INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Non-pharmaceutical Interventions for Rehabilitation of Post-Stroke Cognitive Impairment: A protocol for systematic review and network meta-analysis

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Review question / Objective: **This study is expected to provide the reliable evidence required to evaluate the efficacy and safety of non-pharmaceutical interventions for the rehabilitation from post-stroke cognitive impairment.**
Condition being studied: **Stroke is a disease characterized by high morbidity, high disability rate and high mortality. Post-stroke cognitive impairment (PSCI) is one of the common sequelae after stroke, mainly manifests as a series of abnormalities such as language, memory, understanding, directionality and visual-spatial ability caused by stroke, which seriously affects patients' quality of life, increases the risks of death and readmission, and imposes a burden on patients' families and society. Epidemiological investigation showed that about 2/3 of patients with acute stroke had cognitive impairment of different degrees. At present, the treatments of PSCI mainly include oral drug interventions, physical therapy and cognitive training and so on. Compared with oral drug therapy for PSCI, non-pharmaceutical interventions were more effective. Therefore, it is of great significance for the rehabilitation of PSCI to select the higher cost-effective intervention method among various interventions.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 May 2021 and was last updated on 19 May 2021 (registration number INPLASY202150074).

INTRODUCTION

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METHODS

Search strategy: Search strategy of the PubMed.#1: Stroke[Title/Abstract] OR Apoplexy[Title/Abstract] OR Cerebral stroke [Title/ Abstract] OR Cerebrovascular disease[Title/Abstract] OR Cerebrovascular accident [Title/Abstract] OR Cerebrovascular disorders[Title/Abstract] OR Cerebral hemorrhage[Title/Abstract] OR Hemorrhagic apoplexy[Title/Abstract] OR Hemorrhagic Stroke[Title/Abstract] OR Cerebral infarction[Title/Abstract] OR Brain infarction[Title/Abstract] OR Hemorrhagic apoplexy[Title/Abstract] OR Ischemic stroke[Title/Abstract]. #2: Cognitive disorder[Title/Abstract] OR Cognitive impairment[Title/Abstract] OR Cognitive dysfunction[Title/Abstract] OR Cognitive deficit[Title/Abstract] OR Cognitive decline[Title/Abstract] OR PSCI [Title/Abstract]. #3: randomized clinical trial[Publication Type] OR controlled clinical trial[Publication Type]. #4: #1 AND #2 AND #3.

Participant or population: The studies that will be included shall meet the following requirements: (1) The adult patients(aged over 18 years) with cognitive impairment after stroke, with clear criteria applied to the diagnosis of stroke. (2) The diagnosis of cognitive impairment was made after stroke, regardless of race, nationality or gender. The studies meeting the following conditions will be excluded: (1) The patients have been suffering from brain tumour, brain trauma, brain parasite disease or other diseases that could lead to cognitive impairment. (2) There was no formally diagnosis made of PSCI.

Intervention: Non-pharmaceutical intervention was adopted for the treatment group, mainly including the following methods: (1) Cognitive function training: Regular cognitive function training, Enriching Rehabilitation Training, etc. (2) Modern and new rehabilitation techniques: Artificial intelligence technology, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, hyperbaric oxygen therapy, electromyography feedback technology, etc. (3) Traditional Chinese medicine rehabilitation treatment: Acupuncture, massage, cupping, scraping, Traditional functional exercises of traditional Chinese medicine, etc. (4) Kinesitherapy: Physical activity (aerobic exercise, resistance exercise, flexion and balance exercise), etc. (5) Other therapies: Musicotherapy, Psychotherapeutic intervention, Amily education, etc.

Comparator: The control group adopted internationally recognized treatment methods or routine treatment (such as oral drug therapy, cognitive training and rehabilitation training).

Study designs to be included: Only randomised controlled trials(RCTs) are included to assess the beneficial effects of the treatments. There are no restrictions placed on language or the date of publication.

Eligibility criteria: The two independent reviewers will search and screen literature separately according to the aforementioned inclusion and exclusion criteria. They will identify the appropriate literature by reading titles and abstracts,

include potential references, exclude duplicates and irrelevant literature, and then evaluate the qualified literature by reading through the textual content. In case of any disagreements, they will be discussed and resolved by an experienced reviewer.

Information sources: A search will be conducted of the following databases electronically, including 5 English literature databases (MedLine, PubMed, Embase, Web of Science and Cochrane Library) and 4 Chinese literature databases (China National Knowledge Infrastructure, China Biomedical Literature Database, China Science Journal Database and Wan-fang Database). All of the publications until 1 May 2021 will be searched without any restriction on nationality or language. The reference list of all selected articles will be screened in parallel to identify the additional studies omitted from the initial search.

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 daily living ability assessment, including the daily living ability scale, the Activities of Daily Living (ADL), and Barthel Index (BI) rating scale. The level of safety was evaluated against the occurrence of adverse events.

Data management: 1. Data collection and export The two independent reviewers will search and screen literature separately according to the aforementioned inclusion and exclusion criteria. They will identify the appropriate literature by reading titles and abstracts, include potential references, exclude duplicates and irrelevant literature, and then evaluate the qualified literature by reading through the textual content. In case of any disagreements, they will be discussed and resolved by an experienced reviewer. 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: According to the Cochrane Collaboration's tool for assessing the risk of bias as provided by Cochrane Handbook for Systematic Reviews of Interventions, the assessment will be conducted from 7 perspectives: random sequence generation, allocation concealment, blinding of patients, blinding of testers, blinding of outcome evaluators, outcome data incompletion, and the selective reporting of 7 dimensions for evaluation. The results of the assessment will be classified into 3 levels:low risk, unclear, and high risk. 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 Stata V.14.0.As for continuous data, standardised mean difference (SMD) will be calculated. As for dichotomous data, ORs will be calculated. All outcomes were expressed using 95% confidence intervals (CIs). The statistical heterogeneity across different trials will also be assessed using the I 2 statistics. In case that the p value is ≥0.1 and I 2 ≤50%, SMD or OR will be combined with fixed-effects model (FEM). In case that the p value is<0.1 and I 2>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, the following subgroup analysis will be carried out to assess the heterogeneity of the study: intervention methods, intervention time windows, the clinical course of PSCI, age, the types of stroke.

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: English.

Country(ies) involved: China.

Keywords: Network meta-analysis; Non-pharmaceutical interventions; Post-stroke cognitive Impairment; Protocol.

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