Effects of acupuncture on stroke in patients with type 2 diabetes: A protocol for systematic review and meta-analysis

Fangda Han; Ao Zhang*

*Corresponding Author: Ao Zhang

Nanjing University of Chinese Medicine, Nanjing, China.

Email: stellazhangtcm@njucm.edu.cn

Abstract

Background: Stroke and type 2 diabetes (T2D) are two common diseases that endanger human health, and patients suffer from stroke with T2D at the same time face more threat than patients only suffer from one of them. Acupuncture, as a form of alternative medical treatment based on the theories of Traditional Chinese Medicine, has been showing it's significant effects in improving the conditions of stroke patients with T2D by affecting metabolism, repairing endothelial cells, and protecting the internal structure of neurons; acupuncture also shows the advantages of being cost-efficient and convenient. It is worthwhile to conduct a systematic review and meta-analysis to reach a better understanding of the effects of acupuncture in treating diabetic stroke patients, which helps the development of clinical strategies for both diabetes and stroke.

Methods: We will search the following electronic bibliographic databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, China Biology Medicine disc (Sinomed), WanFang Data, China National Knowledge Infrastructure (CNKI), Chongqing VIP Database (VIP) . Two review authors will be independently assess the risk of bias in included studies by Cochrane risk of bias tool. The five-point Jadad score is also used for the methodological quality assessment, disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Statistical analysis will be performed with Review Manager software 5.3.

Result: A synthesis of current evidence of acupuncture in treating stroke with T2D will be provided in this protocol.

Discussion: This systematic review and meta-analysis of acupuncture' effects on stroke patients with type 2 diabetes can provide evidence for the future development of therapy strategies in treating this comorbidity.

Keywords

Systematic review; Meta-analysis; Stroke; Type 2 diabetes; Acupuncture; RCT; Protocol.

Abbreviations

T2D: Type 2 diabetes; RCT: Randomized Controlled Trial.

Introduction

Stroke is the leading cause of disability and the second highest cause of human death [1]. Type 2 diabetes (T2D) is a kind of common metabolic disease; researches have already proven that T2D is an independent risk factor for stroke [2]. T2D can cause vascular endothelial dysfunction, increased early-age arterial stiffness, systemic inflammation and thickening of the capillary basal membrane and therefor associates with increased risk of stroke. Meanwhile, stroke is increasingly recognized as clinically important complications of T2D [3]. Globally, both stroke and T2D are increasingly common conditions that contribute to human being's morbidity and mortality, which brings serious burden to the society [4]. Currently, the common therapeutic strategies for diabetic stroke patients include glycemic control, blood pressure-lowering, recanalization, and so on [5]. However, problems such as serious adverse reactions, limited effects, and high final burden impact the therapeutic

Studies have shown acupuncture's significant therapeutic effects in improving the conditions of diabetic stroke by affecting metabolism, repairing endothelial cells, and protecting the internal structure of neurons [6,7]. In clinical practice, acupuncture is commonly used in treating the symptoms relate to T2D and stroke; along with the clinical effects such as regulating glycemic levels, decreasing the rate of stroke recurrence, repairing motor function and improving life quality, acupuncture also presents the advantages of safety, cost-efficiency and convenience [8-10].

Though there are plenty of evidence showing acupuncture's effect in treating diabetic stroke [11-13], no systematic review or meta-analysis has been conducted on this topic yet. Therefore, it is necessary to conduct a systematic review and meta-analysis based on the most comprehensive and latest resources to answer the question of "does acupuncture show better therapeutic effects than conventional therapy or sham acupuncture in treating stroke in patients with T2D?", which is meaningful to the development of therapy strategies in treating the comorbidity of stroke and T2D.

Methods

Study registration

This systematic review protocol has been registered on PROSPERO with number CRD42021216450 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=216450).

The protocol followed the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines [14]. Any change of the review will be described if needed. This systematic review and meta-analysis will be published in a peer-reviewed journal. Formal ethical approval and informed consent are not requi-

red for this study, because this study is a secondary research based on previously published studies.

Inclusion criteria

Types of studies: The review will include randomized controlled trials (RCTs) that were reported in English or Chinese without any regional restrictions. First period of randomized cross-over trials will be included. Non-RCT reviews, animal experimental studies, case reports, expert experience, conference articles, and duplicated publications will be removed.

