Cover

Research on key technologies of brain electric field therapy based on acupoint regulation for the treatment of post-stroke cognitive impairment

Study type: Clinical study

Research Center: The Third Affiliated Hospital of Zhejiang Chinese Medical University (Team leader unit)

The Second Affiliated Hospital of Zhejiang University School of Medicine

Hangzhou Hospital of Traditional Chinese Medicine

Zhejiang Provincial Hospital of Traditional Chinese Medicine

Zhejiang Provincial People's Hospital

Department of this hospital: Acupuncture Department

Signature of the person in charge of the hospital:

Date: May 2025

The study will be conducted in accordance with this clinical study protocol and GCP

Contents

Study protocol

I. Research background

Stroke is a global public health problem, which has become the leading cause of death and disability in China. With the rapid aging of the Chinese population, its incidence continues to rise[1-3]. According to the "Report on the prevention and Treatment of Stroke in China (2023)", on average, one person in China will have a first or recurrent stroke every 10 seconds, and one person will die from stroke every 28 seconds. At present, there are 4 million new stroke cases in China every year, and there are 12.42 million stroke cases in people aged 40 years and above, and the incidence population is getting younger. Among the survivors, about 75% are left with disability and 40% are severely disabled, which will lead to huge economic losses and physical and mental pain for the patients' families.

Cognitive Impairment after Stroke (Post - Stroke Cognitive Impairment, PSCI) is a common complication of Stroke patients in 6 months after the Stroke event Cognitive Impairment to Cognitive Impairment diagnosis standard. PSCI is defined as a secondary to incident stroke and cognitive decline as the core characteristics of clinical phenomenon, these obstacles include cognitie impairment caused by a variety of types of stroke, is after stroke survivors functions rely on one[4,5] of the main determinants. The prevalence of PSCI is about 30%-50% within 6 months, of which 10% will progress to dementia. In addition, patients with PSCI face a risk[6-8] of death of up to 61% within 5 years. Around the world have launched specific guidelines, calls for strengthening the focus of the major complications and input, however the PSCI treatment still limited to stroke secondary prevention measures and treatment of alzheimer's disease drugs, are lack of high-level clinical evidence, therefore needs to be effective treatments to improve the prognosis[9, 10] of patients.

PSCI is a dynamic development process, and its occurrence time, influence factors, clinical manifestation and prognosis of recovery of individual differences, unique diagnostic system of traditional Chinese medicine can help to analyze the condition of PSCI evolution, law research may help to explain the evolution of syndrome and to provide reference for treatment. There is no special effects for the treatment of PSCI drugs, and drug treatment were lack of high-level evidence to prove that, in recent years with the development of imaging, artificial intelligence and electromagnetic physics non-drug therapy has gradually become one[11] of research hotspots in the field of PSCI in recent years. It is worth noting that represented by transcranial electrical stimulation of non-invasive brain stimulation is a direct role in the therapy of PSCI brain lesions, is often used to combine the curative [12, 13]effect of acupoint stimulation in order to achieve better. At the same time, the acupuncture therapy in the prevention and control of PSCI reflects a good efficacy [14]and safety. Many clinical studies suggest that cupping therapy can improve the PSCI cognitive impairment of patients, improve

their quality of life, and cupping therapy can also be treated by syndrome differentiation and treatment for patients to provide targeted, to compensate for the limitations of western medicine drugs.

This study intends to study the evolution law of post-stroke cognitive impairment, and to carry out a multi-center, large-sample randomized controlled clinical trial of electroacupuncture intervention for PSCI through the standardization of multi-dimensional and multi-modality data of PSCI patients, so as to establish the characteristic technology of TCM diagnosis and treatment for post-stroke cognitive impairment suitable for promotion. To establish the clinical diagnosis and treatment pathways and standards for the dominant diseases of traditional Chinese medicine. So as to establish the efficacy evaluation system of PSCI based on TCM syndrome diagnosis and evolution law, realize the precise diagnosis and treatment mode of PSCI with traditional Chinese and Western medicine, and improve the overall efficacy and quality of life of patients.

Second, the main research content, goal, plan and schedule, and to solve the key problem:

1. The research content

Of this study was to explore to establish based on the four diagnostic information, subjective scores to the modal data more objective efficacy evaluation system, build multimodal and multidimensional cognitive impairment after stroke of Chinese and western medicine clinical database, application of multivariable space-time map neural network (MTGNN) and the Transformer, Build collections of TCM syndrome identification and treatment decisions and curative effect of prediction function for the integration of cognitive impairment after stroke model, through the study of automatic syndromes, inspection index, depend on biological signal between time and space, to adapt to the reality the complex characteristics of medical data, implement effective quantitative predictions to effect change, To provide a scientific evaluation tool for the recovery of cognitive impairment after stroke treated with traditional Chinese medicine.

