Stellate Ganglion Block in Patients With Advanced Primary Parkinson's Disease: a Small, Open, Randomized, Controlled Clinical Study

Unit in charge of clinical research ： Zhujiang Hospital of Southern Medical University

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Scheme version: No2

Scheme version date: February 11, 2022

Confidentiality statement

Research plan confirmation signature page

Version No.: 2.0

Version date: February 11, 2022

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Consent from the principal investigator on the protocol:

I have read the program carefully, agree with all the necessary information in the program to conduct the research, and agree to execute as described in the program.I understand that the research should not be initiated without the approval of the ethics committee and should fully comply with the relevant regulations of the unit.

Informed consent and appropriate documentation are required for all participants in the study.After obtaining the written informed consent signed by the subjects, the study will be carried out according to the declaration of Helsinki and the requirements of laws and regulations related to clinical research.

Name of principal investigator	signature	date

Catalog

RESEARCH PROPOSAL ABSTRACT

Title	Stellate Ganglion Block in Patients With Advanced Primary Parkinson’ s Disease: a Small, Open, Randomized, Controlled Clinical Study
Bidders	Zhujiang Hospital of Southern Medical University
Leader of the unit	Zhujiang Hospital of Southern Medical University
Research purpose	Main research purpose: To confirm that stellate ganglion block can improve motor symptoms in patients with Parkinson's disease. Secondary research objectives: To determine the efficacy of stellate ganglion block in improving non-motor symptoms, activities of daily living and medication dosage in patients with primary Parkinson's disease.
Research hypothesis	Stellate ganglion block can improve motor and non-motor symptoms in patients with primary Parkinson's disease.
Study design	Single-center, randomized, open-label
Sample size	This study was a randomized controlled trial. The experimental group was treated with standard Parkinson's disease treatment + stellate ganglion block (SGB), and the control group was treated with standard Parkinson's disease treatment. According to the literature review and previous clinical observations, the standard deviation of the MDS-UPDRS scale score in the control group was 9.58 points, and the MDS-UPDRS-Ⅲ score in the experimental group was expected to decrease by 10 points. 80%, and the loss to follow-up rate was 20%. According to the formula for calculating the sample size, 19 subjects were required to be studied in each of the experimental group and the control group, and at least 38 subjects were included in total.
Research object	Diagnostic criteria: Parkinson's disease patients who met the 2016 MDS criteria for "probable PD" or "diagnosed PD" Inclusion criteria: 1. Age 45-80 years old; 2. Patients with Parkinson's disease who meet the diagnostic criteria of "probable PD" or "diagnosed PD" in MDS in 2016; 3. The patients or their legal guardians agree to participate in this trial and sign the informed consent form; 4. Hoehn-Yahr (H&Y) level 3 to 5; Exclusion criteria:

	1. Those who are allergic to local anesthetics; 2. Those who are unable to cooperate with sports or non-motor function monitoring; 3. Exclude patients with Parkinson's superimposed syndromes, such as corticobasal degeneration, dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy; and secondary Parkinson's syndromes, such as vascular parkinsonism, drug poisons or patients with Parkinson's syndrome caused by trauma; 4. Refuse to sign the consent form.
Key Interventions	Experimental group: standard treatment of Parkinson's disease + SGB Control group: standard treatment for Parkinson's disease

Follow-up	Intervention follow-up period: On Day0, Day5 and Day10 of the first, second and third cycles, the visiting schedule was used to record the required information. The interval of each cycle was 1 month, and the total follow-up time was 3 months. Follow-up period: Modified MDS-UPDRS (Revised Movement Disorders Association Unified Parkinson's Disease Rating Scale) III scores were collected every month after treatment.
Evaluation index	Primary end point: MDS-UPDRS score. Secondary end points: NMSS (Parkinson's disease Non-motor Symptom Evaluation Scale), PDQ-39 (39-item Parkinson's disease questionnaire), 10M-WT (walking speed test), H&Y grading (Hoehn Yahr (modified) Parkinson's disease grading), LDE (dopa equivalent dose).
Statistical method	SPSS25.0 software was used to analyze the data, and the measurement data were expressed by mean soil standard deviation (X ± S). For those with normal distribution and homogeneity of variance, paired sample T test was used for intra-group comparison, two independent samples T test was used for inter-group comparison, and t 'test was used for those with uneven variance. The count data were expressed as percentage (%), and the chi-square test was used to compare the total effective rate between groups. $P<0.05$ was considered as statistically significant difference.
Study time	Expected enrollment time of the first subject: 2022-01-01 Expected enrollment time of the last subject: 2022-06-30 Expected end time: 2024-06-30

