Effects of different acupuncture treatment methods on post-stroke cognitive impairment: study protocol for a multicenter randomized controlled trial

Kai-Qi Su (surgdy1008@qq.com)  
Henan University of Traditional Chinese Medicine  
https://orcid.org/0000-0002-7362-3482

Su-Tong Liu  
Henan University of Traditional Chinese Medicine

Jie-Ying Li  
Henan University of Traditional Chinese Medicine

Rui-Qing Li  
The First Affiliated Hospital of Henan University of CM

Hui-Li Feng  
The First Affiliated Hospital of Henan University of CM

Yang Xue  
The First Affiliated Hospital of Henan University of CM

Xiao-Dong Feng  
The First Affiliated Hospital of Henan University of CM

Study protocol

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**Abstract**

**Background:** Cognitive impairment is one of common dysfunctions after stroke, which seriously affects the overall recovery of patients. Cognitive rehabilitation training is currently the main treatment to improve cognitive function, but its curative effect is limited. Acupuncture is a core component of traditional Chinese medicine (TCM) and some previous clinical studies have shown that it might be effective in treating post-stroke cognitive impairment (PSCI), but further evidence from large-sample studies is needed. The overall objective of this trial is to obtain further data for forming an optimized acupuncture treatment for PSCI by comparing the effects of different acupuncture treatment methods on cognitive function in PSCI patients.

**Methods/Design:** In this multicenter, prospective, randomized controlled trial, 206 eligible stroke inpatients who meet the trial criteria will be randomly assigned to 2 groups: Electroacupuncture (EA) plus needle retaining (NR) group and EA group, both groups of patients undergo the same routine cognitive rehabilitation treatments. All treatments will be given 6 times per week for 8 weeks. The primary outcomes will be assessed using the Mini Mental State Scale (MMSE) and the Montreal Cognition Assessment Scale (MOCA). The secondary outcome will be measured by the Bathel Index (BI). All outcomes will be evaluated at baseline, week 4, week 8, and the third and sixth month after the end of treatments.

**Discussion:** Our aim is to evaluate the effects of two different acupuncture treatment methods for treating PSCI patients. This study is expected to provide data to be used in developing an optimized acupuncture treatment method for PSCI treatment.

**Trial registration:** Chinese Clinical Trial Registry, ChiCTR1900027849. Registered on 30 November 2019, http://www.chictr.org.cn/showproj.aspx?proj=46316

**Background**

Stroke is the leading cause of death and disability worldwide, and has a rising incidence and a higher disability rate, often accompanied by many types of dysfunction [1-3]. Post-stroke cognitive impairment (PSCI) is a series of syndromes that meet the diagnostic criteria for cognitive impairment within 6 months after the occurrence of stroke, accounting for about 66% of strokes [4]. However, one study reported that the incidence of PSCI can be as high as 69.8% within 3 months of stroke [5]. PSCI mainly manifests as obstacles in advanced brain functions such as learning, memory, executive ability, visual space/structural ability, which seriously affects patients' quality of life (QOL) and overall rehabilitation [6, 7].

Management of vascular risk factors (hypertension, hyperlipidemia, diabetes, smoking, new atrial fibrillation and other arrhythmias) is critical, the use of antiplatelet drugs (aspirin, clopidogrel, etc.) and anticoagulants is selected according to the stroke prevention guidelines [8, 9]. In addition, the use of angiotensin-converting enzyme inhibitors and diuretics can delay the progress of white matter changes in patients with stroke [10]. Donepalcil, galantamine and memantine have been reported to improve cognitive
function, but there are adverse reactions and certain risks [11-13]. A Cochrane review analyzed the efficacy of non-drug interventions focusing on cognitive rehabilitation on PSCI, and the results showed that more research evidence is needed [14]. Hyperbaric oxygen therapy and Tai Chi may contribute to cognition improvement, but have not yet been proven to be effective independent therapies [15, 16]. Although there are multiple treatments, there are still few effective treatments for PSCI.