Based on multi-center and large-sample clinical randomized controlled trials, an individualized and precise treatment plan will be established, the TCM efficacy evaluation system of post-stroke cognitive impairment will be innovated, the clinical prevention and treatment standards will be formulated, the stimulation parameters of acupoint regulation will be clarified, and the precise diagnosis and treatment standards of TCM for post-stroke cognitive impairment will be explored.

2. Research objectives

(1) To observe the improvement of cognition after brain electroacupuncture intervention

for cognitive impairment after stroke.

(2) Based on the task-related information analysis and analysis methods in the multi-mode data of TCM syndrome data, clinical assessment, biochemical indicators, brain magnetic resonance imaging, electroencephalogram and so on, the systematic syndrome diagnosis and clinical evaluation criteria were established, the evolution rule of TCM syndrome of stroke was systematically clarified, and the individualized and precise treatment plan was established. Based on multi-center and large-sample clinical randomized controlled trials, the establishment of precise diagnosis and treatment standards of traditional Chinese medicine for post-stroke cognitive impairment was explored.

(3) To construct an artificial intelligence big data model of TCM syndrome evolution of post-stroke cognitive impairment based on multimodal data, and to explore the establishment of an objective efficacy evaluation system based on four diagnosis information, subjective scoring and multimodal data.

3. The research plan

Before starting the study, the investigator clearly and orally explained the study and its potential risks and benefits to the patient or her licensor. After obtaining consent from the patient or her licensor, the patient or her licensor and the investigator signed and dated the informed consent form. Patients or their designees could be screened and subsequently enrolled in the study only after they had signed the informed consent form.

Patients who provide written informed consent are then assessed for study eligibility:

(1) Patients' demographic data and medical history;

(2) vital signs;

3.1 Study protocol

This project intends to collect a total of 68 patients with PSCI in five centers (a total of 340 persons), including 34 persons in the general acupuncture group and 34 persons in the electroacupuncture group. The characteristics of PSCI in each group are studied to systematically clarify the evolution rule of TCM syndromes of stroke, establish individualized and precise treatment plan, and based on multi-center randomized controlled trial. To explore the establishment of precise diagnosis and treatment standards of traditional Chinese medicine (TCM) for post-stroke cognitive impairment.

This study was an experimental study. Patients were screened strictly according to the diagnostic criteria, inclusion criteria and exclusion criteria. After confirmation of enrollment, they were randomly divided into groups according to the random number table until the total number of observed cases was completed. The main research object for the third hospital affiliated to zhejiang university of Chinese medicine, acupuncture, the second hospital

affiliated to zhejiang university school of medicine, acupuncture, traditional Chinese acupuncture, Chinese medicine hospital in zhejiang province and zhejiang province people's hospital of hangzhou clinical diagnosis of PSCI patients.

3.1.1 sample size calculations

The mean change was 0.837 in the experimental group and 0.531 in the control group, and the between-group difference was 0.249 and 0.307, respectively. The within-group standard deviation was 0.3, α=0.025 (one-sided), Power 1-β was 0.8, and the dropout rate was 15%. According to the data to get a total sample size of 340 people, that is, each branch (a total of five center) are needed in patients with 68 people (normal acupuncture group including 34 people, 34).

3.1.2 Randomized controlled trial design and implementation

(1) Randomization

The study used the Central Randomization System, and the random order was drawn from the randomization system of the Third Affiliated Hospital of Zhejiang Chinese Medical University. Applicants by contacting the third hospital affiliated to zhejiang university of traditional Chinese medicine two random member, told the participants information, random search random result, group information and will inform the applicant. The randomized participants did not participate in the intervention, data collection or statistical analysis of the study. This study of random solutions by random personnel is responsible for the warehousing, the staff is not involved in this study.

(2) blinded design and implementation

Because the double-blind operation of acupuncture and conventional drug treatment could not be well carried out in this study, this study adopted a single-blind (blinded to the patients) design. In the whole process of the study, the principle of three separation was implemented: the operators, the efficacy evaluation personnel and the statistical analysis personnel were separated, and the three personnel could not communicate with each other in the whole process of the study. That is, third-party professional statisticians who did not know the grouping information performed the efficacy evaluation and statistical analysis of the results, in order to avoid the bias of the data results caused by single blindness.

