INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Different Acupuncture Intervention Time-points for Rehabilitation of Post-Stroke Cognitive Impairment：Protocol For a Network Meta-analysis of Randomized Controlled Trials

Li, ZD[1]; Zhang, CC[2]; Qiu, HJ[3]; Wang, XQ[4]; Zhang, YJ[5].

Review question / Objective: **This study will provide evidence-based references for the efficacy of different acupuncture interventions time-point in the treatment of post-stroke cognitive impairment(PSCI). 1. Types of studies. Only randomized controlled trials (RCTs) of acupuncture for PSCI will be recruited. Additionally, Studies should be available in full papers as well as peer-reviewed and the original data should be clear and adequate. 2. Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria, regardless of nationality, race, sex, age, or educational background. 3. Types of interventions and controls. The control group takes non-acupuncture treatment, including conventional rehabilitation or in combination with symptomatic support therapy. The experimental group should be treated with acupuncture on basis of the control group. 4. Types of outcomes. The primary outcomes are measured with The Mini-Mental State Examination (MMSE) and/or The Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate cognitive abilities.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 May 2022 and was last updated on 07 May 2022 (registration number INPLASY202250043).

INTRODUCTION

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Rationale: Network meta-analysis extends pairwise meta-analyses to enable the pooling of data from many clinical trials, comparing at least two treatments. Inferences regarding the relative efficacy of each treatment are thus reinforced by the inclusion of both direct and indirect information. A network meta-analysis based on Bayes' theorem of existing datasets provides a framework for comprehensive evaluation of different acupuncture interventions' time-point efficacy and safety.

Condition being studied: Among all stroke sequelae, post-stroke cognitive impairment (PSCI) is common, affecting 17.6% to 83% of stroke survivors, depending on the time of assessment, setting of the research, demographic characteristics, and the various cognitive tests and cut-offs. Its core domains impaired include executive function, memory, attention, language, and visuospatial function, which not only lead to disability, dependence, and low quality of life but are also associated closely with the high risk of recurrent ischemic stroke and the reduction in five-year survival. As the tremendous burden of stroke continues to rise, PSCI has become a mounting public healthcare challenge that needs to be addressed urgently. At present, the treatments for PSCI mainly include oral drug interventions, physical therapy, cognitive training, and so on. Compared with oral drug therapy for PSCI, non-pharmaceutical interventions were more effective. Acupuncture is a traditional Chinese medicine treatment that has been widely used in the clinical treatment of PSCI and has shown good efficacy. However, the optimal time point of intervention for acupuncture in the treatment of PSCI is controversial. This study will provide an evidence-based reference to assess the optimal time point of intervention for treatment.

METHODS

Search strategy: Electronic databases including Web of Science, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wangfang database, China Science and Technology Journal Database(VIP), and Chinese Biomedical Medicine (CBM). Search strategy based on MeSH terms combining with free text words was applied in English databases, while counterpart terms in Chinese were used in Chinese databases. A sample search of Pubmed is as follows: #1: ("Stroke"[Mesh]) OR ("Brain Ischemia"[Mesh]) OR ("Cerebral Hemorrhage"[Mesh]) OR (Stroke*[Title/Abstract]) OR (Cerebrovascular Accident*[Title/Abstract]) OR (Brain Vascular Accident*[Title/Abstract]) OR (Apoplexy[Title/Abstract]) OR (Brain Infarct*[Title/Abstract]) OR (Cerebral Infarct*[Title/Abstract]) OR (Brain Stem Infarct*[Title/Abstract]) OR (Subcortical Infarction*[Title/Abstract]) OR (Brain Venous Infarction*[Title/Abstract]) OR (Cerebral Artery Stroke[Title/Abstract]) OR (Cerebral Artery Infarction[Title/Abstract]) OR (Cerebral Circulation Infarction[Title/Abstract]) OR (Circulation Brain Infarction[Title/Abstract]) OR (Choroidal Artery Infarction[Title/Abstract]) OR (CVA[Title/Abstract]) OR (CVAs[Title/Abstract]) OR (Brain Ischemia*[Title/Abstract]) OR (Ischemic Encephalopath*[Title/Abstract]) OR (Cerebral Ischemia*[Title/Abstract]) OR (Brain Hypoxia Ischemia*[Title/Abstract]) OR (Cerebral Anoxia Ischemia*[Title/Abstract]) OR (Cerebral Hemorrhage*[Title/

