Effects of Integrative Medicine on The Post-Stroke Cognitive Impairment (PSCI) Patients: A Study Protocol for A Randomized Multicentric Controlled Trial

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Abstract

Background

Due to limitation of rehabilitation in cognitive impairment after stroke, as the main parts of traditional Chinese medicine, acupuncture and herbs have their advantage effect in clinical practice for post-stroke cognitive impairment (PSCI). Therefore, forming a standardized and propagable TCM project of PSCI becomes necessary. This trail will solve the above problem.

Methods

In total, 126 stroke patients will be recruited from the inpatient and outpatient departments of The Third Affiliated Hospital of Zhejiang Chinese Medical University (Hangzhou, China), Jiaxing Hospital of Traditional Chinese Medicine and Hangzhou Hospital of Traditional Chinese Medicine to participate in this study with randomization. All participants will continue to receive basic treatment and cognitive function regular training, while successive 12 weeks of acupuncture and herbs will be provided to patients assigned to the integrative medicine group. Montreal cognitive assessment (MOCA), mini-mental state examination, activity of daily living (ADL) score, hamilton depression scale (HAMD), functional near-infrared spectroscopy (fNIRS) and RESTing-state functional MRI (RS-fmri) will be used to measure the outcomes.

Discussion

This trial may provide high-quality RCT evidence regarding the clinical effectiveness and safety of acupuncture and herbs for PSCI patient.

Trial registration:

ClinicalTrials.gov (ID: NCT 04596072)

Background

In recent years, stroke has been recognized by the Global Burden of Disease (GBD) as the second major factor affecting disability and loss of healthy life years, videlicet, stroke is the second leading cause of death and disability in the world[1]. A long-term outcome in stroke patients with cognitive impairment clinical study has found that stroke without cognitive impairment is more likely to live longer than with cognitive impairment[2]. Due to abnormalities of the visual spatial function and executive function, structure, memory, orientation, attention in PSCI patients, their daily life and social activity ability are greatly affected, and heavy burden is pressed to the society and family[3].

Currently, the rehabilitation of PSCI includes drug therapy and non-drug therapy[4]. There is no specific effective drug for the treatment of PSCI, but considering that the vascular dementia and dementia have certain overlaps in neuropathology and neurochemistry mechanism, cholinesterase inhibitors and non - competitive N- methyl -D- aspartic acid receptor antagonist have been approved for improving cognitive function after stroke[4]. In addition, new drugs have been developed but not commonly used, such as neurotrophic enhancers like Bryostatin[5]. Other neurotransmitters are also used in clinic, but they are lack of efficiency study on PCSI[6]. The non-drug therapy includes cognitive training therapy, occupational therapy, music therapy[7], repetitive transcranial magnetic stimulation (rTMS)[8], transcranial electrical stimulation[9], psychological intervention[10] and other rehabilitation methods. However, there is still lacking for large sample clinical studies to verify their clinical efficacy and safety of non-drug therapy.

Nowadays, traditional Chinese medicine (TCM) has become an important therapy of PSCI treatment due to its advantages such as low cost, simple manipulation and favorable effectiveness[11]. For TCM clinical application, acupuncture and moxibustion, herbs and Qigong have achieved excellent results in PSCI treatment [12–17]. Although many clinical studies have shown that TCM treatment of PSCI is effective. Hence, a multi-center, large sample and randomized controlled study method is designed to assess the exact efficacy of acupuncture and herbs in the treatment of PSCI, so as to improve the evidence level of TCM application in the clinical treatment and form a standardized and propagable TCM project.

Methods/design

Objectives

The purpose of this study is to evaluate the efficacy and safety of acupuncture combined herbs treating post-stroke cognitive impairment by comparing changes in cognitive assessment, activity of daily living、 depressive state and the changes of brain regions after treatment. This study is expected to develop a standard, systematic and safe TCM integrative treatment plan for cognitive impairment after stroke, and improve the quality of life of patients.