3.1.3 Diagnostic criteria

3.1.3.1 western medicine diagnostic criteria

In this study, stroke included cerebral infarction and cerebral hemorrhage. The diagnostic

criteria of western medicine was based on the "Diagnostic Points of Major Cerebrovascular Diseases in China 2019" formulated by the Chinese Society of Neurology.

(1) Diagnostic criteria for cerebral infarction

① Acute onset of focal or global neurological deficits;

(2) cerebral infarction confirmed by imaging, or symptoms and signs lasting more than 24 hours, or leading to death within 24 hours;

③ Non-ischemic causes were excluded.

(2) Diagnostic criteria for cerebral hemorrhage

① Sudden focal neurological deficit or headache, vomiting, varying degrees of disturbance of consciousness;

② Cranial imaging showed intracerebral hemorrhage;

③ excluding other causes of cerebral hemorrhage.

(3) PSCI diagnostic criteria: Western medicine diagnostic criteria for vascular cognitive impairment in the Chinese Guidelines for the Diagnosis and Treatment of Vascular Cognitive Impairment (2024 edition) formulated by the Vascular Cognitive Impairment Branch of the Chinese Stroke Association: ① There are cognition-related complaints and one or more cognitive domains are impaired by neuropsychological tests; ② Evidence of vascular brain injury: including vascular risk factors, stroke history, neurological syndromes of cerebrovascular injury, and imaging evidence of cerebrovascular injury, but not necessarily all of the above at the same time; (3) vascular brain injury dominated in cognitive impairment: especially in merger dementia symptoms, should clearly define the role of vascular brain damage in cognitive impairment and clinical features need to conform to one of the following situations: 1) The onset of cognitive impairment is sudden, and the occurrence of cognitive impairment is related to one or more stroke events in time, showing a stepwise or fluctuating progression, and the cognitive impairment is within 6 months after the stroke event.

3.1.3.2 TCM diagnostic criteria

According to the Criteria for Diagnosis and Efficacy Evaluation of Stroke issued by the State Administration of Traditional Chinese Medicine:

Main symptoms: unconscious consciousness, hemiplegia, language Jian astringent or no language, partial body sensory abnormalities, tongue deviation.

Secondary symptoms: vertigo, headache, choking on drinking, dysphagia, non-blink eyes, ataxia.

According to the diagnostic criteria, patients with more than two main symptoms, or one main symptom with two secondary symptoms, can be diagnosed as stroke. On the basis of

meeting the diagnosis of stroke, patients with clinical symptoms of cognitive impairment in accordance with the Guidelines for the Diagnosis and Treatment of Vascular mild cognitive Impairment in Traditional Chinese Medicine 2024 Edition were included in the study diagnostic criteria.

3.1.4 Inclusion criteria

(1) Meet the western medical diagnostic criteria of vascular cognitive impairment according to the western medical diagnostic criteria of vascular cognitive impairment in the Guidelines for Diagnosis and Treatment of Vascular cognitive Impairment in China (2024 edition) formulated by the Vascular Cognitive Impairment Branch of the Chinese Stroke Association. 1) patients with cognitive-related complaints and impairment of one or more cognitive domains in neuropsychological tests; 2) presence of evidence of vascular brain injury, including vascular risk factors, stroke history, neurological syndromes of cerebrovascular injury, and imaging evidence of cerebrovascular injury, but not necessarily all of the above; 3) The dominant role of vascular brain injury in cognitive impairment: especially when combined with the pathological manifestations of dementia, the dominant role of vascular brain injury in cognitive impairment should be clarified, and the clinical features should meet the following conditions: The onset of cognitive impairment was sudden, and the occurrence of cognitive impairment was related to one or more stroke events in time, showing a stepwise or fluctuating progression, and the cognitive impairment appeared within 6 months after the stroke event.

(2) meet the TCM diagnostic criteria of vascular cognitive impairment in the Guidelines for the Diagnosis and Treatment of Vascular Mild cognitive Impairment (2024);

(3) simple Mental State scale (Mini - getting the State Examination, MMSE) score in 12 to 24 points, Montreal Cognitive Assessment scale (Montreal Cognitive Assessment, MoCA) score in the < 24 points; Patients with cognitive impairment but without severe dementia; The national institutes of health Stroke Scale (NIH Stroke Scale, NIHSS) scoring eight points or less; Ascertain Dementia 8 (AD-8) score < 2;

(4) aged between 35-80 years old;

(5) have basic communication skills, mainly Mandarin (communication language is sufficient), and have at least one stable caregiver;

(6) Informed consent was obtained.

