Study Protocol

Evaluation on the efficacy and safety of Chinese herbal medication Xifeng Dingchan Pill in treating Parkinson’s disease: study protocol of a multicenter, open-label, randomized active-controlled trial

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BACKGROUND: Parkinson’s disease (PD) is a complicated disease, commonly diagnosed among the elderly, which leads to degeneration of the central nervous system. It presently lacks an effective therapy for its complex pathogenesis. Adverse effects from Western drug-based medical intervention prevent long-term adherence to these therapies in many patients. Traditional Chinese medicine (TCM) has long been used to improve the treatment of PD by alleviating the toxic and adverse effects of Western drug-based intervention. Therefore, the aim of this study is to evaluate the efficacy and safety of Xifeng Dingchan Pill (XFDCP), a compound traditional Chinese herbal medicine, taken in conjunction with Western medicine in the treatment of PD patients at different stages in the progression of the disease.

METHODS AND DESIGN: This is a multicenter, randomized controlled trial. In total, 320 patients with early- (n = 160) and middle-stage PD (n = 160) will be enrolled and divided evenly into control and trial groups. Of the 160 patients with early-stage PD, the trial group (n = 80) will be given XFDCP, and the control group (n = 80) will be given Madopar. Of the 160 patients with middle-stage PD, the trial group (n = 80) will be given XFDCP combined with Madopar and Piribedil, and the control group (n = 80) will be given Madopar and Piribedil. The Unified Parkinson’s Disease Rating Scale scores, TCM symptoms scores, quality of life, change of Madopar’s dosage and the toxic and adverse effects of Madopar will be observed during a 3-month treatment period and through a further 6-month follow-up period.

DISCUSSION: It is hypothesized that XFDCP, combined with Madopar and Piribedil, will have beneficial effects on patients with PD. The results of this study will provide evidence for developing a comprehensive therapy regimen, which can delay the progress of the disease and improve the quality of life for PD patients in different stages.

TRIAL REGISTRATION: This trial has been registered in the Chinese Clinical Trial Registry with the identifier ChiCTR-TRC-12002150.

KEYWORDS: Parkinson disease; levodopa; drugs, Chinese herbal; drug toxicity; randomized controlled trial; clinical protocols

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1 Introduction

Parkinson’s disease (PD) is a chronic degenerative disease of the central nervous system that is a common affliction of the elderly. Its prevalence, morbidity, and mortality, as well as associated economic burdens, have been steadily increasing. Between 1997 and 1998, the incidence of PD in the Chinese population over 65 years of age was 1.7%, and there were more than 170 million PD patients over 55 years of age\(^3\). As the elderly population in China increases, the number of patients with PD is expected to double by 2030\(^2\). In 2010, the annual cost per patient was approximately 13,579.43 yuan, accounting for 17.9% of the family income and 48% of per capita income. Thus long-term care of PD patients brings a great economic burden to families and to society\(^3\). Madopar (levodopa and benserazide hydrochloride tablets), a chemical precursor of dopamine, is known as a “golden drug” for PD for its ability to restore dopamine levels in the brain. However, with chronic administration of Madopar, PD patients experience drug resistance, and an increase in side effects and adverse reactions. Piribedil, a dopamine receptor agonist, will be used when the effect of Madopar is descending. But the same adverse effects as Madopar occur gradually with a long term of administration. Patients usually stop the treatment due to the severity of these adverse effects.

Traditional Chinese medicine (TCM) has been used to treat PD for many years. TCM has potential advantages for improving clinical symptoms of PD — especially for the non-motor symptoms. Thus, appropriate use of TCM may delay the progress of PD and improve the quality of life for patients. Combining Western medicine with Chinese medicine may not only improve the clinical outcomes but also reduce medication dosage and consequently avoid some of the adverse effects of these medications.