Abstract]) OR (Cerebral Brain Hemorrhage*[Title/Abstract]) OR (Cerebral Parenchymal Hemorrhage*[Title/Abstract]) OR (Cerebrum Hemorrhage*[Title/Abstract]) OR (Intracerebral Hemorrhage*[Title/Abstract]) OR (Basal Ganglia Hemorrhage[Title/Abstract]) OR (Subarachnoid Hemorrhage*[Title/Abstract]) OR (Cerebral Hypertensive Hemorrhage*[Title/Abstract]). #2: (Cognition Disorders[MeSH Terms]) OR (Dementia, Vascular[MeSH Terms]) OR (Cognition Disorder*[Title/Abstract]) OR (Vascular Dementia*[Title/Abstract]) OR (Cognitive Dysfunction*[Title/Abstract]) OR (Cognitive Impairment*[Title/Abstract]) OR (Mild Neurocognitive Disorder*[Title/Abstract]) OR (Cognitive Decline*[Title/Abstract]) OR (Mental Deterioration*[Title/Abstract]) OR (cognitive defect[Title/Abstract]) OR (Multi-Infarct Dementia*[Title/Abstract]) OR (Lacunar Dementia*[Title/Abstract]) OR (Arteriosclerotic Dementia*[Title/Abstract]) OR (Chronic Progressive Subcortical Encephalopathy[Title/Abstract]) OR (Subcortical Leukoencephalopathies[Title/Abstract]) OR (cognitive disorder* after stroke[Title/Abstract]) OR (cognitive impairment* after stroke[Title/Abstract]) OR (cognitive Dysfunction* after stroke[Title/Abstract]) OR (Cognitive Decline* after stroke[Title/Abstract]). #3: (Acupuncture[MeSH Terms]) OR (Acupuncture Therapy[MeSH Terms]) OR (Acupuncture Points[MeSH Terms]) OR (Acupuncture[Title/Abstract]) OR (Acupuncture Therapy[Title/Abstract]) OR (Acupuncture Point*[Title/Abstract]) OR (Pharmacopuncture[Title/Abstract]) OR (Acupuncture Treatment*[Title/Abstract]) OR (Pharmacoacupuncture Treatment*[Title/Abstract]) OR (Pharmacoacupuncture Therapy[Title/Abstract]) OR (Acupotom*[Title/Abstract]) OR (Acupoint*[Title/Abstract]) OR (Electroacupuncture[Title/Abstract]) OR (electrical acupoint stimulation[Title/Abstract]) OR (thermoacupuncture[Title/Abstract]) OR (burnt needle therapy[Title/Abstract]) OR (fire needle therapy[Title/Abstract]) OR (fire needling[Title/Abstract]). #4: Randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]. #5: #1 AND #2 AND #3 AND #4.

Participant or population: Patients with cognitive impairment after stroke.

Intervention: Acupuncture.

Comparator: Different Acupuncture Intervention Time-points.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: 1.Types of studies. Only randomized controlled trials (RCTs) of acupuncture for PSCI will be recruited and regardless of population characteristics, blind method, and duration of trials. However, the language is limited to English or Chinese. We will remove Non-RCTs such as meeting abstracts, clinical experience, case reports, system reviews, animal trails, duplications meeting abstracts. Additionally, Studies should be available in full papers as well as peer-reviewed and the original data should be clear and adequate.2.Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria(e.g. confirmed by CT or MRI scan), regardless of nationality, race, sex, age, or educational background. However, the patients who are not medically stable or unable to follow basic commands will be excluded.3.Types of interventions and controls. The control group takes non-acupuncture treatment, including conventional rehabilitation or in combination with symptomatic support therapy. The experimental group should be treated with acupuncture on basis of the control group. Acupuncture therapy including one of the following related treatments: electroacupuncture, head acupuncture, warm acupuncture, and hand acupuncture.4.Types of outcomes. The primary outcomes are measured with The Mini-Mental State Examination (MMSE) and/or The Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate the cognitive abilities. The

secondary outcome indicator was the daily living ability assessment, including the Activities of Daily Living (ADL), and Barthel Index (BI) rating scale. Additionally, safety assessments such as adverse events and drop-out cases may also be taken into consideration.1.Types of studies. Only randomized controlled trials (RCTs) of acupuncture for PSCI will be recruited and regardless of population characteristics, blind method, and duration of trials. However, the language is limited to English or Chinese. We will remove Non-RCTs such as meeting abstracts, clinical experience, case reports, system reviews, animal trails, duplications meeting abstracts. Additionally, Studies should be available in full papers as well as peer-reviewed and the original data should be clear and adequate.2.Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria(e.g. confirmed by CT or MRI scan), regardless of nationality, race, sex, age, or educational background. However, the patients who are not medically stable or unable to follow basic commands will be excluded.3.Types of interventions and controls. The control group takes non-acupuncture treatment, including conventional rehabilitation or in combination with symptomatic support therapy. The experimental group should be treated with acupuncture on basis of the control group. Acupuncture therapy including one of the following related treatments: electroacupuncture, head acupuncture, warm acupuncture, and hand acupuncture.4.Types of outcomes. The primary outcomes are measured with The Mini-Mental State Examination (MMSE) and/or The Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate the cognitive abilities. Additionally, safety assessments such as adverse events and drop-out cases may also be taken into consideration1.Types of studies. Only randomized controlled trials (RCTs) of acupuncture for PSCI will be recruited and regardless of population characteristics, blind method, and duration of trials. However, the language is limited to English or Chinese. We will remove Non-RCTs such as meeting abstracts, clinical experience, case reports, system reviews, animal trails, duplications meeting abstracts. Additionally, Studies should be available in full papers as well as peer-reviewed and the original data should be clear and adequate.2.Types of participants. All adults with a recent or previous history of ischaemic or hemorrhagic stroke and diagnosed according to clearly defined or internationally recognized diagnostic criteria(e.g. confirmed by CT or MRI scan), regardless of nationality, race, sex, age, or educational background. However, the patients who are not medically stable or unable to follow basic commands will be excluded.3.Types of interventions and controls. The control group takes non-acupuncture treatment, including conventional rehabilitation or in combination with symptomatic support therapy. The experimental group should be treated with acupuncture on basis of the control group. Acupuncture therapy including one of the following related treatments: electroacupuncture, head acupuncture, warm acupuncture, and hand acupuncture.4.Types of outcomes. The primary outcomes are measured with The Mini-Mental State Examination (MMSE) and/or The Montreal Cognitive Assessment Scale (MoCA), which have been widely used to evaluate the cognitive abilities. Additionally, safety assessments such as adverse events and drop-out cases may also be taken into consideration.