3.1.5 Exclusion criteria

（1）Merger zang-fu organs such as heart, liver, kidney and severe primary chronic diseases such as endocrine system and hematopoietic system, serious heart cerebrovascular disease;

（2）Patients who are prone to skin diseases such as herpes, ulceration or scar constitution on the body surface, and are not suitable for acupuncture treatment;

（3）Not suitable for repeated MRI examination, such as claustrophobia, aneurysm embolization, etc.

（4）Before the onset of existing cognitive impairment or other serious neurological and psychiatric disorders, control unstable patients;

（5）Other patients deemed by the clinical experimentalists to be unfit for the study;

（6）Participated in clinical research of related diseases in the past 3 months;

3.1.6 Exclusion and drop-out criteria

Exclusion criteria (those who have been enrolled but meet one of the following criteria should be excluded) : (1) Those who do not meet the inclusion and exclusion criteria are found in the trial; (2) obvious adverse reactions occurred during the treatment; (3) The subjects were not treated according to the treatment plan after enrollment.

Drop-out criteria (patients who had been enrolled but had not completed the clinical protocol were considered drop-out in the following circumstances) : (1) patients withdrew or lost follow-up; (2) serious adverse reactions or adverse events occurred during the treatment.

3.1.7 Discontinuation criteria

(1) Specialists will be responsible for the evaluation of severe adverse reactions during the study to determine whether to continue or terminate the study;

(2) if the subjects developed serious complications or other serious diseases during the study period and needed to take emergency measures;

(3) the subjects could not continue the study for other reasons.

3.1.8 Adverse events

The number and reasons of adverse events and dropout from the trial were recorded in detail.

3.2 Treatment Regimens

In this study, a randomized controlled trial of acupuncture and moxibustion for post-stroke cognitive impairment was conducted, which systematically clarified the evolution law of TCM syndromes of stroke, established an individualized and precise treatment plan, and explored the establishment of precise diagnosis and treatment standards of TCM for post-stroke cognitive impairment based on the randomized controlled trial. The proposed study period: January 1,

2025 (after obtaining ethical approval) to December 31, 2026. Treatment methods are described as follows.

3.2.1 Sham EA group:

Conventional medicine, rehabilitation treatment and ordinary acupuncture treatment:

① Conventional drug therapy (basic principles of conventional treatment) : according to the patient's condition, the basic treatment such as anti-platelet aggregation, lipid-regulating, stable plaque, blood pressure and blood glucose control was given, and the specific treatment referred to the "Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke 2023".

(2) rehabilitation treatment, rehabilitation of patients before rehabilitation evaluation, rehabilitation goals determine patients, to formulate individualized rehabilitation plan. The therapist covered the name of the picture with his hand, and asked the patient to read the content of the card and say its purpose. 10 cards/time, 1 time/day; The complete pony puzzle was given to the patient, and the patient was asked to take the picture off, and then the patient was asked to put it back together, 2 times/time, 1 time/day; Executive function training and problem-solving skills training: rehabilitation therapists should observe and evaluate the training from simple to complex; Time and place orientation training; Activities of daily living training; Psychological support therapy. The therapy was given 5 times a week for 30 minutes each time for 3 months.

③ Sham electroacupuncture treatment:

1) Acupoint selection: main acupoint selection: bilateral para-frontal line (MS2), Tianzhu (BL10), Fengchi (GB20), Fuxue (Blood vessels), parietal midline line (MS5) and para-parietal line (MS8). The corresponding acupoints: kidney deficiency and blood stasis syndrome plus Geshu (BL17) and Shenshu (BL23); Zusanli (ST36) and Sanyinjiao (SP6) were added for qi deficiency and blood stasis syndrome. For internal obstruction of phlegm and heat, Yinlingquan (SP9) and Fenglong (ST40) were added. Sanyinjiao (SP6) and Taixi (KI3) were added for Yin deficiency and fire exuberant syndrome. Pishu (BL20) and Shenshu (BL23) were added to spleen-kidney deficiency syndrome. (Refer to "Guidelines for the Diagnosis and Treatment of Vascular Mild cognitive Impairment of Traditional Chinese Medicine (2024)" for the syndrome type and acupoint selection).

2) Positioning: Referring to the national standard of the People's Republic of China (GB/T 12346-2021) "Name and Location of meridians and acupoints", and referring to the national standard of the People's Republic of China (GB/T 21709.2-2021) "Technical Specifications for Acupuncture and Moxibustion Part 2: "Scalp Acupuncture" and China Medical Science and Technology Press in 2024, "Sixteen meridians of high-dimension bin

electroacupuncture".

