, acupuncture has been shown to reduce the dosage of L-DOPA required along with its side effects [11]. Thus, acupuncture has potential as a complementary therapeutic agent to alleviate the symptoms of PD and minimize the side effects of L-DOPA.

Neuroimaging has been used to improve our understanding of the anatomical regions of the brain, connections between these regions, and the associated changes in neurotransmitter (NT) level and function, which are thought to be altered in PD [12]. Functional neuroimaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and functional near infrared spectroscopy (fNIRS) measure cerebral blood flow and have been commonly used to study the activity and functional connectivity of networks within the brain. Among these techniques, fNIRS is suitable for brain imaging in patients with gait disorders.

Previous fNIRS studies have demonstrated changes in hemodynamic

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response within the prefrontal and motor cortices during walking and running [13]. The brain regions associated with PD have previously been identified [12]. PD is characterized by α-synuclein protein aggregation, known as inclusion bodies that develop and spread from the medulla to the entire neocortex [12,14]. These regions coincide with the location of projection neurons of neurotransmitters. A recent study found that the glutamate/gamma-aminobutyric acid (GABA) ratio, and plasma and serum levels of aspartic acid, taurine, and L-serine were lower in patients with PD compared to healthy controls [15]. Although several NTs in the brain are known to be related to the pathogenesis of PD, it has been demonstrated that the levels of NTs in plasma, serum and the central nervous system are partially related [16] and that the permeability of the blood-brain barrier is increased in patients with PD [17]. Taken together, analysis of both neuroimaging and NTs may be important for elucidating the therapeutic mechanisms by which acupuncture may benefit patients with PD. However, few studies have investigated the hemodynamic changes in the prefrontal and motor cortices using fNIRS as well as the changes in NTs in patients with PD.

The aim of this study is to evaluate the clinical effects of acupuncture on gait disturbance in patients with PD and identify hemodynamic changes that occur in the motor and prefrontal cortices using fNIRS. In addition, changes in plasma and serum NTs will be measured to elucidate a possible mechanism for improvement of motor symptoms following acupuncture in these patients.

2. Method and design

2.1. Study design

This study is a prospective, assessor-blinded, randomized, controlled, parallel-group pilot trial. Patients with PD and gait disturbance who meet the inclusion criteria will be enrolled and randomly allocated to the control group (conventional treatment alone) or intervention group (acupuncture treatment + conventional treatment). The duration of the study will be 8 weeks, and comprises the intervention phase (4 weeks), during which the subjects will receive acupuncture 2 days per week, and the follow-up phase (4 weeks), during which subjects will be assessed for sustained effects of acupuncture. The control group will not receive acupuncture treatment and will be followed up for 8 weeks. The study design is summarized in Fig. 1. All interventions and assessments will be performed in the dopaminergic "on" state (the same time in each patient, after taking the last dose of conventional treatment). The primary outcome measure is the speed of gait, which will be measured using the GAITRite system (GAITRite system; CIR Systems Inc, Sparta, NJ, USA). The secondary outcome measures include hemodynamic changes in the motor and prefrontal cortices as measured by fNIRS, changes in neurotransmitter levels, gait parameters (cadence, stride time, stride length, temporal symmetry index, spatial symmetry index) collected from the GAITRite system (except the speed parameter), the Unified Parkinson's Disease Rating Scale (UPDRS) score, and the immediate, cumulative and sustained effects of acupuncture in patients with PD. The timing and number of assessment of outcomes will vary according to the study parameter being measured (Fig. 2).

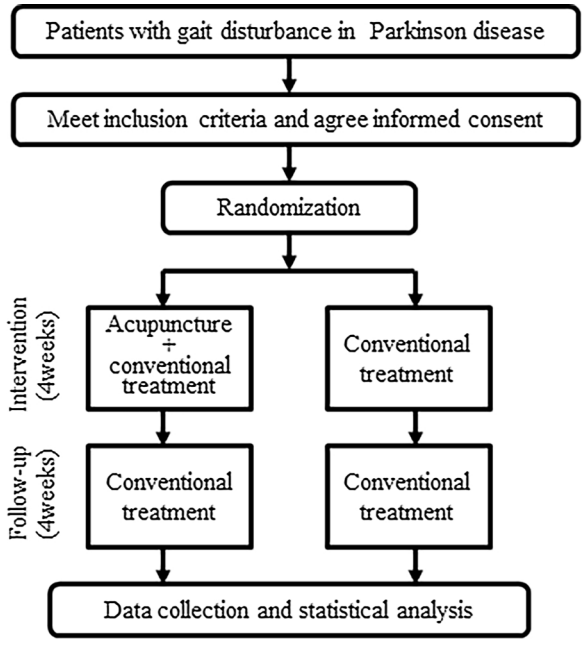

Fig. 1. A flowchart showing details of the parallel-group randomized trial.

2.2. Participants and recruitment

Subjects will be recruited via posters placed in the community and hospital, local newspapers, and the inpatient and outpatient departments at Dunsan Korean Medical Hospital. Recruitment is scheduled to occur from January 2018 to June 2018. After a face-to-face consultation and provision of information regarding the study protocol from the study coordinator, patients who meet the inclusion criteria and provide written informed consent will be enrolled in the study and then randomly allocated to the control group or the intervention group.

2.3. Inclusion and exclusion criteria

The inclusion criteria are as follows: a diagnosis of PD made by a neurologist; ability to walk 10 m; Hoehn and Yahr scale stage 1–4; and a stable dose of conventional treatment for at least 1 month prior to enrollment.

The exclusion criteria are as follows: Patients with Alzheimer's dementia, vascular dementia, Huntington's disease, Amyotrophic lateral sclerosis or hydrocephalus; gait disturbance caused by stroke, brain tumor, or other brain disease; a diagnosis of gastrointestinal disease, endocrine disease, or cardiovascular disease not controlled by diet or medication; unstable medical condition as decided by the research clinician; a history of neuropsychiatric disorder; allergy to stainless steel or metals; treatment for gait disturbance within the last 2 weeks; participation in another clinical trial within the last 4 weeks; inability to undergo fNIRS.

2.4. Randomization and allocation concealment

The Clinical Trial Center at Dunsan Korean Medical Hospital of Daejeon University will be responsible for allocation sequence, enrollment of subjects, and assignment of subjects to interventions. Computer-generated block randomization will be used to allocate all subjects to the control or intervention group and will be performed by an independent statistical researcher not involved in the study. An opaque envelope containing an identification code for each subject will be provided to the research nurse. The research nurse will also provide assignment information to the practitioner and assessor.

2.5. Blinding

In this study, it is impossible to blind the subjects and practitioner because the control group will not be receiving acupuncture treatment. Therefore, the study has been designed to be assessor-blinded to minimize bias. The assessor and statisticians collecting and analyzing the data will be blinded to the group allocation. The outcomes will be evaluated by two assessors, one of whom will be blinded (assessor A) and another, who will not be blinded (assessor B). Assessor A will evaluate outcomes in the control and intervention groups at 0, 4, and 8 weeks. Assessor B will evaluate outcomes in the intervention group, which cannot be blinded.