Xifeng Dingchan Pill (XFDCP) is a traditional Chinese herbal medicine compound, and has been used effectively in treating PD patients with deficiency of both liver yin and kidney yin\(^4\). In view of our 10-year studies, the results of the pharmacological experiments, toxicological experiments and clinical trials suggested that XFDCP was a safe and valuable tool for the treatment of PD. XFDCP may act by reducing the dopamine metabolism of the striatum and protecting striatal cells. This would lead to an increase in the amount of dopamine and its metabolites (dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA))\(^5\) in the brain. In addition, XFDCP can protect the striatum from the damage caused by 6-hydroxydopamine (6-OHDA), which can lead to a low tyrosine hydroxylase (TH) activity and a decrease in dopamine content\(^6\). Previous studies have shown that XFDCP combined with Madopar can enhance clinical effectiveness of the drug by reducing the severity of clinical symptoms and by reducing side effects of Madopar\(^6\). The use of XFDCP can help to reduce drug resistance caused by the accumulation of Madopar in the body and thus reduce the dosage of Madopar necessary to relieve clinical symptoms\(^7\). However, presently, there is a lack of large-sample, multicenter, randomized clinical trials. Therefore, the aim of this proposed study is to evaluate the efficacy and safety of XFDCP combined with Western medicine in treatment of PD patients at different disease stages.

2 Methods and design

2.1 Participants

2.1.1 Diagnostic criteria of PD

PD is diagnosed according to the Diagnostic criteria for PD that have been adopted by the England Association of PD\(^8\), and the Chinese Treatment Guidelines of PD\(^9\).

2.1.2 TCM pattern criteria

The TCM pattern of liver and kidney yin deficiency is recognized by the “Diagnosis and efficacy evaluation criteria for senile tremor disease of traditional Chinese medicine (Draft)\(^10\)” and the “Guidelines for clinical research on new drugs of traditional Chinese medicine (Draft)\(^11\).” Primary symptoms include: (1) trembling of hands, arms, legs, jaw, and face; (2) stiffness of the arms, legs and trunks; (3) slowness of movement; (4) poor balance and coordination; (5) pale or red tongue with thin scanty coating, and wiry and thready pulse. Secondary symptoms include: (6) weakness in the lower back and knees; (7) dizziness; (8) tinnitus or poor hearing; (9) thirsty; (10) heat in the chest, palms and soles; (11) night sweats; (12) constipation; (13) insomnia and (14) amnesia. Diagnosis of liver yin and kidney yin is made when a patient presents all three of the following criteria: A) at least one of symptoms (1) and (2). B) all of symptoms (3), (4) and (5); C) three or more secondary symptoms (6)-(14).

2.1.3 Classification criteria

Based on the Modified Hoehn & Yahr Scale, PD patients participating in this study will be assigned to one of two groups. (1) Early stage: patients with early PD symptoms and Modified Hoehn & Yahr Scale stage between 1 and 1.5; (2) Middle stage: patients with more advanced symptoms and Modified Hoehn & Yahr Scale stage between 2 and 3.

2.1.4 Inclusion criteria

(1) Patients meeting the diagnostic criteria of PD; (2) meeting the TCM pattern criteria of deficiency in both liver yin and kidney yin (TCM diagnosis; 2.1.2); (3) meeting the classification criteria of PD (2.1.3); (4) aged between 50 and 70; (5) receive the treatments voluntarily and sign informed consent form.

2.1.5 Exclusion criteria

(1) Patients with Parkinson’s syndrome, Parkinson plus...
syndrome, hepatolenticular degeneration (Wilson’s disease), hepatic cerebroathy, cerebellar lesions, brain stem lesions, multiple sclerosis, essential tremor or other non-PD patients; (2) with serious heart, liver, or kidney diseases, multiple organ atrophy or mental illness; (3) with drugs and alcohol abuse six months prior to the study; (4) patients have already participate in other clinical intervention research program; (5) allergic to the treatment drug.

2.2.2 Randomization

The stratified and block randomization design will be adopted. The random number will be generated by SAS software and saved in a sealed envelope reserved by statistical professionals and the director of the study. The severity of disease (early and middle stage) is considered as the stratification factor. Patients in the early stage and middle stage will be enrolled equally. At each center, patients in each stage are randomized in a ratio of 1:1 to receive XFDCP or not. The clinical investigator will open the envelope to allocate the patient.