3) Operation: in a sitting position, the skin at the acupuncture site was routinely disinfected, and the local acupoints were selected with 0.25×40mm filiform needles to smooth reinforcing and reducing. At the remote acupoints, 0.25×40mm filiform needle was used for straight needling, and the reinforcing method was applied for lifting and thrusting Deqi. The wires of electroacupuncture apparatus were connected on the ipsilateral para-frontal line (MS2) and Tianzhu (BL10), and sham electroacupuncture was performed with an electroacupuncture apparatus that could not output current.

4) Treatment: once a day, 5 times a week, a total of 8 weeks, a total of 40 times.

5) Needles and fixtures: The needles and fixtures are disposable Huatuo brand acupuncture and moxibustion needles produced by Suzhou Medical Supplies Factory Co., LTD. The manufacturer's license is Jiangsu Drug Supervision and Equipment Production License No. 20010020, and the registration certificate No. 220162200970. The specification is φ0.25×40mm (1.5 inch). The electroacupuncture instrument is SDZ-IIB model, produced by Suzhou Medical Supplies Factory Co., LTD., but the wire has been cut before the factory, and the current cannot be generated.

3.2.2 Electroacupuncture group:

On the basis of conventional medicine and rehabilitation treatment (ordinary acupuncture group), acupuncture electric field therapy was performed:

① Acupoint selection: the main acupoints and the matching acupoints were selected as the sham EA group.

② Positioning: referring to the Name and Location of meridian points of the national standard of the People's Republic of China (GB/T 12346-2021), and referring to the Technical operation specification of Acupuncture and Moxibustion of the People's Republic of China (GB/T 21709.2-2021) Part 2: Head needle and Chinese medicine science and technology press, 2024 "including higher dimensional marina 16 unique".

③ Operation: in a sitting position, the skin of the acupuncture site was routinely disinfected, and the local acupoints were selected with 0.25×40mm filiform needle for flat reinforcement and flat reduction. At the remote acupoints, 0.25×40mm filiform needle was used for straight needling, and the reinforcing method was applied for lifting and thrusting Deqi. **The** electroacupuncture instrument wires were connected at MS2 and **BL10 on the ipsilateral side, and EA was applied to the head in one pair on each side**.

④ Electroacupuncture parameters: dense wave, frequency 100Hz, current size according to the patient's tolerance, treatment time 30 minutes.

⑤ Treatment course: once a day, 5 times a week, a total of 8 weeks, a total of 40 times.

6. Needle and electric acupuncture apparatus: needle with suzhou medical supplies factory co., LTD. Hua tuo brand disposable acupuncture needle, production enterprise licence: Sue drug safety machinery production license no. 20010020, registration number: Sue machinery note no. 220162200970. The specification is φ0.25×40mm (1.5 inch). The electroacupuncture instrument is SDZ-IIB model, produced by Suzhou Medical Supplies Factory Co., LTD.

Observation period and time point:

There were 24 weeks in total, including 1 week in screening period (week 0), 1 week in baseline period (week 0), 8 weeks in treatment period (weeks 1-8 after enrollment), and 16 weeks in follow-up period (weeks 9-24 after enrollment). If the patient's diagnosis was confirmed, the screening period and the baseline period could be combined for 1 week.

Baseline period (week 0) : The main indicators were completed: ①MMSE scale; ② MoCA scale; ③CDR scale; ④NTB scale; Secondary outcome measures ① Functional near-infrared spectroscopy (fNIRS) ② electroencephalogram (EEG) ③ MRI +DWI perfusion imaging ④ Modified RANKIN Scale ⑤ Quality of Life scale (SS-QOL) and Barthel index ⑥ Pittsburgh sleep quality Index (PSQI) ⑦ Hamilton Depression Scale (HAMD)

Follow-up period (week 12) : the main indicators were ①MMSE scale ②MoCA scale ③CDR scale ④NTB scale, and the secondary indicators were ① modified RANKIN scale ② SS-QOL and Barthel index ③ PSQI scale ④ HAMD.

Follow-up period (24th week) : the main indicators were completed: ①MMSE scale; ② MoCA scale; ③CDR scale; ④NTB scale;

3.2.3 Efficacy index and evaluation

(1) Primary outcome measures

1) MMSE scale: It is simple and easy to perform, widely used at home and abroad, and is the first choice for dementia screening. The scale includes the following 7 domains: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language and visuospatial ability. A total of 30 items were included in the scale. Each item was scored 1 point for correct answers and 0 point for incorrect or uncertain answers. The test scores were closely related to the educational level. The normal cut-off points were: illiterates > 17 points, primary school > 20 points, junior high school and above > 24 points. The patients were evaluated before treatment, 12 weeks and 24 weeks after treatment.

