Effectiveness and safety of manual acupuncture therapy in patients with post-stroke depression: a protocol for a systematic review and meta-analysis

Wei Liu 1,2, Chang Rao 1,2, Qi Zhao 1,2, Yuzheng Du 1,2, Xi Nan 1,2, Zefang Li 1,2, Chunsheng Yin 1,2

ABSTRACT

Introduction Acupuncture is widely used on the rehabilitation of stroke survivors, including hemiplegia, constipation, emotional disorders and so on. Although the effectiveness of manual acupuncture therapy on post-stroke depression (PSD) has been confirmed by multiple randomised controlled trials, there were few meta-analyses focused on the connection between different techniques, durations or other detailed operations of manual acupuncture and their effectiveness of improving the depression severity and quality of life for patients with PSD.

Methods and analysis A systematic search will be performed on English databases (PubMed, the Cochrane Library, Medline and Embase), Chinese databases (China National Knowledge Infrastructure, WanFang Data, VIP and Chinese biomedical databases) and Japanese databases (Japan Science and Technology Agency and CNii). The retrieval time limit will be from the establishment of the database to November 2020. Two researchers will independently screen the literature works, extract data and evaluate the quality of the included studies. Meta-analysis will be conducted by using STATA V.14.0 and Review Manager V.5.3.

Ethics and dissemination The results of this meta-analysis will be disseminated through publication in peer-reviewed journals or conference presentations. The data used in this meta-analysis will not contain individual patient data: therefore, ethical approval is not required.

PROSPERO registration number CRD4202022825.

INTRODUCTION

Stroke is currently the second leading cause of death worldwide, the burden of which has increased substantially over the past few decades due to expanding population numbers and aging as well as the increased prevalence of modifiable stroke risk factors. 1-2 Depression is a common and recurrent psychiatric disorder that starts shortly after stroke and affects patients in the long term. A meta-analysis of the frequency of depression after stroke shows that approximately one-third of stroke survivors experience depression at any time point in the first year. 3 Depression after stroke is independently associated with poor health outcomes, including increasing mortality, disability, anxiety and lowering quality of life (QoL). 4 In addition, there is a two-way relationship between depression and stroke: stroke could increase the risk of post-stroke depression (PSD); meanwhile, depression is an independent risk factor for stroke and stroke mortality. 5-6

This bidirectional relationship makes it more difficult to develop the treatment of PSD. Currently, few guidelines mentioned the assessment, treatment or prevention for it. 7 For depressive disorder, Canadian Network for Mood and Anxiety Treatments, the American Psychiatric Association and the World Federation of Societies of Biological Psychiatry guidelines supported that selective serotonin uptake inhibitors (SSRIs) could be used as first-line treatment. 8-10 But the pharmacotherapy of PSD needs to be more cautious, as some studies 11-13 showed that the use of SSRI may relate to the potential risk of haemorrhagic stroke.

Acupuncture, a historic complementary therapy from China, has potential beneficial effects on improving dependency, global
neurological deficiency, and some specific neurological impairments for people with stroke in the convalescent stage.\textsuperscript{14} In the treatment of depression, a recent meta-analysis\textsuperscript{15} suggests that acupuncture combined with antidepressant medication is effective for the treatment of depression and has an early onset of action, safe and well tolerated over the first 6-week treatment period. However, few systematic reviews or meta-analysis focused on the effectiveness of acupuncture in treating PSD, although the number of papers related to this area has an upward trend recently.\textsuperscript{16,17} Besides, there are no meta-analysis focusing on the effectiveness of manual acupuncture on improving the depression severity and QoL of patients post stroke, so far. What’s more, there is a general problem of high heterogeneity in existing meta-analysis. One recent meta-analysis\textsuperscript{18} showed that the curative effect of acupuncture for post-stroke cognitive impairment may be related to manipulation and retention time; however, most of the existing meta-analysis on PSD did not conduct subgroup analysis for such content due to the lack of attention to the details of acupuncture treatment. Therefore, we considered that the higher heterogeneity may be relevant with the difference in the type of acupuncture (manual acupuncture, electroacupuncture, dry needle, etc) and the treatment schedule (acupoints selection, twist technique, retention time, frequency, etc). Hence, we would like to extract the detailed description of manual acupuncture treatment in the included articles and conduct subgroup analysis according to them.

**Objectives**
The primary purpose of this meta-analysis is to examine the efficacy of manual acupuncture in improving depression severity in individuals with PSD. Secondary aims are to evaluate its role in enhancing QoL and to assess the safety of this treatment.