Trail design

126 patients treated in the Third Affiliated Hospital of Zhejiang Chinese Medical University, Jiaxing Hospital of Traditional Chinese Medicine, Hangzhou Hospital of Traditional Chinese Medicine will be recruited from April 2019 to December 2023. The study plan has got approved by the ethics committee of the three hospitals. The clinical trial will be conducted in accordance with the 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines[18, 19] and the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) [20]. The 126 patients will be distributed to the control group and the TCM group in a 1:1 ratio. The control group will receive basic treatment and cognitive function regular training for 12 weeks, while the TCM group will receive basic treatment, cognitive function regular training, acupuncture and herbs for 12 weeks. The results will be measured by Montreal Cognitive Assessment (MOCA), mini-Mental State Examination, Activity of Daily Living (ADL)

score, Hamilton Depression Scale (HAMD), Functional near-infrared spectroscopy (fNIRS) and RESTing-state functional MRI (RS-fmri). Fig 1 shows the trial design.

Participants recruitment

Patients admitted to the Acupuncture and Moxibustion Department, Neurology Department and Rehabilitation Department of the Third Affiliated Hospital of Zhejiang Chinese Medical University, Rehabilitation Department of Jiaxing Hospital of Traditional Chinese Medicine, and Rehabilitation Department of Hangzhou Hospital of Traditional Chinese Medicine. The public obtain the message of this study by each hospital's WeChat Official Account, local newspapers, hospital's roll up banners and brochure. Interested patients can contact the investigator through phone, message, email, or WeChat.

Inclusion criteria

The patients should meet all the following criteria, which will be screened by a neurologist:

(1) Diagnosis of stroke in traditional Chinese medicine[21] and PSCI [22];

(2) Age above 18;

(3) The course of disease ranges from 30 to 180 days;

(4) The patient's legal guardian signs the informed consent;

(5) Montreal Cognitive Assessment (MoCA) score is 17-26, and if the duration of patient's education is less than or equal to 12 years, one score will be deducted;

(6) Hamilton Depression Scale (HAMD) score <20;

(7) Patient meets the requirements for indications of acupuncture and moxibustion techniques, and volunteers to accept acupuncture treatment without serious complications.

Exclusion criteria

The patients who meet the following criteria should be excluded and it will be screened by a neurologist:

(1) Cognitive impairment caused by subarachnoid hemorrhage, transient ischemic attack, or other intracranial lesions such as intracranial tumors, aneurysms, vascular malformations, cysticercosis, schistosomiasis, encephalitis, meningitis, hydrocephalus, sequelae of brain trauma;

(2) non-atherosclerotic thrombotic cerebral infarction (such as cardiac embolism, coagulation state, endovascular shedding, arteritis);

(3) Pregnant or lactating women;

(4) Patients with severe primary chronic diseases including heart, liver, kidney and other viscera, as well as the endocrine system and hematopoietic system), severe dementia, serious language understanding disorders, mental illness;

(5) Patient with a variety of bleeding tendency diseases;

(6) Patients who do not meet the inclusion criteria and are not suitable for clinical observation.

Interventions

Both of the two groups will receive basic treatment and cognitive function regular training, which is conducted by experienced doctors and rehabilitation therapists following the Standard Operation Procedure document (SOP) and Chinese Stroke Association guidelines for clinical management of cerebrovascular disorders[23]. During the whole study process, training sessions for investigators will be held regularly so that the equal quality of all the interventions will be guaranteed.

Control group

The control group will receive basic treatment and cognitive function regular training, including cognitive function training, daily life activity training, psychological support therapy and so on. Treatment will be performed 30min each time, and 5 times a week for 12 weeks.

Integrative Medicine group

The integrative medicine group will receive basic treatment and cognitive function regular training, which are the same as the control group. Besides, acupuncture and herbs are administered 5 times a week for 4 weeks.

Acupuncture

Acupoints: Shenting (GV24) (bilateral), Benshen (GB13), Baihui (GV20), Sishencong (EX-HN1), Fengchi (GB20) (bilateral), Fenglong (ST40) (bilateral), Zusanli (ST36) (bilateral), Xuanzhong (GB39) (bilateral), Top midline, Forehead midline, No.1 line near the top (bilateral).