Types of participants: People who are diagnosed both stroke and T2D will participate without considering any information related to their age, race, nationality, education, sex, or economic status; patients with both stroke and T2D are between the ages of 18 and 70 years. There will be no race or other restrictions and participants of any sex and ethnicity will be enrolled.

Types of interventions: Acupuncture or acupuncture related combined therapies, such as body acupuncture, electro-acupuncture, scalp acupuncture, auricular acupuncture, etc. Cupping, moxibustion, and transcutaneous electrical nerve stimulation will be excluded. In addition, there were no limitations to the test cycle and treatment frequency.

Types of comparators: The comparators include conventional therapy, sham acupuncture, or no treatment.

Types of outcome measures: The primary outcome measurement will be blood glucose levels, glycosylated hemoglobin levels A1c (HbA1c), and the rate of stroke recurrence.

The secondary outcomes of this review will include other clinical parameters associated with stroke and T2D, including fasting and post-load blood glucose levels, cholesterol, triglycerides, score of quality of life scale, etc.

Exclusion criteria

(1) Retrospective study, case report, review, experiences, letters, animal experiments, and studies in which stroke or T2D were not formally diagnosed will be excluded.

(2) Articles published as abstracts or with incomplete data, or complete articles could not be obtained even after contacting the author(s). Articles without full text or with data which are missed or cannot be used.

(3) Studies exhibiting a high-risk bias.

(4) Experiences, letters, animal experiments and systematic reviews.

Search methods for identification of studies

Electronic searches: The following electronic bibliographic databases will be included in the electronic search strategy: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, China Biology Medicine disc (Sinomed), WanFang Data, China National Knowledge Infrastructure (CNKI), Chongqing VIP Database (VIP). All retrieval up to December 30, 2021.

No publication date or language restrictions will be applied. The reference lists of included studies will be screened for additional eligible studies not retrieved by our search. The searches will be re-run just

before the final analyses to retrieve the most recent studies eligible for inclusion.

Searching strategy: The full search strategy is based on the search components "stroke", "acupuncture" and "T2D". The search strategy for PubMed is shown in Table 1, and other electronic databases will be searched with the same strategy.

Data collection and analysis

Selection of studies: All reviewers will receive professional training to understand the objective and process of the review before the selection of studies. Literature search results will be imported into ENDNOTE X8 software. The duplicates will be removed. For studies that have been updated, the older one will be excluded, or can be used as supplementary data in further research. Titles and abstracts will be screened independently by two reviewers (FDH and AZ). Full texts will be obtained for eligible studies and will be screened independently (FDH and AZ). Discrepancies will be resolved through discussion, or by consulting a third reviewer. The procedures of study selection will be performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis flow chart (Figure 1).

Table 1: Search strategy for PubMed database.

Number	Search Terms
#1	"Stroke" [Mesh] OR "Cerebral Infarction" [Mesh] OR "Brain Infarction" [Mesh] OR "Brain Ischemia" [Mesh] OR "Cerebral Infarction" [Mesh] OR "Brain Infarction" [Mesh] OR "Brain Ischemia" [Mesh] OR "Cerebral Hemorrhage" [Mesh] OR "Intracranial Hemorrhages" [Mesh]
#2	"Stroke" [Title/Abstract] OR "Cerebral Ischemia" [Title/Abstract] OR "Cerebral Ischaemia" [Title/Abstract] OR "Brain Ischaemia" [Title/Abstract] OR "Ischemic Brain" [Title/Abstract] OR "Ischaemic Brain" [Title/Abstract] OR "Cerebral Infarct" [Title/Abstract] OR "Brain Infarct" [Title/Abstract] OR "Cerebral Artery Infarct" [Title/Abstract] OR "Cerebral Artery Infarction" [Title/Abstract] OR "Cerebral Circulation Infarction" [Title/Abstract] OR "Cerebral Artery Thrombosis" [Title/Abstract] OR "Cerebral Artery Thrombotic Infarction" [Title/Abstract] OR "Cerebral Artery Embolic Infarction" [Title/Abstract] OR "Brain Venous Infarction" [Title/Abstract] OR "Cerebral Hemorrhage" [Title/Abstract] OR "Intracranial Hemorrhage" [Title/Abstract] OR "Hemorrhagic Stroke" [Title/Abstract]
#3	#1 OR #2
#4	"Diabetes Mellitus, Type 2" [Mesh] OR "Type 2 Diabetes" [Title/Abstract] OR "Diabetic" [Title/Abstract] OR "Diabetes" [Title/Abstract] OR "Mellitus" [Title/Abstract] OR "Hyperglycemia" [Title/Abstract]
#5	"Acupuncture" [Mesh] OR "Chinese External Medicine" [Title/Abstract] OR "Electroacupuncture" [Title/Abstract] OR "Fire Needle" [Title/Abstract] OR " Needling" [Title/Abstract]
#6	"Randomized Controlled Trial" [Title/Abstract] OR "Controlled Clinical Trial" [Title/Abstract] OR "Clinical Trial" [Title/Abstract] OR "Clinical Trial" [Publication Type] OR "RCT" [Title/Abstract]
#6	#3 AND #4 AND #5 AND #6