Acupuncture is a core component of TCM, and it has a definite effect on PSCI [17-19]. However, there are shortcomings such as numerous acupuncture points, inconsistent treatment time, and unclear cumulative effect of acupuncture and needle retaining. At present, there is no unified acupuncture treatment method has been released yet. Therefore, in order to study the clinical efficacy and safety of EA and needle retaining at PSCI, we design this multicenter, prospective, large-sample randomized controlled trial with a sufficient follow-up period. As a preliminary experiment, we aim at observing the effects of EA treatment on cognitive function by subjective and objective assessments. The results will be helpful to demonstrate if EA plus NR treatment is an effective and safe therapy for improving cognitive function for patients with PSCI. The findings will be shared with the healthcare professionals, general public, and relevant organizations through publication of manuscripts and conference presentations.

**Trial Objectives**

1. To observe and compare the difference between two treatment methods in improving cognitive impairment and daily living ability in patients with PSCI.
2. To provide more evidence for developing an optimized acupuncture treatment method for PSCI treatment in the future.

**Methods/design**

**Trial Design**

This is a multicenter, prospective, randomized controlled trial supported by the Henan Administration of Traditional Chinese Medicine. The trial will be conducted jointly by three centers in Zhengzhou, China: the First Affiliated Hospital of Henan University of Chinese Medicine, the Henan Province Hospital of TCM, and the Third Affiliated Hospital of Henan University of Chinese Medicine. 206 patients who meet the pre-defined criteria will be randomly assigned to 2 groups, receiving EA plus NR and routine rehabilitation treatment or EA plus routine rehabilitation treatment, respectively. After one week of washout period, patients will accept 5 times a week for 8 weeks of observation. Participants will be assessed at 4 time points, the baseline (0 week), the middle of the treatment (4 weeks after treatment starts), end of the treatment (8 weeks after treatment starts), and follow-up (12 weeks, 24 weeks after treatment finishes). All participants will complete the assessments by the MMSE, MOCA and BI. The study flow chart is shown in Fig. 1. Trial process chart is shown in Table 1.

Figure 1
Table 1 Timing of treatment assessments and data collection

| TIMEPOINT | STUDY PERIOD | Baseline | Treatment phase | Follow-up phase |
|-----------|--------------|----------|-----------------|----------------|
|           | Enrolment    |          |                 |                |
| -1 Week   |              | 0 Week   | 4 Weeks         | 8 Weeks        |
| 0 Week    |              |          |                 |                |
| 4 Weeks   |              |          |                 |                |
| 8 Weeks   |              |          |                 |                |
| 12 Weeks  |              |          |                 |                |
| 24 Weeks  |              |          |                 |                |

**ENROLMENT**
- Eligibility screen ×
- Informed consent ×
- Medical history ×
- Merger disease ×
- Randomization ×

**INTERVENTIONS**
- Treatment group × × × ×
- Control group × × ×

**ASSESSMENTS**
- MMSE × × × × ×
- MOCA × × × × ×
- BI × × × × ×
- Safety evaluation × ×
- Adverse events × × × ×

**Ethics**

This trial has been approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine on 5 September, 2019 (reference number: 2019HL-102-01). All participants will sign an informed consent form, and to protect their privacy, their real names will not appear in relating reports.

**Study setting**

All participants in this trial will be recruited from the First Affiliated Hospital of Henan University of Chinese Medicine, the Henan Province Hospital of TCM and the Third Affiliated Hospital of Henan
University of Chinese Medicine. Interventions for all participants will be carried out in hospitals where participants are recruited. The First Affiliated Hospital of Henan University of Chinese Medicine will be responsible for this trial coordination and data management.

**Sample size**

We will conduct this study in a randomized controlled trial design method, and the main observed outcome is the improvement of patients’ cognitive function. Our previous small sample (20 cases) clinical observation found that 2-week EA plus routine cognitive rehabilitation treatment and EA plus NR and routine cognitive rehabilitation treatment can reduce the level of the MOCA scale by 3.17±2.12 and 4.40±2.59, respectively. The significance test level is 0.05, and the test power is 0.9. Sample size is calculated by using:

\[ N = 2 \times \left[ (z_\alpha + z_\beta) \times \sigma / \delta \right]^2 \]

\( N \) is the required sample size for each group, and the sample size of each group is equal. Where \( \alpha \) is 0.05 and \( \beta \) is 0.1, the normal distribution quantile table shows that:

\[ Z_{\alpha/2} = 1.96, \quad Z_\beta = 1.282. \]

\( \sigma \) and \( \delta \) represent the larger standard deviation and the mean difference between two groups, which are 2.59 and 1.23, respectively. By substituting the above data into the formula, it is calculated that 93 cases will be needed in each group. Accounting for a 10% expulsion rate, the final estimated sample size will be about 103 cases in each group (206 in total).