Information sources: An all-round online search for published related studies will be conducted in the following academic databases from their inception throughout Dec 2021: Web of Science, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Wangfang database, China Science and Technology Journal Database(VIP), and Chinese Biomedical Medicine (CBM). Search strategy based on MeSH terms combined with free text words was applied in English databases, while counterpart terms in Chinese were used in Chinese databases. In addition, relevant references

will also be checked carefully under the guidelines of the snowball strategy.

Main outcome(s): The primary outcome indicator was the assessment of cognitive function, and the RCTs included at least either the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment(MoCA).

Additional outcome(s): The secondary outcome indicator was the daily living ability assessment, including the daily living ability scale, the Activities of Daily Living (ADL), and the Barthel Index (BI) rating scale. In addition safety assessments such as adverse events and drop-out cases may also be taken into consideration.

Data management: 1.Data collection and export. Two independent reviewers will search and screen the literature according to inclusion and exclusion criteria respectively. Firstly, duplicates will be removed by endnote software, then suitable literature, including potential references, will be identified by reading the title and abstract, and finally eligible literature will be assessed by reading the text content. Any objections will be discussed and resolved by experienced reviewers. 2. Data extraction and analysis. Two reviewers will independently extract data. The following data will be extracted: (1)General characteristics: first author, the year of publication, and nationality. (2)The characteristic of participants: sample size, average age, sex, the progression of disease. (3)The characteristics of intervention: intervention type, control interventions, the time of each intervention, total treatment duration, follow-up time. (4)Outcomes: primary outcomes and secondary outcomes, adverse events. If necessary, the authors will be contacted for more information to supplement the missing data.

Quality assessment / Risk of bias analysis: The assessment of the risk bias will be conducted According to the Cochrane Collaboration's tool provided by Cochrane Handbook for Systematic Reviews. The assessment will be conducted by two independent authors, with any disagreements to be settled by an experienced reviewer.

Strategy of data synthesis: The pairwise meta-analyses of direct evidence will be performed using review manager 5.4. Mean Difference (MD) will be calculated for continuous data and Odds Ratios (OR) will be calculated for dichotomous data. All outcomes were expressed using 95% Confidence Intervals (CIs). The statistical heterogeneity across different trials will also be assessed using the I2 statistics. In case that the p value is ≥0.1 and I2 ≤50%, MD or OR will be combined with fixed effects model (FEM). In case that the p value is<0.1 and I2＞50%, the random effects model(REM) will be applied. The Markov Chain Monte Carlo (MCMC) in OpenBUGS3.2.3 will be employed to perform network meta-analysis on PSCI patients under a Bayesian framework. To assess the consistency of the NMA, the node-split method will be used to locate the inconsistency between direct and indirect effects of treatment. In addition, the surface under the cumulative ranking curve(SUCRA) will be estimated for the effectiveness of each intervention, and then funnel plots will be drawn to analyze publication bias. SUCRA has a value of 0 to 1. The closer it is to 1, the more effective the intervention is considered.

Subgroup analysis: If necessary, age, the types of stroke, and the types of acupuncture will be carried out as subgroup analysis to assess the heterogeneity of the study.

Sensitivity analysis: In addition, sensitivity analysis will be conducted to exclude those studies of lower quality and to determine the robustness and consistence of the combined results.

Language: The language is limited to English or Chinese.

Country(ies) involved: China.

Keywords: Network meta-analysis; Post-stroke cognitive Impairment; Acupuncture; Protocol.

Dissemination plans: The results of this study will be submitted to a peer-reviewed journal for publication.

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