Two reviewers (FDH and AZ) will establish a sheet using Microsoft Excel 2010, pilot and refine this form using 10 initial studies. After the form has been developed, the two reviewers will extract data from the text and figure/table independently, including: (1) general information (e.g. author, year of publication, country where the study was conducted, study period, original inclusion criteria); (2) participants (e.g. age, gender, sample size); (3) details about intervention (e.g. acupuncture parameters, acupuncture points and duration of study, follow-up time); (4) study design (e.g. randomization, blinding and allocation concealment); (5) outcomes and adverse reactions.

In multiarm RCTs, we will extract data from RCTs of 2 arms, while we will select 1 group, which

contains the treatment of acupuncture as the treatment group, we will also choose another group the treatment of which without acupuncture as the control group.

Figure 1: Flow diagram of the study selection process.
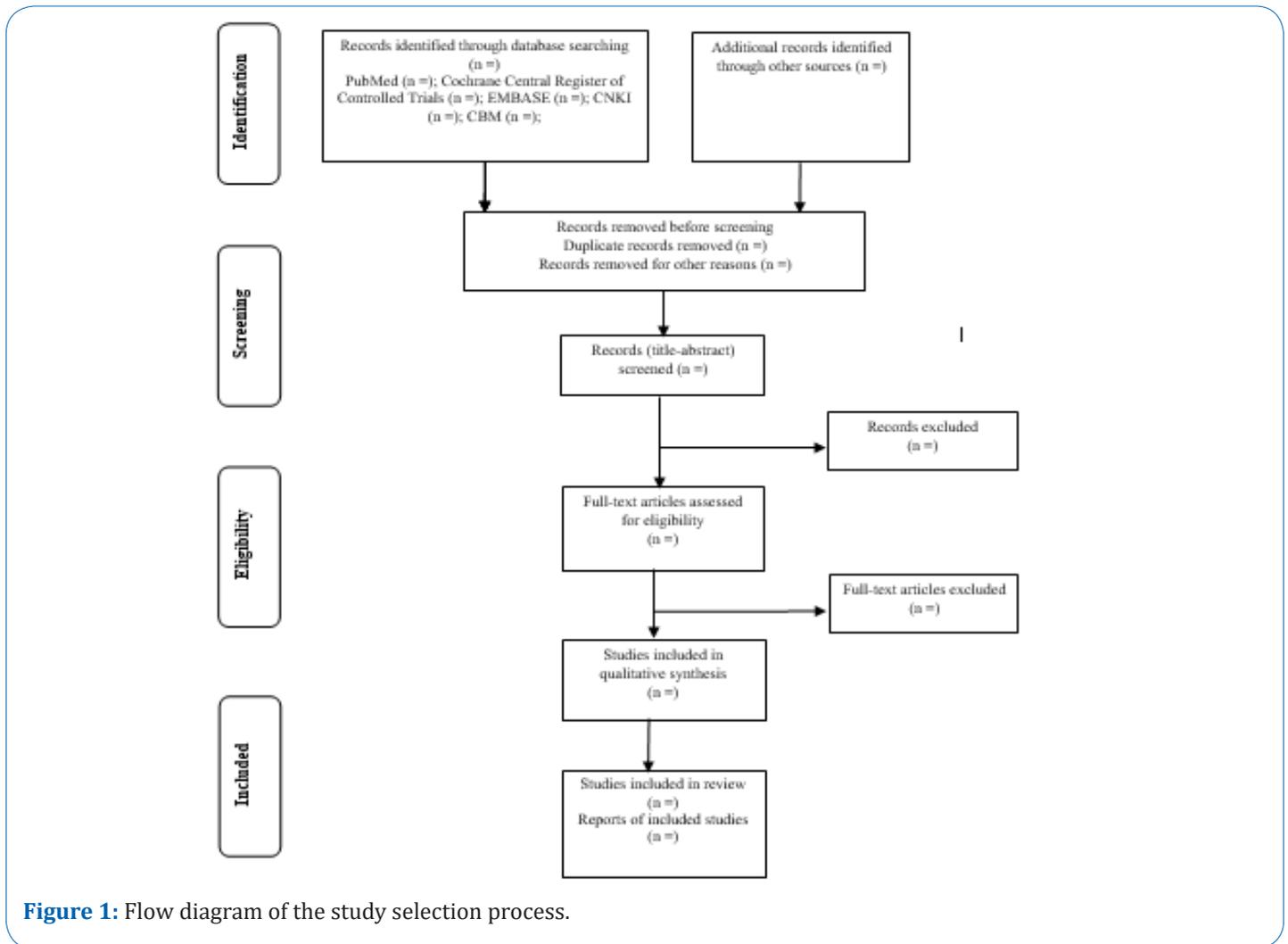
Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary), or by consulting a third reviewer. We first try to extract numerical data from tables, text or figures. If these are not reported, we will extract data from graphs using digital ruler software. In case data is not reported or unclear, we will attempt to contact authors by e-mail (max. 2 attempts).