**Inclusion Criteria**

Participants meeting the following criteria will be included:

1. Male or female participants aged 30–75
2. Participants who meet the diagnostic criteria of stroke by computed tomography (CT) or magnetic resonance imaging (MRI)
3. Participants with cognitive impairment identified on MMSE scale and MOCA assessment scale
4. Patients with cognitive impairment occurred after stroke, but not for other reasons
5. Patients with a disease course within one month to one year who did not use any cognitive improvement drugs before enrollment
6. Patients with clear consciousness and stable vital signs
7. Patients who voluntarily agree with the investigation and sign a written informed consent form for the clinical trial
**Exclusion Criteria**

Participants who report any of the following conditions will be excluded:

1. Patients with non-stroke diseases that can cause cognitive impairment such as intracranial space occupying lesions, brain trauma, aneurysmal aneurysms, etc.
2. Patients with diseases that seriously affect cognitive tests, such as abnormal audiovisual functions, mental disorders, etc.
3. Patients with a significant history of cognitive decline or dementia prior to this onset
4. Patients with other serious diseases such as immune diseases, endocrine diseases and abnormal liver and kidney functions
5. Pregnant or lactating women
6. Patients participating in other clinical trials affecting the evaluation of this study's results

**Elimination criteria**

1. Patients who are not included in the PSCI diagnosis and are mistakenly included
2. Patients with poor compliance, self-withdrawal, or patients who are judged by the investigator as unsuitable to continue the trial because of serious adverse complications

**Recruitment**

The main participants in this trial will be recruited simultaneously through the outpatient and inpatient systems of the three centers, and we will also recruit online through websites and hospital-based Wechat ads of three centers. Posters, pictures and videos related to the study will be produced to help participants understand the purpose of this study, while explaining the advantages and disadvantages of the treatment and what they need to do to participate in this study. Based on the inclusion/exclusion criteria, we will make a preliminary judgment and screening of the possibility of inclusion of participates who are interested in participating in the study, and determine whether the subject is included according to the results of the examination. Participants who meet the inclusion criteria will be informed of the study details, and subjects or their legal guardians will be required to sign an informed consent form before treatment begins. The recruitment of participates began on 1 December 2019, and is expected to end in June 2021, or can be completed early when the number of centers required is sufficient.

**Randomization**

All included patients will be randomly divided into two groups with a ratio of 1:1, EA plus NR group and EA group. A specialized statistician who is not a researcher on this study will be entrusted to use randomization software to generate random-number sequences for randomization. Meanwhile, the allocation should be hidden. Strips reminding participants of grouping information will be hidden in sealed opaque envelopes with sequential numbers. The envelopes will not be opened until informed consent is obtained. Each clinical research center will select cases strictly according to the inclusion and
exclusion criteria, and determines the eligible cases that can be included, and then will obtain random numbers and grouping information by phone until the total number of observed cases (206) is completed.

**Intervention**

Participants in the two groups will receive different treatment methods 5 times a week for 8 weeks in separate compartments. All acupuncturists will be physicians with at least 3 years of experience in acupuncture practice. Meanwhile, each participant will receive same routine cognitive rehabilitation treatments from therapists who will be blinded to the treatment allocation. The interventions in the two groups are as follows:

1. **EA plus NR group**

In addition to routine cognitive rehabilitation treatments, participants in this group will receive EA treatment. Regular acupuncture method will be applied at Baihui (GV20), Shenting (GV24). With the patient in the supine position, use a 75% alcohol cotton swab to routinely disinfect the two acupuncture points, and use Huaying stainless steel acupuncture needles (0.25mm×25mm), keeping the angle between the needle tip and the scalp is 30 degrees, and then move the needle tip backwards along the anterior-posterior midline, insert the needle for 0.5 cun. After insertion, manipulations will be applied for “Deqi” sensation. The EA therapeutic apparatus (G6805-2A, Shanghai Huayi Medical Instrument Co., Ltd., China) will be connected to the needles at the two acupuncture points with 15 minutes of continuous wave and 15 minutes of dense wave at a frequency of 2.5 HZ. After a total of 30 minutes of stimulation, the EA therapeutic apparatus will be removed. Then keep needles at acupuncture points for 1 hour, and perform manipulations every 30 minutes until needles are ejected.