Visit Schedule

	Screening stage	Intervention follow-up period			Observational follow-up period	Exit supervision
		Into the group	Follow-up 1	Follow-up 2	Follow-up 3	
Supervision stage	V_S	V_1	V_2	V_3	V_4	
Supervision time	-1day	0	4weeks ±3	8weeks ±3	12weeks±3	
Informed consent	*					
Main evaluation indicators （MDS-UPDRS）	*		*	*	*	when necessary
Secondary evaluation indicators （NMSS、PDQ-39、10M-WT、H&Y、LDE）	*		*	*	*	when necessary
Demographic information[A]	*					
Medical history[B]	*					
Vital signs[C]	*		*	*	*	*
Physical examination[D]	*		*	*	*	*

Laboratory tests (hematology/biochemistry/urinalysis)[E]	*		*	*	*	必要时
Blood biomarkers[F]	*				*	
Film degree exam[G]	*				*	
Previous/concomitant medications[H]	*					
Adverse event	*	*	*	*	*	*

Remark：

A. Demographics will include the subject's date of birth, gender, ethnicity, education, marriage, occupational information;

B. Medical history includes comorbid diseases and other clinically significant past medical history, medication history, and surgical trauma history;

C. Vital signs will include blood pressure, pulse rate, respiration and temperature;

D. Physical examination includes medical physical examination and neurology specialist physical examination;

E. Clinical laboratory examination: blood routine, serum biochemistry, coagulation, ceruloplasmin, gene expression level;

F. Blood biomarkers: IL-2, APEO, α-synuclein, DJ-1 protein, etc.;

G. Imaging examination: MRA, SWI;

H. The type, dose, and time of previously used drugs.

1. Research background

Parkinson's disease (PD) is a relatively common degenerative disease of the central nervous system, and China's population has grown significantly over the past few decades, resulting in a rapid increase in the number of elderly people; 2016 Global Burden of Disease Study Report It is said that the number of PD patients in China accounts for about 23% of the total PD population in the world[1]; by the end of 2020, it is estimated that the number of people with Parkinson's in China will be about 3.62 million, and it is estimated that by 2030, 50% of PD patients in the world will be Chinese[2]. Parkinson's disease is mainly manifested by motor symptoms such as bradykinesia, rigidity, and tremor, as well as non-motor symptoms such as autonomic dysfunction, sleep disturbance, and hyposmia[1].

Both motor symptoms and non-motor symptoms can significantly affect the quality of life of patients[3]. At present, drug treatment represented by dopa is still the first choice for Parkinson's treatment guidelines at home and abroad. However, in the middle and late stages of the disease, side effects such as symptom fluctuations or dyskinesia complicated by long-term medication gradually appear, and the efficacy of levodopa in patients declines[4-5], seriously affecting the quality of life of patients. For patients with advanced Parkinson's disease, the current anti-parkinsonian guidelines advocate drug therapy combined with non-drug therapy for comprehensive treatment. Deep brain stimulation (DBS), as the main non-drug method for Parkinson's treatment, has limited its wide clinical application due to its complicated operation, invasiveness, high cost and many side effects[6-7]. Functional exercises limited to a certain aspect such as language and swallowing have limited efficacy[8-9], so it is imperative to find new treatments for Parkinson's disease.