Assessment of risk of bias in included studies: Two reviewers (FDH and AZ) will be independently assess the risk of bias in included studies by Cochrane risk of bias tool [15], after being trained and calibrated to ensure uniformity in the evaluation of the criteria. The five-point Jadad score is also used for the methodological quality assessment. Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third reviewer were necessary.

Measurement of treatment effect and data analysis: Review Manager 5.3 and Stata 15.1 will be used in data analysis. For dichotomous data, a risk ratio with 95% confidence intervals will be used for analysis. For continuous data, a mean difference or a standard mean difference with 95% confidence intervals will be used for analysis.

Assessment of heterogeneity: I^2 statistic will be calculated for quantifying heterogeneity among in-

cluded studies (I^2>50%, means large heterogeneity; 25%< $I^2 \leqq$ 50%, means medium heterogeneity; and 0$\leqq I^2 \leqq$25%, means small heterogeneity), and meta-regression will be used to investigate sources of heterogeneity [16].

Assessment of publication bias: We plan to implement publication bias when more than 10 studies are included for one outcome. The methods for assessment of publication bias will be: Funnel plot, Egger's linear regression and adjusted for trim and fill.

Data synthesis: Fixed effect model will be used when the heterogeneity was not significant, and random effect model will be used when the heterogeneity was significant. Sensitivity analysis will explore potential sources of heterogeneity by removing one study at a time and reassessing the effect of the combination. However, if the level of heterogeneity is significant, descriptive statistics will be performed.

Subgroup analysis: If the necessary data are available, subgroup analyses will be performed. The following study characteristics will be examined as potential source of heterogeneity: species (stratified per species); sex (stratified per sex); duration of treatment(linear); treatment frequency(linear); linding of outcome assessment reported (stratified yes vs no); comorbidities (stratified yes vs no); study quality (linear); forms of acupuncture is giving (e.g. electroacupuncture versus non-electro acupuncture). For stratified analyses, a minimum number of 5 studies per subgroup is required.

Sensitivity analysis: Stratified meta-analysis will be used as an alternative method to investigate sources of heterogeneity. Stratifications will be considered in two domains: study design and study quality. Each domain will be tested at P<0.05 overall and a HolmBonferroni adjusted critical P value will be calculated to account for the number of parameters tested within each domain. Other sensitivity analyses will be carried out if necessary (e.g. if there are outliers that may skew results the analysis will be re-run excluding any outliers and the results of both analyses reported).