2.2.3 Blinding method

This study is open-label. However, for strengthening quality control, the data collectors and the data analyst will be blinded to the group allocation. They are separated from the clinical investigators who will be assigned in each center as the contact person to enroll the patients and preserve the randomization information. Therefore, the clinical investigators do not have any effects in enrolling patients or randomizing. Meanwhile outcome assessments will be made by an independent clinical statistician blinded to group allocation and uninvolved in providing intervention or management. All the data will be evaluated by the Henan Province Chinese Medicine Research Institute.

2.3 Interventions

According to the Modified Hoehn & Yahr, patients will be divided into early stage and middle stage (as above). For the early stage, patients in the trial group will take XFDCP, while in the control group patients will take Madopar. For the middle stage, patients in the trial group will take XFDCP combined with Madopar and Piribedil, while in the control group patients will take Madopar and Piribedil. The specific therapies are shown in Table 1.

Madopar (batch number: H10930198) is produced by Shanghai Roche Group, 250 mg/tablet. Piribedil (batch number: H20030699) is produced by French Servier Pharmaceutical Factory, 50 mg per tablet. XFDCP (batch number: Z05010604) is produced by the Pharmacy Department of the First Affiliated Hospital of Henan University of Traditional Chinese Medicine. It is mainly composed of prepared Heshouwu (Radix Polygoni multiflori preparata), Guiban (Tortoise plastron), Tianma (Gastrodia elata Blume), Baijiangcan (Bombix batryticatus), Shichangpu (Acorus tatarinowii Schott), Chuanxiong (Ligusticum wallichii) and Baishao (Radix Paeoniae alba), 6 g per package. All the patients will be observed for 12 weeks and follow-up for another 6 months. Patients will be required to provide a brief description of every adverse effect and record what treatment measures have been taken. If a patient has a serious adverse event, he will be given symptomatic treatment and will be withdrawn from this study. The adverse event will be recorded.

2.4 Outcome measures

2.4.1 Primary outcome measures

2.4.1.1 Unified Parkinson’s Disease Rating Scale score

The Unified Parkinson’s Disease Rating Scale (UPDRS)
score will be measured to evaluate the effectiveness of treatments in this study. Patient evaluation data will be recorded at weeks 0, 4, 8, and 12 during the treatment period, and at months 3 and 6 during the follow-up period. Based on the UPDRS score, Nimodipine method is adopted to calculate the efficacy rate\textsuperscript{[13,15]}.  

2.4.1.2 TCM symptoms scores  
A TCM syndrome integral scale based on current accepted methodologies\textsuperscript{[12,13]} will be formulated to evaluate the treatment response. These data will be recorded at weeks 0, 4, 8, and 12 during the treatment period, and at months 3 and 6 during the follow-up period.  

2.4.1.3 Quality of life  
The Chinese version of 36-item Short Form Health Survey (SF-36) will be adopted to evaluate the quality of life\textsuperscript{[16]}. These data will be recorded at weeks 0, 4, 8, and 12 during the treatment period, and at months 3 and 6 during the follow-up period.  

2.4.2 Secondary outcome measures  
2.4.2.1 Madopar dosage  
The size and frequency of Madopar daily doses will be adjusted according to individual response. The change in dosage of Madopar will be recorded at weeks 0, 4, 8, and 12 during the treatment period, and at months 3 and 6 during the follow-up period.  

2.4.2.2 Toxic and adverse effects of Madopar  
The IV part of UPDRS will be adopted to evaluate the toxic and adverse effects of the medications. These data will be recorded at weeks 0, 4, 8, and 12 during the treatment period, and at months 3 and 6 during the follow-up period.  

2.4.3 Safety  
Before treatment and after the 12-week treatment period, patients will undergo routine blood, urine and stool tests, a liver and kidney function test (alanine aminotransferase, aspartate aminotransferase, creatinine, and urea nitrogen) and will have an electrocardiograph administered. Adverse events will be observed and recorded throughout the treatment and follow-up period.  