Stellate ganglion block(SGB) is a commonly used sympathetic nerve regulation method in clinic. It can treat and protect various CNS diseases by regulating inflammatory response, oxidative stress level and immune endocrine function. role[10]. The mechanism of action of SGB can be divided into the central action mechanism and the peripheral action mechanism. The central action maintains the stability of the internal environment by regulating the hypothalamus, so as to keep the body's endocrine function, autonomic function and immune function normal[11]. It has curative effects on inflammation and pain relief, reducing free radicals, inhibiting neuronal apoptosis, improving cognitive function, regulating cerebral oxygen metabolism, regulating sleep, and dilating blood vessels. SGB can inhibit the occurrence and maintenance of mechanical hyperalgesia in PD rats by reducing inflammatory cytokines in the striatum and PAG[10]. SGB can reduce the production of free radicals, reduce the levels of serum β-amyloid (Aβ)-42, phosphorylated Tau-181 protein and IL-6, and reduce the expression of abnormal phosphorylation of Tau protein to protect neuronal cells[12]; It may improve cognitive function by down-regulating hippocampal neuronal adenylate-activated protein kinase (AMPK) and inhibiting astrocyte activation[13]; the right SGB may alleviate the MT effect by reducing excessive hippocampal inflammatory response and neuronal apoptosis. It can effectively alleviate spatial learning and memory dysfunction[14], and restore various biological rhythms by correcting melatonin rhythm[15]. Uchida et al also believed that SGB can reduce sympathetic nervous tension, thereby regulating sleep[16]. SGB can increase blood flow, make the anterior, middle and posterior cerebral arteries, vertebral arteries, carotid arteries, brachial arteries, blood flow velocity, blood flow, and blood vessel diameters all increased, vascular resistance decreased, and the diameter of small arteries increased more significantly[17], stimulates the olfactory nerve by increasing blood flow, which improves the olfactory dysfunction for a long time[18]. SGB may inhibit the secondary apoptosis of injured neurons by promoting the conduction of anti-apoptotic signaling pathways; regulating the levels of lymphocyte NF-κ

B protein, IL-1β and TNF-α, and CGRP through the neuro-endocrine-immune system; and It has neuroendocrine regulating effect: can regulate calcitonin, NO, endothelin, serum adrenocorticotropic hormone(ACTH), α-melanocyte stimulating hormone (MSH) and β-endorphin (β measurement end), etc[19]; Parkinson's patients have neuro-endocrine-immune system dysfunction. When we used SGB to treat dizziness in PD patients in our previous clinical practice, we unexpectedly found that SGB significantly improved the patients' motor and non-motor symptoms.

At present, there are no reports on the application of SGB in the treatment of Parkinson's patients at home and abroad. Based on the previous clinical observation, this topic intends to use SGB to treat patients with advanced Parkinson's disease through an open, randomized controlled small-sample clinical study, so as to clarify the ability of SGB to treat patients with Parkinson's disease. Effectively improve motor symptoms and non-motor symptoms in patients with advanced Parkinson's disease.

2. Research purpose

Main research purpose: To confirm that stellate ganglion block can improve motor symptoms in patients with Parkinson's disease.

Secondary research objectives: To determine the efficacy of stellate ganglion block in improving non-motor symptoms, activities of daily living and medication dosage in patients with primary Parkinson's disease.

3. Research hypothesis

Stellate ganglion block can improve motor and non-motor symptoms in patients with Parkinson's disease.

4. Study Design

4.1Type of design and duration of follow-up

This study is a randomized controlled, open-label clinical study initiated by Zhujiang Hospital of Southern Medical University, with a follow-up period of 6 months.

4.2Grouping method and blinding level

Grouping: The study was divided into an experimental group (standard antiparkinsonian therapy + SGB) and a control group (standard antiparkinsonian therapy).

Random: Use a stratified randomization method. Group study subjects by age. After grouping, there will be 2 subgroups: ① patients aged 45-60 years, ② patients aged 61-80 years. The 2 subgroups were divided into the experimental group and the control group according to 1:1, and finally the experimental group and the control group in the 2 subgroups were pooled.

Open: Both investigators and patients were aware of the grouping of patients.

4.3Sample size calculation

This clinical trial adopts the sample size calculation formula of 2 groups of quantitative data.