2. **EA group**

In addition to routine cognitive rehabilitation treatments, the intervention of this group will be the same as that in the EA plus NR group except that the needles will be directly removed after 30 minutes of electrical stimulation. There will be no NR process.

3. **Routine cognitive rehabilitation treatments**

According to the actual situation of all participants in the two groups, we will follow the theory of neuropsychology and use a combination of artificial training and computer training to give each participant different category classification exercises, rule (response) suppression exercises, plan analysis exercises, reasoning comprehension exercises, working memory exercises and comprehensive ability exercises, etc., in order to achieve the therapeutic purpose of improving participants’ daily life ability.

**Outcome measures**
All participants will be evaluated at these time points: baseline, week 4, week 8, and weeks 12 and week 24 of follow-up after all treatments are completed. All treatment evaluations will be conducted by researchers who will be blinded to the treatment allocation.

**Primary outcomes**

**Mini Mental State Scale (MMSE)**

The MMSE scale is a questionnaire mainly used to assess cognitive function [20]. It consists of 30 questions including orientation, memory, calculation, recall, and language. Each answer is worth 1 point for a total of 30 points. The assessment criteria for cognitive impairment vary with the patient's educational level: illiterate or semi-illiterate ≤ 17 points, primary school ≤ 20 points, middle school ≤ 24 points. The lower the MMSE scale score, the worse the cognitive function can be considered.

**Montreal Cognition Assessment Scale (MOCA)**

MOCA is a rapid screening cognitive impairment rating scale [21], which mainly includes items such as attention and concentration, executive function, memory, speech, visual structure, abstract thinking, computing power, and orientation. The total score is 30 points. If the subject has been educated for 12 years or less, 1 point is added, and a score of <26 points is considered to be cognitive impairment.

**Secondary Outcome**

**Bathel Index (BI)**

BI is a questionnaire for assessing daily living ability [22]. It mainly includes the ability to control urination, eating, wearing, walking, bathing and other daily life contents. Each item is 0, 5, 10, or 15 according to the degree. Each item has a score of 0, 5, 10 or 15 points according to the degree of disease, and the total score is 100 points. A higher score indicates a worse living ability. BI classification: heavy dependence (score 0-40), moderate dependence (41-60), light dependence (61-99), without dependence (100).

**Safety evaluation and adverse events**

The safety evaluation mainly refers to the evaluation of safety indicators and adverse events. The safety indicators will be tested once before and after treatments, including general physical examination (blood pressure, breathing, pulse), blood routine test, urine routine test, stool routine test, electrocardiogram, liver and kidney function, etc. Adverse events in this study will be defined as any discomfort, symptoms or diseases that occurred during this acupuncture clinical trial, such as fainting, allergies or pain. If someone faints, researchers should immediately remove needles, then keep the patient in a supine position and a ventilated place, and give him/her warm water or sugar water to let him/her rest fully until the body recovers. If allergy or pain occurs, needles should be immediately withdrawn and treated.
symptomatically. All the above detailed information of safety evaluation will be reported in case report forms (CRFs) in detail, and the impact of all adverse events will be analyzed at the end of the study.

Data management

All information of participants will be truthfully, completely, accurately and timely recorded in CRFs, codes and initials will be used to replace the information of participants. Special personnel will be asked to manage the relevant data, and each participants’ personal information will be kept strictly confidential. Without the explicit permission of the person in charge of the research group, any data will not be shared with third parties other than data recorders and data administrators. At the end of the trial, study participants should submit the CRFs on time, and then the quality control team members will check the completeness and accuracy of the CRFs.

Quality control

In order to guarantee the research quality of this trial, we will invite a qualified clinical trial expert from the Clinical Research Center of the First Affiliated Hospital of Henan University of Chinese Medicine to monitor this study, and detailed regulations for each link of data collection and management will be formulated to clarify the responsibilities of researchers. If any problems in the project are identified, the center will decide to change the research plan after approval by the application ethics committee. Reasonable and feasible data standard operating procedure (SOP) will be established to ensure the quality of each stage of data collection and management. Data management should be carried out by relevant personnel who have been trained and operated strictly in accordance with the SOP. Meanwhile, a quality control team will be established to conduct quality control and inspections on a regular basis.