2) MoCA, which included 11 items in 8 cognitive domains including attention and concentration, executive function, memory, language, visual structure skills, abstract thinking, calculation and orientation. The total score is 30 points, and ≥26 points are normal. Assessments

were performed before treatment and 12 and 24 weeks after the end of treatment.

3) Neuropsychological test battery (NTB)：Is composed of nine cognitive tests, including visual matching memory, wechsler memory scale (WMS) WMS word matching, Rey auditory memory vocabulary learning test, WMS test of digit span, language fluency, and category fluency test, can be more comprehensive assessment of the cognitive function and its damage degree. All patients were assessed at baseline, 12 weeks and 24 weeks after the treatment.

(2) Secondary efficacy indicators

1) functional near infrared imaging: technical parameters: use between 700-900 - nm wavelength near infrared spectrum instrument and record the change of the blood oxygen level and cerebral blood flow. The changes of blood oxygen level and cerebral blood flow were recorded at 0 week before treatment and 8 weeks after treatment.

2) Electroencephalogram (EEG)：EEG was recorded. The EEG was performed at 0 week before treatment and 8 weeks after treatment.

2) magnetic resonance imaging (MRI)：has important value in diagnosis and evaluation of stroke, the comprehensive assessment of electric effects on brain structure and function. In week 0 before and after treatment respectively for 8 weeks.

3) nerve functional assessment: Modified RANKIN Scale (Modified RANKIN Scale, mRS), respectively 0 weeks before and after treatment to evaluate 12 weeks and 24 weeks after treatment.

4) the quality of life: the modified Barthel index rating scale (modified Barthel index, MBI) in 0 weeks before and after treatment to evaluate 12 weeks and 24 weeks after treatment.

5) Sleep quality assessment: Pittsburgh sleep quality index (PSQI) was used to evaluate sleep quality. PSQI was composed of seven dimensions: subjective sleep quality, sleep onset time, sleep duration, sleep interference, use of hypnotics, daytime dysfunction and sleep efficiency. The total score of the seven dimensions was the total score of PSQI. In this study, sleep quality was divided into "very good" (0-5 points), "good" (6-10 points), "fair" (11-15 points) and "poor" (16-21 points). In week 0 before treatment and after treatment to evaluate 12 weeks and 24 weeks after treatment.

6) The Hamilton Depression Scale (HAMD) was used to evaluate the improvement of depression: <7 points indicated no, 7-17 points indicated possible, 17-24 points indicated definite, and >24 points indicated severe depression. The patients were evaluated at 0 week before treatment, 12 weeks after treatment, and 24 weeks after treatment.

7) in evaluation of syndromes: refer to the Chinese administration of traditional Chinese medicine department of the mild cognitive impairment of vascular origin of traditional Chinese