Calculation formula: $$n = \frac{(Z_\alpha + Z_\beta)^2 * 2\sigma^2}{\delta^2}$$

n represents the sample size of each group。

Take α as 0.05, Z value as two-sided, Zα=1.96; β as one-sided, take power (test power) as 0.8, Zβ=0.84.

σ represents the difference between the standard deviations of the treatment group and the control group, which is about 9.58 according to previous observations; δ represents the difference of the mean, that is, the difference between the mean of the treatment group and the control group, which is 10; the loss to follow-up rate is 20%.

According to the formula for calculating the sample size, there were 19 subjects in each of the experimental group and the control group, and a total of 38 subjects were included.

5. Subject recruitment

A total of 38 middle-advanced primary PD patients and controls who met the requirements in the inpatient or outpatient department of neurology of Zhujiang Hospital were continuously recruited.

6. Research subjects

6.1Diagnostic criteria

Parkinson's disease patients who met the 2016 MDS criteria for "probable PD" or "confirmed PD".

6.2Standard constrain

（1） Age 45-80 years old;

（2） Parkinson's disease patients who meet the 2016 MDS "probable PD" or "diagnosed PD" diagnostic criteria;

（3） Patients or their legal guardians agreed to participate in this trial and signed the informed consent form;

（4） Hoehn-Yahr (H&Y) grades 3 to 5;

6.3Exclusion criteria

（1）Allergic to local anesthetics;

（2）Those who cannot cooperate with exercise and non-exercise monitoring;

（3）Exclude Parkinsonian-plus syndromes, such as corticobasal degeneration, dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy; and secondary parkinsonism, such as vascular parkinsonism, drug toxicity, or trauma Patients with Parkinson's syndrome caused by;

（4）Those who refused to sign the informed consent form.

6.4Exit criteria

（1）Subjects should withdraw from the trial when they have abnormal vital organ function, allergic reactions to drugs, poor compliance, exacerbation of the disease, or serious adverse reactions that need to stop the treatment of the trial drug or use other treatment methods;

（2）Subjects who are ineffective, cannot tolerate adverse reactions, wish to take other treatment methods, or request to withdraw from the trial without any reason.

7. Research Interventions

7.1Description of the research intervention

（1） Interventions in the experimental group: standard antiparkinsonian therapy + stellate ganglion block.

（2） Control group intervention: standard antiparkinsonian therapy.

7.2Dosage and start and end times

Test group: Oral standard anti-Parkinsonian drugs, including compound levodopa, pramipexole hydrochloride, ropinirole, entacapone, amantadine, antan, etc. A total of three cycles of stellate ganglion block were performed, with 10 stellate ganglion blocks per cycle (once a day), with a 20-day interval between the two cycles;

Control group: Oral standard antiparkinsonian drug

8. Research Process

8.1Screening Phase (Vs, -1 Day)

During the screening visit, the following procedures will be performed/collected:

Informed consent: After introducing the study to the subjects in detail and answering the subjects' doubts, the informed consent form signed by the patients was obtained. Sign up for pre-informed laboratory tests and imaging evaluations for routine clinical care, if relevant data are available within the specified window period. (If the subjects or their guardians cannot sign the informed consent form before the trial in the event of an emergency in the project, it needs to be clearly explained here) After the informed consent, the following procedures can be carried out.

Demographics: gender, date of birth, race, education, marriage, occupational information;

Relevant medication/surgery history;

vital signs: blood pressure, pulse rate, respiration and temperature;

Physical Exam: Internal Medicine and Neurology Physical Exam;

Laboratory tests: blood routine, serum biochemistry, coagulation, ceruloplasmin, gene expression level;

Previous/concomitant medications;

Blood biomarkers: IL-2, APEO, α-synuclein, DJ-1 protein, etc.;

Imaging examination: head MRI + susceptibility-weighted imaging;

Madopa equivalent dose;

Modified MDS-UPDRS scale;

NMSS scale;

PDQ-39 scale;

H&Y；

LDE；

10M-WT；

8.2Randomization phase（V_1，0 Day）

Randomize the eligible patients by stratified randomization method;

8.3Follow-up period

Treatment stage: V2 4 weeks, V3 8 weeks, V4 12 weeks

During each treatment visit, the following procedures will be performed or the following metrics will be collected:

Detailed description: The following examinations need to be completed: vital signs; physical examination; laboratory examination; blood biomarkers: IL-2, APEO, α-synuclein, DJ-1 protein, etc.; imaging examination: head MRI + Susceptibility-weighted imaging (V4 only), etc.; Madopa equivalent dose; Modified MDS-UPDRS scale score; NMSS scale; PDQ-39 scale; H&Y classification; LDE; 10M-WT.

