INPLASY PROTOCOL

To cite: Zhang et al. Chinese herbal medicine for vascular cognitive impairment in cerebral small vessel disease: a protocol for systematic review and meta-analysis of randomized controlled trials. Inplasy protocol 202080120. doi: 10.37766/inplasy2020.8.0120

Received: 28 August 2020

Published: 28 August 2020

Corresponding author:
Xinyang Zhang

zhangxinyang1992@163.com

Author Affiliation:
Beijing University of Chinese Medicine

Support: **National Natural Science Fund**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None.

Chinese herbal medicine for vascular cognitive impairment in cerebral small vessel disease: a protocol for systematic review and meta-analysis of randomized controlled trials

Zhang, XY[1]; Liu, XM[2]; Xia, RY[3]; Li, NN[4]; Liao, X[5]; Chen, ZG[6].

Review question / Objective: **What is the efficacy and safety of Chinese herbal medicine (CHM) in the treatment of vascular cognitive impairment (VCI) in cerebral small vessel disease (CSVD, CSVD-VCI)?**
Condition being studied: **Cerebral small vessel disease (CSVD) is the most frequent reason of vascular cognitive impairment (VCI). VCI in CSVD (CSVD-VCI) shows a progressive course with multiple stages and is also associated with dysfunctions such as gait, emotional and behavioral, and urinary disturbances, which seriously affect the life quality of elderly people. Chinese herbal medicine (CHM) is clinically used for CSVD-VCI and presenting positive efficacy, but the evidence revealed in relevant clinical trials has not been systematically evaluated.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 August 2020 and was last updated on 28 August 2020 (registration number INPLASY202080120).

INTRODUCTION

Review question / Objective: **What is the efficacy and safety of Chinese herbal medicine (CHM) in the treatment of vascular cognitive impairment (VCI) in cerebral small vessel disease (CSVD, CSVD-VCI)?**

Condition being studied: **Cerebral small vessel disease (CSVD) is the most frequent reason of vascular cognitive impairment (VCI). VCI in CSVD (CSVD-VCI) shows a**

progressive course with multiple stages and is also associated with dysfunctions such as gait, emotional and behavioral, and urinary disturbances, which seriously affect the life quality of elderly people. Chinese herbal medicine (CHM) is clinically used for CSVD-VCI and presenting positive efficacy, but the evidence revealed in relevant clinical trials has not been systematically evaluated.

METHODS

Search strategy: We will identify trials from Cochrane Library, PubMed, EMBASE, Chinese National Knowledge Infrastructure Database (CNKI), Chinese Science and Technology Journals Database (VIP), Wanfang Database, Chinese Biomedical Literature Database (SinoMed). We will also conduct a search of ClinicalTrials.gov and Chinese Clinical Trial Registry (ChiCTR). In addition, we will search reference lists of included studies and existing systematic reviews, with no restriction on language. The search strategy that guides the selection of search terms is made up of the following two parts: CSVD and CHM. These terms will then be translated and applied in the search of Chinese databases. The selection of searching fields of title, abstract, or keywords will be different depending on the characteristics of databases.

Participant or population: Patients with the clinical diagnosis of cerebral small vessel disease. Study populations consisting solely of patients aged under 18 years will be excluded.

Intervention: CHM alone or CHM combined with conventional treatments (CTs), such as adjustments of living habits, management of traditional risk factors of cerebrovascular disease, including antihypertensive, hypolipidemic, hypoglycemic, antiplatelet treatments, anti dementia treatments like cholinesterase inhibitors, and cognitive training.

Comparator: It can be a placebo, a blank, or CTs distinct from CHM.

Study designs to be included: Randomized controlled trials (RCTs).

Eligibility criteria: Participants of included studies should be diagnosed with CSVD-VCI treated with CHMs. Only peer-reviewed, full-reported randomized controlled trials (RCTs) will be included in this systematic review. The reporting language of included studies will be confined to English and Chinese. Duplicate studies and studies incorrectly reporting data will be excluded.

Information sources: We will identify trials from Cochrane Library, PubMed, EMBASE, Chinese National Knowledge Infrastructure Database (CNKI), Chinese Science and Technology Journals Database (VIP), Wanfang Database, Chinese Biomedical Literature Database (SinoMed). We will also conduct a search of ClinicalTrials.gov and Chinese Clinical Trial Registry (ChiCTR). In addition, we will search reference lists of included studies and existing systematic reviews, with no restriction on language.

Main outcome(s): Cognitive function, measured by scales such as: Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Vascular Dementia Assessment Scale-cognitive subscale (VADAS-cog), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), Hastgawa Dementia Scale (HDS), Wechsler Memory Scale (WMS), Clock Drawing Test (CDT), the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) Neuropsychological Assessment, or any other standardized and validated scales.

