PROTOCOL

The components in this Supplementary Material document are as follows:

Part I: Research Plan

Part II: Modifications

Title: A Prospective Cohort Study of Exercise Rehabilitation in the Treatment of Parkinson's Disease

Place: Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine

Document Date: Jan. 1st, 2015

Modification Date: Modification 1 (Jan. 1st, 2016); Change 2: (Aug. 22nd, 2020)

Part I: Research Plan

Overview

We proposed to conduct a cohort study to observe whether Tai Chi intervention could delay the disease progression of Parkinson's disease (PD).

PD patients were enrolled into 5 Tai Chi classes which began at different timepoints from Jan. 2016 to Jan. 2019. Each participant was assessed before they joined the Tai Chi class. After the recruitment, they accepted continuous Tai Chi training in the classes till the last follow-up. We performed three times of follow-up in Nov. – Dec. 2019, Oct. - Nov. 2020 and Jun. – July 2021. Using propensity score matching, we matched PD patients who did not receive Tai Chi training as control group in gender, disease duration, age, and Hoehn – Yahr staging. The aim is to observe the effect of Tai Chi on delaying the disease progression of PD. This original study is registered at Chinese Clinical Trial Registry (Registration No.: ChiCTR2000036306; Registration date: August 22, 2020).

1. Participants

We recruited PD patients aged 50-80 years with Hoehn -Yahr stage 1-2.5. The medication was stable at least 3 months before recruiting and not changed during follow-up unless increasing antiparkinsonian drugs or the need of deep brain stimulation (DBS) is required according to the disease severity. PD was diagnosed by senior movement disorder specialists (SDC, YYT) based on diagnostic criteria brought up by United Kingdom Brain Bank diagnostic criteria and MDS diagnostic criteria of PD in 2015 [1,2]. Patients who fitted any following item were excluded:

1) Secondary causes, such as inflammatory, drug-induced, vascular and toxin-induced parkinsonism.

2) Parkinsonism with other neurodegenerative diseases, such as progressive supranuclear palsy, multiple system atrophy, cortical basal ganglia degeneration, Wilson's disease.

3) Other neurological diseases, such as stroke.

4) Patients who were receiving any other clinical trials or regular exercise protocols.

5) Patients who had fall incidents in the 6 months before recruiting due to safety considerations.

6) Patients whose Mini-Mental State Examination (MMSE) scores were less than 24.

7) Patients who had medical history that did not fit to exercise, such as orthopedics diseases or cardiopulmonary dysfunction.

8) Patients who received education less than 6 years.

9) Patients who could not walk and live independently.

10) Patients who received brain surgery (e.g. deep brain stimulation);

11) Patients whose exercise length longer than 50 minutes per week.

All participants were fully informed and signed written consent forms. This study was approved by the ethic committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine.

2. Randomization, Blinding and Follow-Up

There was no randomization adopted. Assessments were done at baseline and the three follow-ups (Nov. – Dec. 2019, Oct. - Nov. 2020 and Jun. – July 2021). We also monitored the frequency and lengths of Tai Chi exercise for each patient. Patients whose training were less than 60 minutes per time or less than twice per week were regarded as giving up training. The flow chart of recruitment and follow up was shown in Part II.

PD patients who did not receive Tai Chi training were matched to Tai Chi training PD patients with similar age, sex, disease duration and initial Hoehn - Yahr staging by propensity score matching methods. They also received evaluation at baseline and three follow-ups (Nov. – Dec. 2019, Oct. - Nov. 2020 and Jun. – July 2021).

Since this is an interventional study of movement, we cannot perform the blinding on patients. Thus, the assessors and the statisticians were blinded to study design. The ethic committee monitored the whole process of blinding. Patients were demanded not to tell their group assignments to the assessors.