2.5 Statistical analysis  
Data analysis will be conducted with SPSS 20.0 software. All t-tests will be two-tailed and the significance level will be set at $\alpha = 0.05$. Measurement data will be represented as mean $\pm$ standard deviation. The independent-sample t-tests will be used to compare the difference between the trial group and the control group of the early stage and middle stage respectively. This test will be repeated based on the data that collected at weeks 0, 4, 8, and 12 during the treatment period, and at months 3 and 6 during the follow-up period respectively. To compare the difference between before and after treatment within one group, paired t-test (the normal distribution data) or Wilcoxon signed-rank test (the abnormal distribution data) will be used. Before statistical analysis processing, data will be examined for normal distribution and appropriate transformations will be applied to the data. See Figure 1 for the procedure of this study.  

3 Discussion  
PD is a common and degenerative disease that is characterized by trembling of hands, arms, legs, jaw and face, stiffness of the arms, legs and trunk, slowness of movement, poor balance and coordination. PD is due to decreased dopamine production by the nerve cells in the brain. Although the pathogenic mechanisms are still unclear, it is believed that the degeneration of dopaminergic neurons in the substantia nigra (SN) and apoptosis of the striatum cells are closely related to PD\textsuperscript{[17]}. At present, a variety of medications, including levodopa, coenzyme Q10, pramipexole, rasagiline, ropinirole, and selegiline, can help patients ameliorate symptoms to a certain extent. Dopamine replacement is regarded as the most effective therapy for this disease\textsuperscript{[11]}. However, long-term treatment with Madopar is often complicated by the development of various types of motor response oscillations as well as
drug-induced dyskinesia, a complication characterized by erratic involuntary movements\(^ {14}\). Piribedil, a dopamine receptor agonist, combined with Madopar can reduce the motor complications and improve the effect. But it has the same adverse effects as Madopar, especially hypotension and psychiatric symptoms\(^ {19}\). Thus managing both PD symptoms with medication, and adverse drug reactions is difficult. Although TCM has been shown to be effective in PD patients, quantitative clinical evidence for TCM treatment is still limited. Therefore, as the PD caseload grows, the clinical study of PD treatment and prevention is becoming an important subject for contemporary integrative medicine.

The current popularity of TCM in the treatment of PD implies its potential advantage in improving symptoms, reducing the drug-induced side effects and improving patients’ quality of life\(^ {4,6}\). PD belongs to tremor syndrome in TCM. It is mainly caused by depletion of the liver-kidney, deficiency of qi and blood, and vacuity in the sea of marrow due to aging. These conditions allow exterior pathogenic influences to invade the brain orifices which results in loss of control in the sinew vessels and subsequent the sinew vessel dystrophy. The latter is likely due to phlegm-heat and blood stasis in the meridians. Tonifying liver and kidney yin is an important therapy for this disease\(^ {55}\). XFDCP is sweet and salty in taste and has functions of tonifying the liver and kidney as well as extinguishing wind. It is effective in reducing clinical symptoms, especially for the non-motor symptoms, thus can delay the progress of this disease and improve the quality of life. Combined with Madopar, it can not only improve the clinical effectiveness but also reduce the necessary dosage and minimize the adverse effects of Madopar\(^ {9}\).

The recommended treatment proposed by the guideline is minimized the dose of Western medicine to achieve the most satisfactory effects. Delay to use of Western medicine can reduce the incidence of motor complications. Based on this principle, this study designed a scheme of staging treatment for PD patients. For patients in the early stage with lighter symptom, they will receive TCM treatment or Madopar. The difference of clinical effects between these two treatments will be compared. PD patients with serious symptom in the middle stage will receive Madopar combined with Piribedil. However, the adverse effects will become more serious due to the increase in dose size and frequency. For this complex situation, TCM is necessary to reduce the adverse effects and relieve the symptoms. The results of this study will provide evidence for developing a comprehensive therapy regimen, which can delay the progress of the disease and improve the quality of life of PD patients at different stages.

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5 Competing interests

The authors declare that they have no competing interests.

REFERENCES