9. Subject withdraws from study or discontinues study treatment

9.1Withdrawal Criteria

Reasons for a subject to withdraw from the study may include:

Subjects should withdraw from the trial when they have abnormal vital organ function, allergic reactions to drugs, poor compliance, exacerbation of disease or serious adverse reactions that require stopping the treatment of the trial drug or using other treatment methods;

Subjects who are ineffective, cannot tolerate adverse reactions, wish to take other treatment methods, or request to withdraw from the trial without any reason.

Subject withdrew informed consent and refused further follow-up;

Subjects lost to follow-up;

Subject died.

9.2 Criteria for discontinuation of study treatment

Criteria for subjects to discontinue study treatment are as follows:

（1）Subjects withdrew their informed consent for any reason or no reason and refused to continue receiving study drug treatment;

（2）According to the judgment of the investigator, the subject's clinical symptoms have deteriorated/physical condition has decreased, the study endpoint has been reached, or there are intolerable side effects, including any abnormal clinical or laboratory tests or other medical conditions;

（3）Other circumstances that the investigator deems necessary to terminate the study drug treatment;

（4）The sponsor terminated the study.

9.3Steps to withdraw from the study or discontinue study treatment

Subjects must be checked for efficacy and safety in accordance with the protocol for withdrawal from the study and final observation and follow-up, and AEs and outcomes must be fully recorded. The researcher can suggest or provide alternative treatment methods to the subjects according to the actual situation of the subjects.

If the subject refuses to come to the research center for further visits, their survival status should continue to be tracked unless the subject withdraws informed consent. In this case, no further study evaluations should be conducted and no further data should be collected.

10. Evaluation indicators

10.1Primary endpoint: Modified MDS-UPDRS scale score (the revised version of the Movement Disorders Association Unified Parkinson's Disease Rating Scale, which has four main parts, including both physician and patient aspects, the first part is psychological, behavioral and emotional; the second Part is activities of daily living; the third part is motor symptoms; the fourth part is complications), SGB is carried out in three cycles, each cycle is carried out for 6-10 days, and the interval between each cycle is 20±7 days; The first, second, and third cycles of Day0, Day5, and the last day were measured and recorded.

10.2Secondary endpoints： NMSS (Non-motor Symptom Evaluation Scale), PDQ-39 (Self-rating scale for clinical evaluation of the quality of life in patients with Kinson's disease), H&Y classification (Classification of Parkinson's disease), LDE (levodopa equivalent dose), 10M-WT (10m walk test), cerebrospinal fluid and blood biomarkers, SGB were carried out for a total of three cycles, each cycle was carried out for 6-10 days, and the interval between each cycle was 20±7 days; On Day0, Day5, and the last day of the third cycle, the scale data were measured and recorded. The researchers performed head MRI + susceptibility-weighted imaging on Day 0 of the first cycle and Day 10 of the third cycle, respectively, to compare the changes in the "swallowtail sign" of two successive head MRIs.

11. Adverse events, serious adverse events, adverse reactions

11.1Definition

Adverse Event（Adverse Event, AE）：

（1）Allergies: Subjects experienced anesthesia allergies during the planetary ganglion block therapy;

（2）Nerve damage: Accidental nerve damage, transient upper limb numbness, and hoarseness during planetary ganglion block therapy;

（3）Adverse reactions caused by local anesthetics: such as dizziness, chills, tinnitus, and anesthetics accidentally entering blood vessels during planetary ganglion block therapy;

（4）Pneumothorax: the puncture needle accidentally penetrates the lung;

（5）Improper puncture site: Brachial plexus block, high epidural block, and subarachnoid block occur when the puncture site is improper.