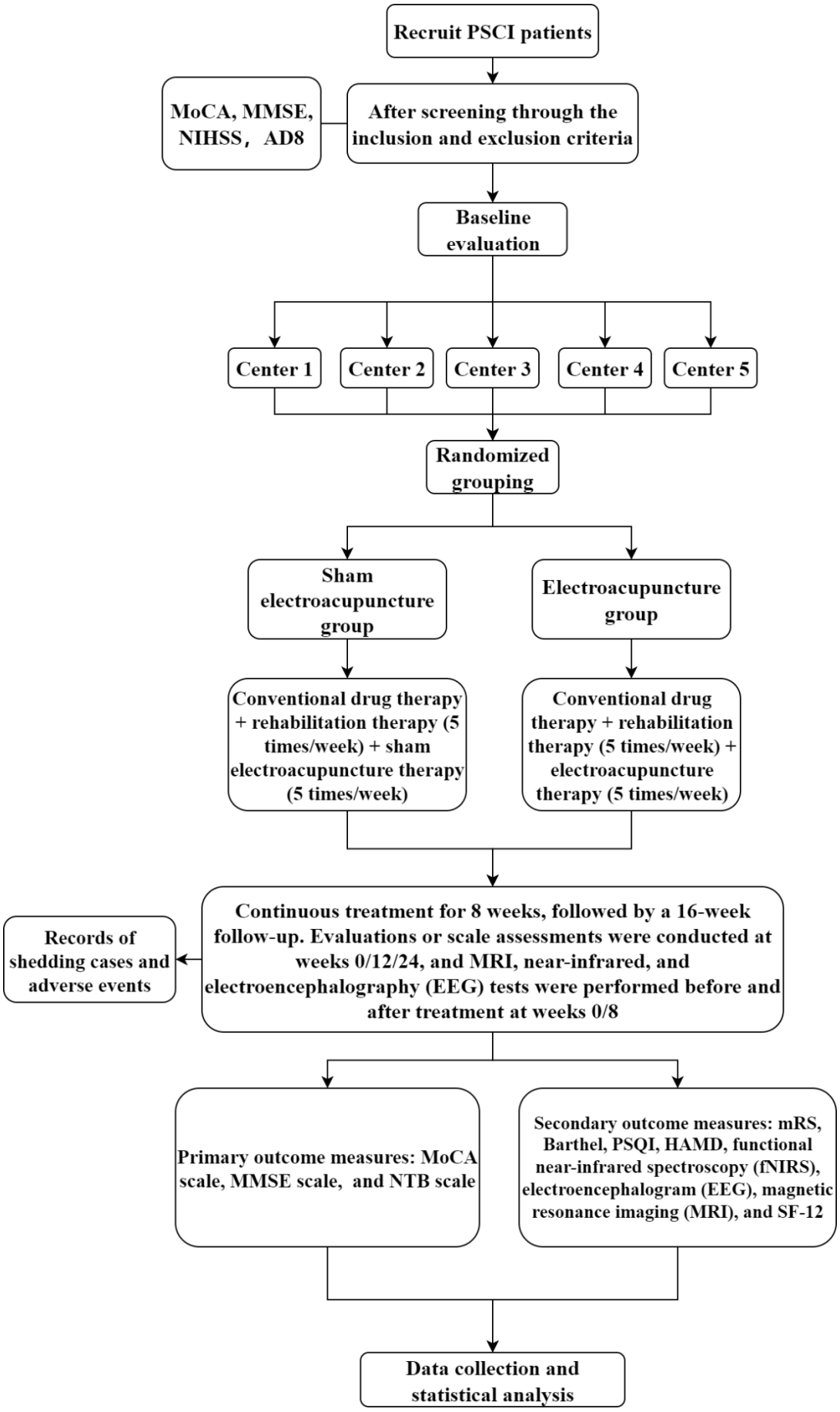
medicine diagnosis and treatment guidelines (2024), 2 by the attending physician or above title of doctor of traditional Chinese medicine according to the stroke onset symptoms and signs of TCM four diagnostic data acquisition, the advice which assist, doctor evaluation by the supervisor. The patients' syndromes were diagnosed dialectically. The patients were evaluated at 0 week before treatment, 12 weeks after treatment, and 24 weeks after treatment.

8) health measuring 12 profiles: use the SF - 12 scale assessment, the scale covers eight aspects: function, physical character, body pain, general health, mental health, social function, mental health, emotional role. The overall score range of 0-100, said the higher the score, the better health. In each dimension of health, standardized scores of 50, said compared with the general population, individual health level in the dimension. Outcomes were assessed at the end of treatment (week 8).

3.3 Emergency response

During the trial, acupuncture should be performed under the guidance of a specialist or by a senior doctor. If the patient's disease worsens or cannot be relieved by the existing treatment during the treatment, which seriously affects daily work and life, emergency adjustment of treatment plans and emergency measures can be adopted after the evaluation and diagnosis of a specialist, and the specialist can evaluate whether to stop the study. The use of all kinds of emergency drugs or other treatment measures the date and time and dose must record in a timely manner.

3.4 Technical route



Iii. Adverse Events (described according to the subject)

1. Definitions of adverse events and serious adverse events

(1) adverse events: currently, the cognitive impairment after stroke in acupuncture treatment and no significant adverse events, but there are some unforeseeable factors, such as demographic characteristics, age, female and low education level; Stroke-related factors included history of stroke or recurrent stroke, hemorrhagic stroke, multiple lesions, large volume lesions, dominant hemisphere lesions, etc. After acupuncture, some patients may experience fatigue, head and neck discomfort, etc.

(2) Serious adverse events were defined as adverse events occurring during the study period that met one or more of the following criteria: death; Life-threatening; Requiring or prolonged hospitalization; Permanently or severely disabled; Causing congenital malformation defects.

Medical events that do not result in death, life threatening, or hospitalization are considered serious adverse events when they are judged by appropriate medical judgment to be likely to cause harm to the subject or to require medical or surgical treatment to avoid the occurrence of the above conditions.

2. Obtain information about adverse events

All adverse events that were either directly observed by the physician or spontaneously reported by the participant were reported by the study physician in concise medical terms. In addition, subjects were asked about adverse events each time they were asked after the start of treatment to collect trial data. The question could be, "Have you had any health problems since you started taking tongue measurements?" "Or" Have you had any unwell health problems since you started receiving XX?" "Etc.