**METHODS AND ANALYSIS**
This systematic review protocol has registered in PROSPERO. It will follow the new edition of the Cochrane handbook for systematic reviews of interventions\textsuperscript{19} and be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.\textsuperscript{20}

**Criteria for considering studies for this review**

**Types of studies**
Randomised controlled trials (RCTs) in English, Chinese and Japanese will be included. Animal studies or studies with incomplete data will be excluded.

**Participants**
We will include patients who suffered PSD. The diagnosis of stroke should be based on CT, MRI or clinical criteria. Meanwhile, depression should be diagnosed according to the International Classification of Diseases Tenth Edition, the Diagnostic and Statistical Manual of Mental Disorders, Chinese Classification of Mental Disorders or Hamilton Depression Rating Scale (HAMD).\textsuperscript{21–23}

**Types of interventions**
The relevant RCTs will be included if the following criteria were met: (1) using manual acupuncture alone, or in combination with another rehabilitation therapy, or in combination with pharmacotherapy in experiment group (EG); (2) using rehabilitation therapy other than manual acupuncture, pharmacotherapy, sham acupuncture or no treatment in control group (CG). In addition, other kinds of acupuncture therapies, such as electroacupuncture, dry needle, laser needle or acupoint injection, could not be used as interventions in EG or CG.

**Types of outcomes measures**

**Primary outcomes**

**Depression severity**
It is evaluated mainly by HAMD, Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Zung Self-Rating Depression Scale (SDS), etc.

If the included studies used two or more of above scales, we will give preference to clinician-rated scales. Following hierarchy will be applied:\textsuperscript{1} HAMD,\textsuperscript{2} MADRS,\textsuperscript{3} BDI,\textsuperscript{4} SDS and\textsuperscript{5} all other depression scales.

**Secondary outcomes**
1. QoL: evaluated mainly by the Medical Outcomes Study Short Form 36, the Stroke Specific Quality of Life Scale or the WHO Quality of Life Scale.
2. Safety: evaluated mainly by the total numbers and severity of adverse events.

**Search methods for identification of studies**
The following 10 databases will be searched from establishment to November 2020: PubMed, the Cochrane Library, Medline, Embase, Japan Science and Technology Agency, CiNii (National Institute of Informatics), China National Knowledge Infrastructure, WanFang Data, VIP and Chinese Biomedical Databases. The combination of free words and medical subject headings, including ‘depression, depressive disorder, acupuncture therapy, acupuncture, needle, needling, stroke, etc’, will be used as the retrieval mode. The search strategy for the Cochrane Library is presented in table 1.

**Study selection and data extraction**
EndNote VX8.2 will be used to manage studies. First, duplicate literature will be excluded by electronic-based and manual-based steps in EndNote. Second, two reviewers will independently screen the titles and abstracts and select the studies which meet the eligibility criteria. If there are disagreements, the third reviewer will be consulted. The evaluators will read the full text of the included literature, and then preliminarily extracted relevant data, mainly including the following information: (1) inclusion and exclusion criteria; (2) the number of included samples (total number of cases, the number...
of cases in the treatment group and the number of cases in the CG); (3) grouping method and process; (4) basic data of the included research samples (mainly including gender, age and disease); (5) the intervention of the treatment group and the CG: (a) the treatment method, drug dose, treatment frequency, course of treatment, etc and (b) a detailed description of manual acupuncture treatment, including acupoints selection, twist technique, retention time, frequency, etc (6) and evaluation of the final research results (including the treatment efficiency of different treatment measures, the scale score at the beginning and end point, etc).

Quality assessment
The quality of evidence for main outcomes will be assessed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Two reviewers will do this independently through GRADEpro Guideline Development Tool. GRADE approach provides guidance for rating quality of evidence and grading strength of recommendations for healthcare. It has important implications for those summarising evidence for systematic reviews. It assessed a body of evidence by referring to the concepts of the GRADE system, and determined and recorded the quality of a body of evidence for each clinical question; there are four quality levels: high, moderate, low and very low.25

Assessment of heterogeneity, sensitivity analysis and subgroup analysis
We will use the $I^2$ statistic to assess the heterogeneity. If the $I^2$ value is below 50%, the fixed effect model will be used. Otherwise, sensitivity analysis will be conducted to explore the main sources of heterogeneity, after which, the random effect model will be used if the $I^2$ is still equal or greater than 50%. Both types of effect sizes will be presented with 95% CIs, and p values <0.05 will be regarded as statistically significant.