11.2Adverse events/serious adverse events recording

All adverse events and serious adverse events that occurred during the trial, such as local anesthetic allergy, organ dysfunction, intolerance to operation, etc., regardless of whether they were causally related to the trial drug, should be recorded in the original records and case reports. in the table. Records of adverse events and serious adverse events should include:

（1）Event name;

（2）The duration of the event, including the time of occurrence and the time of its end;

（3）The severity of the incident;

（4）Judgment of the causal relationship between the event and the research product;

（5）Take measures; if treatment is required, record the treatment methods and medications given;

（6）The outcome of the event;

（7）The researcher should sign and sign the date.

11.3Evaluation of Adverse Events and Serious Adverse Events

11.3.1 Severity rating

Grade 1: Mild; asymptomatic or mild; clinical or diagnostic only; no treatment required.

Grade 2: Moderate; requires minor, topical, or non-invasive treatment; age-appropriate instrumental ADL.

Grade 3: Severe or medically important but not immediately life-threatening; leading to or prolonging hospitalization; disability; limited self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent medical attention required.

Grade 5: AE-related death.

11.4Treatment, Follow-up, and Duration of Adverse Events/Serious Adverse Events

For all adverse events/serious adverse events, investigators should take necessary measures according to their severity, and follow up until resolved, returned to baseline levels, proved unresolvable, or died.

11.5Judgment and treatment of abnormal laboratory test indicators

The clinical significance of all abnormal laboratory data obtained during the trial was evaluated and analyzed, and any clinically significant laboratory abnormal data was fully reported.

（1）Laboratory indicators related to Parkinson's disease: truthfully record abnormal data values, detection time, etc. of laboratory indicators, and perform statistical analysis after summarizing to evaluate whether relevant laboratory indicators are statistically significant;

（2）Other laboratory indicators: truthfully record the abnormal data values of laboratory indicators, detection time, etc., to evaluate whether it affects the efficacy and effect of Parkinson's disease-related basic drug treatment, whether it interferes with subsequent stellate ganglion block therapy, and whether it affects Parkinson's disease-related basic drugs. Subjects who received Jinson drug treatment and stellate ganglion block treatment continued the original treatment plan; for subjects who affected Parkinson drug treatment and stellate ganglion block treatment, the relevant disease status was recorded and symptomatic and supportive treatment was given. After the abnormal data returns to normal or returns to the baseline level, evaluate whether the subjects can continue to meet the inclusion and exclusion criteria. For those who do not meet the criteria, the trial process needs to be terminated and recorded.

11.6Reporting of Serious Adverse Events

During clinical trials, investigators should pay close attention to the occurrence of serious adverse events. Once a serious adverse event occurs, the trial should be stopped immediately, and necessary measures should be taken to ensure the safety of the subjects, and reported to the ethics committee and other relevant departments within 24 hours.

12. Data Management

Data collection：

Data records: The original medical records and CRFs should be recorded truthfully and carefully as required, and the contents should not be easily changed once filled in. If it is necessary to make corrections due to errors in filling in, the original records shall not be changed, but only in the form of an additional description, signed and dated by the responsible research doctor.

All observed results and abnormal findings in clinical trials should be carefully verified and recorded in a timely manner to ensure the reliability of data.

Various instruments, equipment, actual and standard products used in various inspection items in clinical trials should have strict quality standards, and ensure that they are used under normal conditions.

13. Statistical analysis

13.1 Statistical Analysis Data Set Definition

① Intentional analysis set（Intention-to-treat population）

All subjects who participated in randomization were included.

② Full analysis set（Full Analysis Set）

According to the principle of intention-to-treat analysis (ITT), all subjects who were randomized and who had received at least one post-treatment efficacy assessment were included.

③ Compliant with the scheme set（Per-protocol Set）

All patients who met the trial protocol, had good compliance (80%-120% of medication), did not use prohibited medication during the trial or completed the contents of the case report form.

④ Security Analysis Set（Safety Analysis Set）

All enrolled cases, all patients who have used the trial drug at least once and have safety records after drug use, belong to the safety analysis set. This dataset is used for safety analysis.