Needles: 0.25mm×40mm stainless steel needle of Huatuo Brand (produced by Suzhou Medical Supplies Factory Co., LTD.).

Manipulation: The patient will lie in prone position, and the acupoints skin will be disinfected with 75% ethanol. Different manipulations are used for different acupoints (table 1). Acupuncture will be applied five times weekly for 12 weeks, and every treatment lasts 30min.

Herbs

The herbal treatment will be based on the syndrome differentiation. All the syndromes and treatments will be divided into the following five types. The herbs will be given five times weekly for 12 weeks, and twice

for one day.

(1) Liver and kidney yin deficiency syndrome

Treatment: To tonify liver and kidney, fill essence and restore energy.

The formulas: Liu-Wei-Di-Huang-Wan (Six-Ingredient Rehmannia Pill) or Chinese patent medicine with similar efficacy.

(2) Spleen and kidney deficiency syndrome

Treatment: To tonify kidney and spleen, replenish qi to invigorate essence.

The formulas: Gui-Pi-Tang (Spleen-Restoring Decoction) and Huan-Shao-Dan, or Chinese patent medicine with similar efficacy.

(3) Phlegm and turbidity obstruct brain

Treatment: To clear phlegm for resuscitation, invigorate the spleen and transform turbidity.

The formulas: Di-Tan-Tang (Phlegm-Flushing Decoction) or Chinese patent medicine with similar efficacy.

(4) Stagnation of blood stasis syndrome

Treatment: To promote blood circulation to remove blood stasis, awake and enlighten brain

The formulas: Tong-Qiao-Huo-Xue-Tang （Orifice-Opening and Blood-Invigorating Decoction）or Chinese patent medicine with similar efficacy.

(5) Hyperactivity of liver-yang syndrome

Treatment: To calm liver wind, active blood and clear heat, tonify the liver and kidney.

The formulas: Tian-Ma-Gou-Teng-Yin (Gastrodia and Uncaria Decoction) or Chinese patent medicine with similar efficacy.

Outcome measures

Table 2 Outcome measurements at each timepoint

Primary outcome measures

Improvement of Cognitive function: we will use Montreal Cognitive Assessment (MOCA) score from baseline to 12 weeks. This assessment has high sensitivity and specificity of assessing cognitive impairment, and it is evaluated from visual spatial function, language function, image ability, orientation and so on.

Secondary outcome indicators

1. Montreal cognitive assessment scale score change trend

The MoCA scores of baseline, 0 week, 8 weeks, 12 weeks, 16 weeks and 24 weeks will be analyzed to evaluate the Montreal cognitive assessment scale score change trend.

2. Changes in memory, attention and computational ability, language function

We will divide MoCA scores of baseline and 12 weeks into memory, attention and computational ability, and language function. Different analyses will be used to evaluate different abilities.

3. The rate of change in the scores of mini-Mental State Examination (MMSE)

MMSE scores will be analyzed at baseline, 0 week, 8 weeks, 12 weeks, 16 weeks and 24 weeks.

4. Changes in Daily Living ability

The Activity of Daily Living (ADL) score will be analyzed at 0 week, 12 weeks, 16 weeks and 24 weeks.

5. Changes in depressive status

Hamilton Depression Scale (HAMD) scores will be analyzed 0 week, 12 weeks, 16 weeks and 24 weeks.

6. Changes in the patterns of related brain regions in cognitive impairment

The changes of amplitude of low-frequency fluctuations (ALFFs), regional homogeneity (ReHo) and functional connecting (FC) of RESTing-state functional MRI (RS-fmri) will be analyzed at baseline and 12 weeks.

7. Neural activity in the brain

The changes of the concentration of oxy-hemoglobin (HbO2), deoxy-hemoglobin (Hbb), cerebral blood flow (CBF) and cerebral blood volume of Functional near-infrared spectroscopy (fNIRS) will be analyzed at baseline and 12 weeks.