3. Exercise Interventions and Quality Control

3.1 Tai Chi

As for Tai Chi training, standardized Tai Chi was taught by professional Tai Chi coaches from Sino Taiji of Fuxing International in classes: *Qishi* ("Starting Posture"), *Shangsanbu* ("Twist Step"), *Yema Fenzong*("Part the Wild Horse's Mane on Both Side"), *Jingang Daozhui* ("Buddha's warrior attendant pounds mortar"), *Shoushi* ("Closing Posture"). Patients participated in this class were trained, twice a week, 60 min per time. PD patients whose attendance rate less than 75% were excluded.
The detailed Tai Chi protocols are referenced as our previous work [3].

3.2 Control

We did not give any exercise interventions to the control group. They continued to use anti-parkinsonism therapy and keep daily activities as usual. They did not exercise regularly as we additionally required.

4. Evaluation: Motor and non-motor symptom assessment by rating scales

The following rating scales were used to assess the status of patients at "on" periods at movement disorders clinic.

(1) Overall assessment of PD: Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn -Yahr stage;

(2) Non-motor symptoms:

1) overall assessment: Non-Motor Symptoms Questionnaire (NMS-Quest);

2) autonomic function: Scales for Outcomes in Parkinson's Disease-Autonomic questionnaire (SCOPA-AUT);

3) mood disorders: Hamilton anxiety rating scale (HAMA) and Hamilton depression rating scale (HAMD);

4) sleep: Parkinson's disease sleep scale (PDSS), Epworth Sleepiness Scale (ESS), Rapid eye movement sleep behavior disorder questionnaire-Hong Kong version (RBD-HK) were used.

5) cognitive function: MMSE – simplified Chinese version and Parkinson's disease cognitive rating scale (PDCRS);

(3) Quality of life: 39-item Parkinson's Disease Questionnaire (PDQ-39).

All patients were assessed by experienced doctors (PH, YCH, GL, SSC), who all passed the tests for proving the inter-rater reliability.

5. Outcomes

5.1 Primary Outcome

The primary outcome was the annual change of UPDRS total score measured in "ON" state at three follow-ups.

5.2 Secondary Outcomes

The secondary outcomes were annual change of the following indicators except the need of increasing antiparkinsonian therapies which were analyzed by survival analysis:

(1) the change of LEDD[4]

(2) the need of increasing antiparkinsonian therapies, including both the need of increasing antiparkinsonian drugs and the need of surgery, such as DBS or lesion surgery.

(3) Motor evaluations: UPDRS part III as overall motor evaluations; TUG and BBS.

(4) Other non-motor symptoms, including autonomic function, mood, sleep and cognition, assessed by rating scales.

(5) Quality of life: PDQ-39;

(6) the difference of prevalence of complications (dyskinesia, on-off phenomenon, dystonia, PD-MCI, hallucinations, restless legs syndrome).

NOTE: We consider the following aspects as the evidences for delaying disease progression:

(1) the annual change of UPDRS total score;

(2) the annual change of LEDD;

(3) the need of increasing antiparkinsonian therapies.

6. Statistical Analysis

R (version 3.5.1) and RStudio (version 1.1463) were used to perform statistical analysis.

Packages stats (version 3.5.1), base (version 3.5.1), spinds (version 2.2.0), lars (version 1.2), nlme (version 3.1-145), plyr (version 1.8.5), PGEE (version 1.5), ggplot2 (version 3.2.1), survival (version 2.43-3) and survminer (version 0.4.3) were introduced into statistical analysis. Figures were plotted in Prism 9 (version 9.3.1, San Diego, CA).

All analysis about primary and secondary outcomes were conducted on an intention-to-treat basis. Analysis of variance (ANOVA) were used in comparing at numerical demographic information. Pearson Chisq-Square test or Fisher test were used in analysis at categorical demographic information. Shapiro-Wilk normality test was used to assess the normality of variables. Independent-sample t-tests (with 95% confidence intervals) were used to compare group means. Data were presented in the way of between-group differences. The longitudinal effects of self-changes were calculated using repeated measures ANOVA.