13.2 Statistical Analysis Program

13.2.1 Statistical analysis software

Statistical analysis was performed using SPSS 25.0 statistical software.

13.2.2 Basic Principles of Statistical Analysis

All statistical inferences were two-sided tests, the test level for statistical significance was set at 0.05, and the confidence intervals for parameters were estimated using 95% confidence intervals. The parametric method should be used as much as possible. When the data does not meet the conditions of the parametric method, the data conversion method can be used to make it meet the conditions. If it still does not meet the conditions, the non-parametric method can be considered.

13.2.3 Missing data imputation

If the patient fails to complete the corresponding scale or CRF due to force majeure factors, it should be completed within one week of missing data; if the patient withdraws from the study or terminates the study treatment, the corresponding missing data need not be completed.

13.2.4 Descriptive analysis

Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). For those with normal distribution and homogeneous variance, paired-samples t-test was used for intra-group comparison, two independent samples t-test was used for inter-group comparison, and t' was used for unequal variances. test. The enumeration data were expressed as percentage (%), and the total effective rate between groups was compared by chi-square test. $P<0.05$ was considered to be statistically significant.

13.2.5 Analysis of Baseline Data

Descriptive analysis of baseline data (including demographic indicators, etc.).

13.2.6 Effectiveness Analysis

① **Primary endpoint:** Modified MDS-UPDRS scale score

Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$). For those with normal distribution and homogeneous variance, paired-samples t-test was used for intra-group comparison, two independent samples t-test was used for inter-group comparison, and t' was used for unequal variances. test. $P<0.05$ was considered to be statistically significant.

② **Secondary endpoints:** NMSS scale, PDQ-39 scale, H&Y grade, LDE, 10M-WT, cerebrospinal fluid blood biomarkers, MRI+SWI changes

Measurement data were expressed as mean ± standard deviation (x ± s). For those with normal distribution and homogeneous variance, paired-samples t-test was used for intra-group comparison, two independent samples t-test was used for inter-group comparison, and t' was used for unequal variances. For skewed data, median + interquartile range (m±Q) was used, and nonparametric test was used; $P<0.05$ was considered statistically significant.

15.2.7 Security Analysis

Describe the types of adverse events, their frequency, and their relationship with the trial drug. Discontinuation of the study due to adverse events and cases of severe or serious adverse events will be specifically noted.

14. Quality Control and Quality Assurance

14.1Standard operating procedures developed

Before the start of the trial, the investigator and the sponsor/CRO (if applicable) shall discuss and formulate the standard operating procedure of the clinical trial, so as to unify the operation method, judgment standard and recording form during the trial process, so that the investigator can strictly follow the protocol.

14.2Research staff training and authorized division of labor

Before the trial begins, the principal investigator organizes a team that matches the study, including doctors, coordinators, etc.

Before the trial, the principal investigator will train all medical staff participating in the trial, including clinical trial protocol, clinical trial manual, standard operating procedures, special precautions, etc. During the test, if the project process is changed, relevant training will be organized again. Keep true and complete training records.

The relevant personnel shall be authorized by the principal investigator, and the relevant personnel must perform their obligations in accordance with the authorized division of labor. During the trial, the principal investigator can add, delete, and adjust personnel and division of labor according to the actual situation, and update the authorized division of labor table at the same time. Relevant personnel must be fully trained before operation.

14.3Subject compliance management

Researchers should actively take measures (eg: through follow-up visits, follow-up) to control the dropout rate within 20%.

15. Ethical considerations

To ensure that this clinical study complies with the declaration of Helsinki and relevant Chinese regulations on clinical research.Subjects can be selected for clinical study only after signing the informed consent.The researchers guaranteed to maintain the privacy of the subjects.

16. Research progress

(1) November 2021 to December 2021: Improve the research plan and pass the ethics defense of the Zhujiang Hospital Ethics Committee.

(2) From January 2022 to December 2022: Recruit patients with advanced PD and complete observation and follow-up.

(3) January 2023-June 2024: Statistical processing of data, writing and publication of 1 related paper.

17. References

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