8. Effective rate of cognitive function treatment

MoCA score will be calculated from baseline to 12 weeks of treatment and effective rate of treatment will follow the specific criteria. Recovered: the score increased by ≥90% compared with the baseline. Significantly effective: the score increased between 70% and 89% compared with the baseline. Effective: the score increased between 30% and 69% compared with the baseline. Ineffective: the score increased < 30% compared with the baseline.

Sample size

The calculation of sample size will be based on the change of MoCA scores. Research and clinical experience suggest that in an acupuncture group and a non-acupuncture group, a clinically significant therapeutic effect is defined as a MoCA score difference of 2.6 between [12, 24, 25]. A two-sided, two-sample t test at the 0.05 significance level will be used. With an estimated 20% dropout rate at final follow-up, 63 cases are required for each group, which means 126 patients in total will be enrolled.

Randomization and blinding

Eligible patients will be randomly assigned (1:1) to either the TCM group or the control group. Randomisation will be stratified by centers. The permuted block (4 or 6 patients per block) randomisation sequence, including stratification, will be prepared by a statistician not involved in the trial using R (version 4.0.0).

Because it is an open trial, no blind will be required. The acupuncture and herbal treatments will be performed by licensed acupuncturists with a master degree. The efficacy of acupuncture will be evaluated by a RA. Patients who are enrolled will be aware of their group assignment.

Statistical analysis

No matter the primary or secondary outcomes will be analyzed by using modified intention-to-treat exposed population. In this study, the primary and secondary outcomes will be analyzed by using the modified intention-to-treat analysis. The primary outcome measures will be analyzed using a hybrid effects model (MMRM) designed by repeated measurements. The secondary outcome measures (MMSE, ADL, HAMD) will be analyzed by means of covariance analysis. The study will carry out statistical description of the adverse events, and compare the differences between groups using Chi-square test or Fisher's exact as an appropriate method.

The results of rs-fMRI and fNIRS will be imputed using multiple imputation methods, and the specialized analysis will be supported by Jia XZ group from Hangzhou Normal University.

Collection and management of data

The designed case report form (CRF) will collect each participant's data and transfer them into our database. We set up a data collection database to make sure the integrity of the trail, which is established on O-trial + Clinical Trial Execution management platform V4.0 (o-Trial). The core management system of platform is applied for the registered clinical projects. With mobile internet technology, the experimental trial is able to finish completely, and achieve the steady progress of the trail.

Safety monitoring

Presently, adverse events (AEs) of acupuncture are few and mild, such as pain, numbness, skin bruising. And herbs may cause allergy, liver and renal dysfunctions. We will record any serious AEs associated with

the trial, and immediately report to the main researchers and take corresponding measures. If the AEs are too severe, the patients will be withdrawn from the study.

Quality control

All the intervention and measures will be conducted by experienced physicians and therapists with the professional license. All the physicians and therapists will receive two-day professional training to familiarize with treatment options and training sessions will be held regularly.

To standardize clinical practices and provide clinical quality assurance, a Standard Operation Procedure document (SOP) will be developed to ensure consistency among different investigators. The SOP will include how to screen the participants, how to carry out randomization and blinding, and standardized manipulation procedures. Therefore, the management will be standardized and achievable.

Discussion

TCM has significant advantages in the treatment of PSCI and its main therapies include acupuncture, herbs, and *tuina*, all of which are proved effective [26–33]. However, most of the clinical researches are based on personal experience, and there is no unified method to standardize the TCM treatment of PSCI. Moreover, there are few large-scale, multi-center, high-quality RCT studies. This protocol will make up the imperfections.

Nevertheless, there are still some limitations in this study. 1) Acupuncture and herbs may be perceived by patients, thus blinding method is impossible, and the patients of the control group will be suspicious and interfere with treatment. For this purpose, we will require the patients of the two groups not being treated in the same room at the same time, and manipulators, valuator and data processor are needed to be isolated from each other, so it will reduce bias of nonblinding as much as possible. 2) During the fNIRS and fMRI exams, the patients need to keep clam and maintain the head position. Due to some patients with cognitive disorder, they have a poor cooperation degree. Thus, we will assess patient status before exam and repeat exam if the results are wildly inaccurate. Hence, we will complete collection of the follow-up phase in all manner of ways, such as inviting participants to the clinic for further consultation, or visiting them at their homes, or using Internet video chat with them.