Additional outcome(s): 1) Activities of daily living, measured by scales such as: Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Barthel Index of ADL (BI), Functional Activity Questionnaire (FAQ), Alzheimer's Disease Cooperative Study-ADL Inventory (ADCS-ADL), Disability Assessment for Dementia (DAD), or any other standardized and validated scales. 2) Behavioural and psychological symptoms, measured by

scales such as: Blessed-Roth Behaviour Scale (BBS), Neuropsychiatric Inventory (NPI), Hamilton Depression Scale (HAMD), Cornell Scale for Depression in Dementia (CSDD), the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), or any other standardized and validated scales. 3) Global performance, measured by scales such as: Clinical Dementia Rating (CDR), Global Deterioration Scale (GDS), Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-plus), or any other standardized and validated scales. 4) Neurological function, measured by National institutes of health stroke scale (NIHSS) or any other standardized and validated scales. 5) Hematologic biomarkers of cerebrovascular diseases, such as homocysteine (HCY), high-sensitive C- reactive protein (hs-CRP), etc. 6) Clinical effective rate, means using the unified standard to estimate the effective rate. It is calculated by dividing the number of effective cases according to a specific outcome by the total number of cases in the same group.

Data management: EndNote X9 software will be used to manage records and data. In order to identify studies that potentially meet the requirements of predetermined inclusion and exclusion criteria, preliminary qualified titles and abstracts obtained using the search strategy will be separately screened by two review authors. Further, two review authors will retrieve the full text of studies above and assess independently the eligibility of their inclusion in our study according to predetermined inclusion and exclusion criteria, during which any discrepancy among these two authors on the eligibility of certain studies will be reasonably solved by discussion together with a third reviewer. Two authors independently use standardized, pre-tested forms to extract data from included studies for assessing quality of studies, and synthesizing needed information. Forms of extraction mainly focus on study methods, participants, baseline characteristics, specific content of the intervention and control group, cognitive functions, hematologic biomarkers, dropouts, safety, neurological function, assessment of the risk of bias. Any disagreement occurring in this process will be settled through discussion with a third review author. Any missing needed information will be required from the research teams of included studies.

Quality assessment / Risk of bias analysis: Cochrane risk of bias tool for assessing risk of bias will be independently applied by two review authors to assess the risk of bias in the included studies, for following aspects: selection bias, randomization sequence generation and allocation concealment; performance bias, blinding of participants and personnel; detection bias, blinding of outcome assessment; attrition bias, completeness of outcome data; reporting bias, selective outcome reporting. And also, other bias will be examined, such as funding bias, conflict of interest, balance of baseline, sample size, and follow-up period. If two review authors disagree on assessment of bias of a certain study, it will be solved by discussion involving another author.

Strategy of data synthesis: Review Manager Version 5.3 software will be applied. If the outcomes needed are dichotomous data, we will figure out the relative risk (RR) with 95% CI and p values for them. Meanwhile, the weighted mean differences (WMD) and its 95% confidence intervals (CIs) for changes from baseline level will be calculated when processing with continuous data collected using the consistent clinical measurement scale. The standardized mean differences (SMD) and its 95% CIs for changes from baseline level will be calculated when processing with continuous data collected using the inconsistent clinical measurement scale. Heterogeneity of effect sizes among included studies will be assessed statistically using both the ?2 test and I2 test. A meta-analysis model of fixed-effect will be conducted to estimate pooled effect if statistical homogeneity is detected (p ? 0.1, I2 ? 50%), while a model of random-effect will be used if statistical heterogeneity is detected (p < 0.1, I2 > 50%). For this heterogeneity, we will

explore potential sources of its significance through the meta-regression and sensitivity analysis, considering the variation in overall design of included study, numbers and characteristics of study participants, detailed content of interventions and controls, measuring means and points of outcomes, and other methodological quality.

Subgroup analysis: According to the actual situation of included studies, if possible, the subgroup analysis anticipated involves: varied types of CSVD based on neuroimaging standards, demographic characteristics (such as average age, gender, disease duration, vascular risk factors, etc.), severities and diagnoses of cognitive impairment of participants at baseline, differences in cognitive function between the intervention and control group at baseline, improvements of cognitive function in the intervention group, durations of the intervention, durations of follow-up, types of interventions (CHM alone or in combination with the CT), types of controls (a placebo, a blank, or a CT distinct from CHM), detailed implementing methods of the intervention and control (ingredients of CHM, dosage and routes of administration), types and means of outcome evaluations, reports on sub items of the scales, and methodological factors (such as sequence generation, blinding, etc.).

Sensibility analysis: If possible, we will conduct sensitivity analyses to challenge the robustness of the pooled effects when there were clinically meaningful differences in primary outcomes considering: multi-center versus single-center, trials without high or unclear risk of bias either in sequence generation or allocation concealment domains versus all included trials, reported loss-to-follow-up versus not reported.

Language: Chinese-Simplified and English.

Country(ies) involved: China.

Keywords: cerebral small vessel disease, vascular cognitive impairment, Chinese herbal medicine.

Contributions of each author:

Author 1 - Xinyang Zhang - Conceive this study and work for study selection, quality assessment, and data extraction and synthesis.

Author 2 - Xuemei Liu - Work for study selection, quality assessment, and data extraction and synthesis.

Author 3 - Ruyu Xia - Provide the methodological support and work for study selection, quality assessment, and data extraction and synthesis.

Author 4 - Nannan Li - Work for study selection, quality assessment, and data extraction and synthesis.

Author 5 - Xing Liao - Conceive this study and provide the methodological support.

Author 6 - Zhigang Chen - Conceive and supervise this study.