3. Observation and recording of adverse events

Any symptoms, signs, and laboratory abnormalities that occurred from the time of signing the informed consent to the end of the last visit were included. The occurrence of adverse events, including the time of occurrence, severity, duration, measures taken, and outcomes were described. Adverse events were recorded in the designated pathology Report Form Adverse Events Table.

4. Management of adverse events and serious adverse events

(1) Severity: Physicians can use the following definitions to judge the severity of all adverse events and serious adverse events as the end point/data cutoff point of the study.

Mild adverse events were transient and easily tolerated by patients.

Moderate adverse events made the subject uncomfortable and prevented the normal activities of the subject.

Severe adverse events affected subjects' activities of daily living to a considerable extent and may have resulted in loss of function or be life-threatening.

(2) Management of adverse events: During the study period, if a patient has adverse reactions such as fatigue and weakness, local skin allergy, please tell your study physician immediately, and he/she will suspend the study and observe and deal with your discomfort. The tongue image information method of this study has a high safety. If you have any injury in the process of this study that has been confirmed by relevant institutions and related to this study, the researchers will compensate and compensate you in accordance with the relevant national laws and regulations.

For the adverse events that occurred during the trial, the type, degree, occurrence time, duration, treatment measures, and treatment process should be recorded in the medical record and pathological report form, and whether they were related to the trial should be comprehensively analyzed. After the occurrence of adverse events, the investigator can decide whether the subject should discontinue the trial according to the patient's condition. Patients who discontinued the trial because of serious adverse events should be followed and their outcomes recorded.

(3) Recording and reporting of serious adverse events: if a serious adverse event occurred during the trial, regardless of whether it was related to the trial, emergency measures should be taken immediately, and the principal investigator and the ethics committee should be notified by telephone within 24 hours. A serious adverse event report form was then completed and promptly reported to the above departments.

Iv. Ethics and Quality

Prior ethics committee approval will be obtained before the start of this study.

It is important to obtain authorized consent for the use and/or disclosure of personal and/or health data before enrolling patients. To protect patient privacy, the patient's initials will be recorded on the CRF.

Case report form data collected from the study centers will be checked for consistency, and a data query form will be issued for inconsistent data, requiring clarification by the physician.

5. Data management

The investigators will fill in the case report form and collect or record the collected data in Excel according to the requirements of the study protocol. Chen Bowen and Fu Luyao are

responsible for data management to ensure the authenticity, completeness and accuracy of the clinical trial data. At the end of the study, investigators will submit completed and signed case report forms for all enrolled patients to the data management center. Case-report form data collected from the sites will be checked for consistency, and a question form will be issued in response to inconsistent data, requiring clarification by the investigator.

6. Statistical Analysis

1. Statistical software

The data were analyzed by a third party statistician who was not involved in the preliminary study. Statistical software SPSS 26.0 and GraphPad Prism 8.0 were used for statistical analysis.

2. Data Description

Measurement data were described by mean ± standard deviation (), median, maximum, minimum and quartile, and enumeration data were described by percentage (%). $\bar{x} \pm s$

3. Statistics

SPSS 26.0 and GraphPad Prism 8.0 software were used for data analysis. Quantitative variables (normal distribution) were described by mean and standard deviation ($\bar{X}$±s) and compared by Analysis of Variance (ANOVA). The non-normal distribution data were described by median and quartile [M(QL-QU)], and the rank sum test was used for comparison. Categorical variables were described by frequency and percentage, and compared by chi-square test and Fisher's exact test. Univariate and multivariate Logistic regression models were used to explore the relationship between different exposure factors and cognitive function of patients. Mixed linear models were used to capture individual differences and to analyze the differences in multimodal brain function data between groups. All tests were two-sided, and $P<0.05$ was considered statistically significant.

4. Statistical Analysis Plan

Done by professional statisticians. After all data entry and review, the statistician should complete the statistical analysis work in time and issue a written statistical analysis report.

Vii. Final report and publication

After the study is completed, the study report will include a description of the study's objectives, the methods used in the study, and the results and conclusions.

Viii. Quality control

(1) The test SOP should be formulated by the research group.

(2) A special training meeting was held one month before the official start of the clinical

trial, and unified training was conducted for all investigators. The training mainly focused on the project implementation plan and various standard operating procedures (Sops), so that each clinical researcher could be familiar with the research process and specific implementation rules, and ensure the reliability of the clinical research conclusions.

(3) All observations in clinical research should be verified and repeatedly confirmed to ensure the reliability and originality of the data, and to ensure that the results and conclusions in clinical research are derived from the original data.

(4) To control the bias of the trial, special personnel should be employed to collect and count the trial data. A professional data management company was commissioned for clinical data management.

(5) The quality inspection of clinical research should be strictly carried out once a month.

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