Trial Status

This study is currently in the recruitment phase. The first patient was enrolled in November 2020, and the study is expected to end in December 2023. (The protocol version number is V1.0, the protocol ID: 2020ZJZS002, 11/14/2020)

Declarations

Acknowledgements

Author contributions

Xinyun Li and Kelin He contributed equally to this work as co-first authors.

Ruijie Ma designed this study.

Competing interests None declared.

Patient consent for publication Not required.

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Data sharing statement The submitted manuscript is a study protocol which includes no primary data now. Further information unaddressed can be obtained from the corresponding author by the contact

methods provided in the manuscript.

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Tables

Table 1 Acupoints selected for use in the study

acupoints	location	Manipulation
Shenting(GV24) (bilateral)	On the head, the hairline up straight about 0.5inch	Insert forward 1inch, with at an angle of 15-30°oblique along the scalp, twist for 200 times /min and keep twisting for 1min until getting Qi, electric acupuncture with Qianding(GV 21),
Benshen (GB13)	On the head, 0.5 inch above the front hairline, 3 inch beside the Shenting(GV24), the intersection point between the inner 2/3 and outer 1/3 of the connection line between the Shenting(GV24) and Tou Wei(ST8)	Insert forward 1inch, with at an angle of 15-30°oblique along the scalp, twist for 200 times /min and keep twisting for 1min until getting Qi
Baihui(GV20)	On the head, the intersection of the midline and the line tips of the ears	Insert forward 1inch, with at an angle of 15-30°oblique along the scalp, twist for 200 times /min and keep twisting for 1min until getting Qi, electric acupuncture with Houshencong
Sishencong(EX-HN1)	On the head, conclude four acupionts(Qianshencong, Houshencong, Zuoshencong and Youshencong),which 1 inch beside Baihui on the four directions(front, back, left and right)	Insert toward Baihui 1inch, with at an angle of 15-30°oblique along the scalp, twist for 200 times /min and keep twisting for 1min until getting Qi. Houshencong is used electric acupuncture with Baihui
Fengchi(GB-20)(bilateral)	On the nape, below the occipital, on a level with Fengfu (DU-16), in the depression between the upper portion of trapezius and the sternocleidomastoid	Normal manipulation, electric acupuncture will be use between left Fengchi and Zuoshencong, right Fengchi and Youshencong
Fenglong (ST40) (bilateral)	On the crus anterolateral, 8inch above the tip of the lateral malleolus	Normal manipulation
Zusanli(ST36) (bilateral)	On the crus anterolateral, 3inch below the knee and 1inch beside the tibial crest.	Normal manipulation
Xuanzhong(GB39) (bilateral)	On the crus anterolateral, 3inch above the tip of the lateral malleolus	Normal manipulation
Top midline	On the top of the head, the line between the Baihui and Qianding	Insert forward 1inch, with at an angle of 15-30°oblique along the scalp, twist for 200 times /min and keep twisting for 1min until getting Qi
Forehead midline	In the middle of the forehead, above and down 0.5 inch of front hairline	Insert forward 1inch, with at an angle of 15-30°oblique along the scalp, twist for 200 times /min and keep twisting for 1min until getting Qi
No.1 line near the top (bilateral)	On the top of the head, 1.5 left and right sides beside the Du meridian	Insert forward 1inch, with at an angle of 15-30°oblique along the scalp,