Meanwhile, subgroup analysis will also be conducted to explore the main sources of heterogeneity. Compared with previous studies, we will extract more detailed information on the treatment schedule of acupuncture, which could provide us more analytical basis for subgroup analysis. If the necessary information is available, subgroup analyses will be carried out according to certain factors (acupoints selection, twist technique, retention time, frequency, period of treatment and different types of CG). After grouping, two or more groups of studies will be analysed and compared in order to explore the causes of high heterogeneity.

Data synthesis
Continuous outcomes will be calculated as mean differences (MDs) or standardised mean differences (SMDs). If different scales are used to measure continuous outcomes, like depression severity and QOL, SMD will be used as a measure of effect size in efficacy outcome. It is calculated as the difference in mean outcome between groups divided by the SD of outcome among participants. If the same scale is used in the included literature, MD will be used. In addition, safety outcome will be the number of participants who dropped out due to adverse effects and the number of participants who reported at least one adverse event or effect. For these dichotomous outcomes, the OR will be calculated as the effect estimate.

Assessment of the risk of bias in individual studies
According to Cochrane Handbook for Systematic Reviews of Interventions, version 6 (https://training.cochrane.org/handbook/current/chapter-08), the risk of bias 2.0 (ROB 2.0) tool will be used to mean the methodological quality and the risk of bias of the included studies. One researcher assessed the ROB of included studies by using ROB 2.0 and another researcher confirmed the judgement. If there are any differences, the third researcher will be asked to solve the problem.

Publication bias
STATA V.14.0 will be used to evaluate publication bias. Begg’s test and Egger’s test will be used to assess the publication bias of the included trials and form the publication bias plot.

Patient and public involvement
It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION
This meta-analysis will focus on the different techniques, durations or other detailed operations of manual acupuncture applied in patients with PSD to explore their influence on depression severity and QoL. PSD are generally more disabled.26 As an important part of traditional Chinese medicine, acupuncture plays an important role in clinical treatment.27 In terms of clinical efficacy, acupuncture can assist in eliminating negative emotions.

Table 1  Search strategy for the Cochrane Library

<table>
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<th>ID</th>
<th>Search</th>
</tr>
</thead>
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<tr>
<td>#1</td>
<td>MeSH descriptor: [Stroke] explode all trees</td>
</tr>
<tr>
<td>#2</td>
<td>poststroke or post-stroke. t.i,ab,kw</td>
</tr>
<tr>
<td>#3</td>
<td>MeSH descriptor: [Cerebral Infarction] explode all trees</td>
</tr>
<tr>
<td>#4</td>
<td>MeSH descriptor: [Cerebral Hemorrhage] explode all trees</td>
</tr>
<tr>
<td>#5</td>
<td>#1 or #2 or #3 or #4</td>
</tr>
<tr>
<td>#6</td>
<td>MeSH descriptor: [Depression] explode all trees</td>
</tr>
<tr>
<td>#7</td>
<td>depress* or affective disorder or affective symptoms. t.i,ab,kw</td>
</tr>
<tr>
<td>#8</td>
<td>#6 or #7</td>
</tr>
<tr>
<td>#9</td>
<td>MeSH descriptor: [Acupuncture] explode all trees</td>
</tr>
<tr>
<td>#10</td>
<td>acupunctur* or acupoint* or needl* t.i,ab,kw</td>
</tr>
<tr>
<td>#11</td>
<td>#9 or #10</td>
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<td>#12</td>
<td>#5 and #8 and #11</td>
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</tbody>
</table>

by significantly improving the functional communication and language function, cognitive and limb movement function of stroke patients. At the mechanism level, acupuncture can modulate glutamate receptor and excitatory amino acid transporter expression, downregulated the levels of unclear factor kappa light chain enhancer of activated B cells protein, inducible nitric oxide synthase and nitric oxide, so as to achieve the purpose of relieving PSD.

**Ethics and dissemination**

The results of this meta-analysis will be disseminated through publication in peer-reviewed journals or conference presentations. The data used in this meta-analysis will not contain individual patient data; therefore, ethical approval is not required.

**Contributors**

WL and CR conceived, designed and wrote this protocol. WL provided a clinical perspective, especially to the manual acupuncture. QZ provided the writing and modification of part of the article. YD is the guarantor of this review and approved the final manuscript. WJ, ZL and CY provided a preliminary data retrieval.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Open access**

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**ORCID iD**

Wei Liu http://orcid.org/0000-0001-7974-849X

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