Statistical analysis

Statistical analysis of all data will be performed using SPSS 22.0 software by specialized statisticians and major researchers. Classified variables will be analyzed using Pearson’s χ² test or Fisher’s exact test, and continuous variables will be evaluated using Student’s t test or an appropriate non-parametric method. The measurement data of different treatment groups will be statistically described by mean ± standard deviation. When comparing within groups or between groups, normality test and homogeneity of variance test will be performed before data analysis of each group. If the data satisfy the normal distribution and homogeneity of variance, then the t test will be used for comparison between two groups, and the LSD or SNK method will be used for multiple comparisons. Conversely, the rank sum test will be used for non-normality or non-uniformity of variance. The significance level used for statistical analysis with 2-tailed testing will be set at 5%.

Discussion

The effective improvement of cognitive impairment after stroke is particularly important to improve the rehabilitation and quality of life of patients after stroke, so it is necessary to take effective treatment
measures to improve cognitive function. Acupuncture therapy has a history of more than 2,000 years in China, and has been widely used in Western countries in recent years. Our previous clinical research found that EA treatment at Baihui (GV20), Shenting (GV24), and NR on head can effectively relieve cognitive impairment after stroke. However, the best acupuncture treatment mode and the cumulative effect of acupuncture still need further research and confirmation. Therefore, we propose a prospective, multi-center, large-sample randomized controlled trial to explore the cumulative effect of acupuncture and needle retaining. It is expected to provide a preliminary basis for the optimization of treatment methods for PSCI, so as to further form a standardized, simple, effective, and easy-to-promote TCM clinical comprehensive rehabilitation treatment method.

Although most of the previous studies on acupuncture treatment of cognitive impairment used a combination of body acupuncture points and head acupoints [23-25], we will use only two acupuncture points on the head (GV20 and GV24) for treatment, which is based on the results of literature analysis and a continuation of previous research [26, 27]. On the other hand, unified acupuncture points may reduce variables and increase the accuracy and persuasion of this study. In recent years, MMSE, MOCA and BI scales can assess various aspects of cognitive function, so we use these three items as outcome indicators to reduce the interference of subjective factors and assessment simplification on cognitive impairment assessment. In addition, the multi-center design of the study may be biased, mainly including differences between acupuncture operator techniques. Therefore, in order to eliminate the bias caused by operator inconsistency, we will conduct unified training for all the acupuncturists participating in this study and strictly regulate the acupuncture operation to maximize the elimination of this bias. However, although all results will be measured and recorded by independent researchers to minimize the risk of detection bias, as a limitation of this protocol, we cannot use a double-blind procedure to conduct this study due to the nature of acupuncture treatment.

In order to achieve our clinical goals, we will strive to standardize every step of this study. We expect that this trial will provide strong evidence for acupuncture treatment of PSCI, with a view to incorporating or updating to the corresponding TCM rehabilitation guidelines, and further formulate a clinical rehabilitation treatment method suitable for grassroots promotion and application.

**Trial Status**

The recruitment of patients for this study began on 1 December 2019, and this study is ongoing. Protocol version number and date: V2.0, 1 September 2019. The recruitment of patients is expected to be completed in June 2021.

**Abbreviations**

BI: Bathel Index; CRF: Case report form; CT: Computed tomography; EA: Electroacupuncture; MMSE: Mini Mental State Scale; MOCA: Montreal Cognition Assessment Scale; MRI: magnetic resonance imaging; NR:
Declarations

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We wish to thank all the participants who contributed to this study.

Authors’ contributions

The trial was designed and developed by X-DF and R-QL. K-QS, S-TL and J-YL are the main performers of this research and drafted this manuscript. H-LF and YX participated in the revision and editing of this manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable; no data have yet been generated.

Ethics approval and consent to participate

This trial has been approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine on 5 September, 2019 (reference number: 2019HL-102-01). All participants will sign an informed consent form, and to protect their privacy. Their real names will not appear in relating reports.

Consent for publication

Not applicable.

Competing Interests

The authors declare that they have no competing interests.

Author details

1 Henan University of Chinese Medicine, No. 156 East Jinshui Road, Zhengzhou 450046, China. 2 Rehabilitation Center, the First Affiliated Hospital of Henan University of Chinese Medicine, No. 19 Renmin Road, Zhengzhou 450000, China.
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Figures
Figure 1

Flowchart of the trial

Supplementary Files

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