Table 2 Outcome measurements at each timepoint

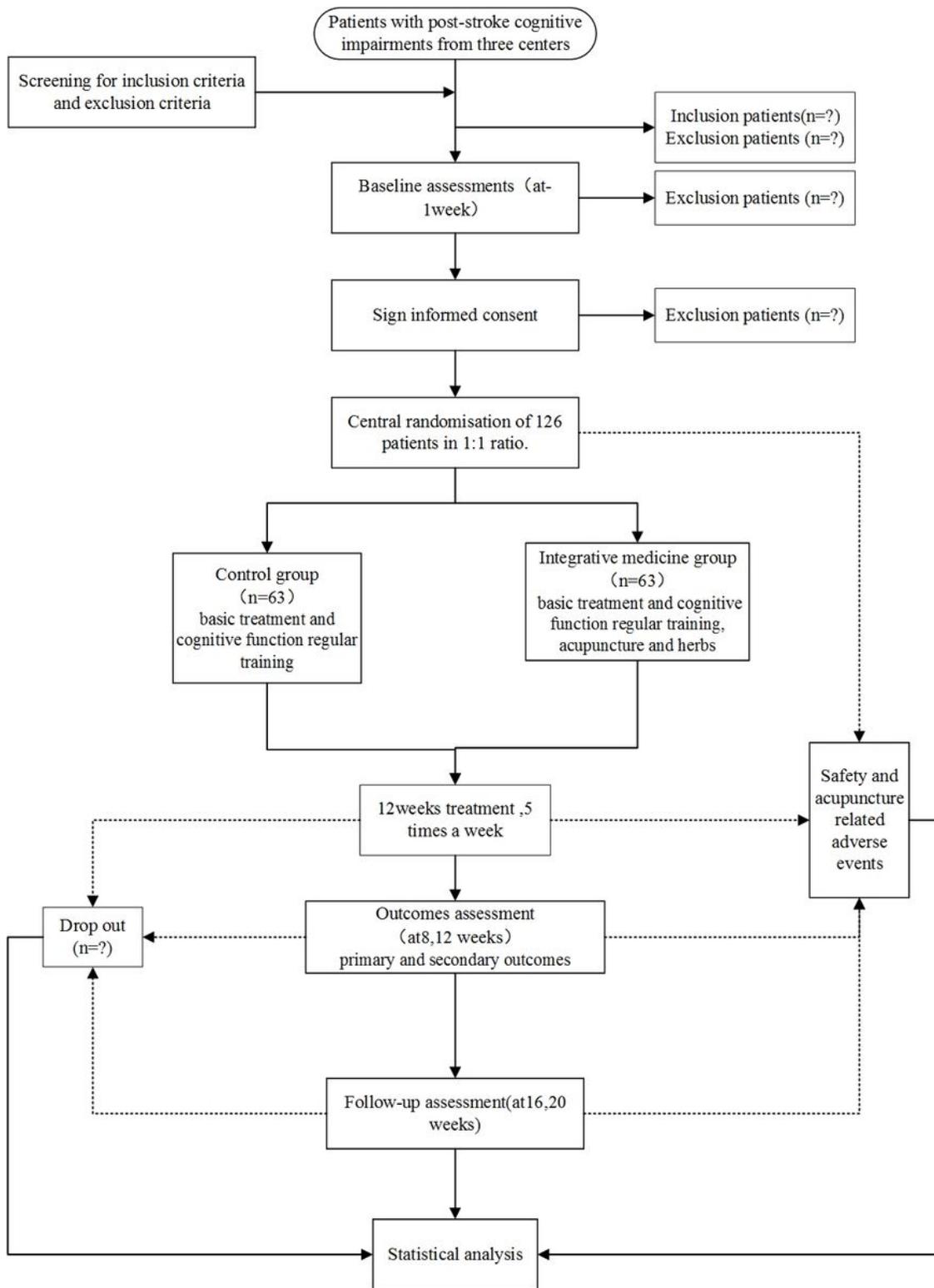| Measurements	Baseline		Treatment phase		Follow-up phase	
	−1weeks	0week	8weeks	12week	16weeks	24weeks
MoCA	×	×	×	×	×	×
MMSE	×	×	×	×	×	×
ADL		×		×	×	×
HAMD		×		×	×	×
RS-fMRI	×			×		
fNIRS	×			×		

Figures

Figure 1

Fig 1 shows the trial design.

Supplementary Files

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