We built a cohort which started enrollment since 2016, then more patients were enrolled gradually into another 4 classes (2^{nd} Class: start from Nov. 2016; 3^{rd} Class: start from Mar. 2017; 4^{th} Class: start from Sept. 2017; 5^{th} Class: start from Jan. 2018). All the patients in those 5 classes were trained continually and has been received assessment in the follow-up of 2019, the follow-up of 2020 and the follow-up of 2021.

We set the rate of UPDRS total score change (per year) as the primary outcome. As for the secondary outcomes, UPDRS part III, other motor evaluations (TUG and BBS), evaluations of non-motor symptoms (autonomic function, mood, sleep, and cognition, assessed by rating scales), quality of life evaluated by PDQ-39, the change of LEDD, and the difference of prevalence of complications (dyskinesia, on-off phenomenon, dystonia, PD-MCI, hallucinations, restless legs syndrome). We also observed the need for increasing antiparkinsonian therapy, including increasing antiparkinsonian drugs, and deep brain stimulation (DBS). LEDD of patients who received DBS were not taken into account.

We make the comparisons between the patients who received Tai Chi training and patients who did not receive Tai Chi training as controls. Analyses of the adjusted means of change from baseline to each follow-up in rating scales were done with logarithmic linear model of covariance that included the following fixed effects: treatment group

(Tai Chi = 1, control group = 0), months in this trial, the changed amount of LEDD and baseline Hoehn-Yahr score. Years of education were also included when analyzing PDCRS. We calculated the *p* value with the bootstrap method for resampling 1000 times. To demonstrate the results, mean change with its 95% confidential intervals (CIs) was introduced. Kaplan Meier plot with table of number at risk was introduced. Bonferroni correction was introduced.

7. Safety Reporting: Adverse events (AEs) and serious adverse events (SAEs)

7.1 Adverse events (AEs)

We defined AE as undesirable experience of patients during the study. All AEs were reported by the patients or observed by the research team. Each AE will be recorded.

7.2 Serious adverse events (SAEs)

SAEs were defined as the following:

1. Life threatening or resulted in death;
2. Required hospitalization or prolonged the time of hospitalization;
3. Resulted in disability or incapacity;
4. Other medical conditions considered as serious adverse experiences based on the medical judgement of all research team members.

7.3 Safety committee

The safety committee was composed as our research team. AEs and SAEs were judged by the meetings of safety committee.

References

1. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181-4. (In eng). DOI: 10.1136/jnnp.55.3.181.
2. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1591-601. (In eng). DOI: 10.1002/mds.26424.
3. Li G, Huang P, Cui SS, et al. Mechanisms of motor symptom improvement by long-term Tai Chi training in Parkinson's disease patients. Transl Neurodegener 2022;11(1):6. (In eng). DOI:

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4. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25(15):2649-53. (In eng). DOI: 10.1002/mds.23429.

Part II: Modifications

Basically, there were no significant changes made in the original research protocol as we reported. The following changes were done. All modifications were approved by the ethics committee and the meeting of authors.

Change 1: (Jan. 1st, 2016)

Patients were met both UK brain bank diagnostic criteria and MDS diagnostic criteria. The MDS diagnostic criteria were not published when we got the approval from Ruijin Hospital Ethic Committee, Shanghai Jiao Tong University School of Medicine at December 04, 2014. However, when we put the protocol into effect, the MDS diagnostic criteria of PD were published at 2015 year. Thus, we enrolled PD patients both met UK brain bank diagnostic criteria and MDS diagnostic criteria from 2016 year.

Change 2: (Aug. 22nd, 2020)

We noticed the inappropriate information were submitted due to inappropriate operation in 2016 (register number: ChiCTR-OPC-16008074). We mis-clicked “interventional” as “observational” when we registered at the Chinese Clinical Trial website. We found this incorrect information in 2020. So we re-registered a new project called “A prospective cohort study of exercise rehabilitation in the treatment of Parkinson's disease and its mechanism” after the approval of our ethic committee (register number: ChiCTR2000036306).