Discussion

Both stroke and T2D are huge threats that impact human health world widely. The prevalence of diabetes in developed and developing countries has been rising, and the number of first-time stroke patients will reach 23 million by 2030 [17,18]. To face the challenges at present and also in the future, it is important to find the rational and effective medical option for stroke patients with T2D. This study aims to analyze whether acupuncture is more effective in treating stroke patients with T2D. Our systematic review and meta-analysis can show the advantages and limitations of the current literature in this field; additionally, this research can also preclude unnecessary study replication, improve the development of future clinical therapy strategies for endocrinologic and cerebrovascular diseases, and bring more hope to diabetic stroke patients.

Declarations

Author conflicts of interest: The authors have no conflicts of interest to disclose.

Author contributions: Fangda Han designed this research, drafted the manuscript, and tested the feasibility of the study, Ao Zhang contributed to the development of the selection criteria, and read, provided feedback and approved the final manuscript. Both authors approved the final version of the manuscript.

References

1. Brønnum HH, Davidsen M, Thorvaldsen P. Long-term survival and causes of death after stroke. Stroke. 2001; 32: 2131-2136.

2. Lukovits TG, Mazzone T, Gorelick PB. Diabetes mellitus and cerebrovascular disease. Neuroepidemiology. 1999; 18: 1-14.

3. Wang F, Wang S, Zong Q, Ng CH, Ungvari GS, et al. Prevalence of comorbid major depressive disorder in Type 2 diabetes: a meta-analysis of comparative and epidemiological studies. Diabet Med. 2019; 36: 961-969.

4. Sander D, Sander K, Poppert H. Stroke in type 2 diabetes. Br J Diabetes Vasc Dis. 2008; 8: 222-229.

5. Nathaniel TI, Ubah C, Wormack L, Gainey J. The telestroke and thrombolysis therapy in diabetic stroke patients. Diabetol Metab Synd. 2019; 11: 36.

6. Jing XH, Shi H, Cai H, Chen SL, Jin ZG, et al. Effect of acupuncture on long-term potentiation of hippocampal CA 1 area in diabetic rats with concurrent cerebral ischemia. Zhen Ci Yan Jiu. 2008 ; 33 : 397-401.

7. Choi S, Lee GJ, Chae SJ, Kang SW, Yin CS, et al. Potential neuroprotective effects of acupuncture stimulation on diabetes mellitus in a global ischemic rat model. Physiol Meas. 2010; 31: 633.

8. Meyer-Hamme G, Friedemann T, Greten J, Gerloff C, Schroeder S, et al. Electrophysiologically verified effects of acupuncture on diabetic peripheral neuropathy in type 2 diabetes: The randomized, partially double-blinded, controlled ACUDIN trial. J Diabetes. 2021; 13: 469-481.

9. Sui M, Xue L, Ying X. Association of acupuncture treatment with mortality of type 2 diabetes in China: evidence of a real-world study. Int J Environ Res Public Health. 2020; 17: 7801.

10. Li S, Chen J, Liu M, Wang YP, Zhou X, et al. Effect and safety of acupuncture for type 2 diabetes mellitus: a systematic review and meta-analysis of 21 randomised controlled trials. Chin J Integr Med. 2021; 28: 463-471.

11. Zhao H, Yang D, Shi M, Liang J, Yang X, et al. Clinical efficacy and safety of traditional Chinese medicine combined with Western Medicine in patients with diabetic acute ischemic stroke. J Tradit Chin Med. 2014; 34: 145-149.

12. Lee AL, Chen BC, Mou CH, Sun MF, Yen HR, et al. Association of traditional Chinese medicine therapy and the risk of vascular complications in patients with type II diabetes mellitus: a nationwide, retrospective, Taiwanese-registry, cohort study. Medicine. 2016; 95: e2536.

13. Weng SW, Chen TL, Yeh CC, Liao CC, Lane HL, et al. An investigation of the use of acupuncture in stroke patients in Taiwan: a national cohort study. BMC Complement Altern Med. 2016; 16: 1-8.

14. Shamseer L, Moher D, Clarke M. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015; 350: 7647.

15. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clin Res ed). 2011; 343: d5928.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002; 21: 1539-1558.

17. Dieren S, Beulens JW, Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. Eur J Cardiovasc Prev Rehabil 2010; 17: s3–s8.

18. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. Lancet Neurol. 2007; 6: 182-187.

Authors Information: Fangda Han[1]; Ao Zhang[2]*
[1]Shenzhen Longgang Fourth People's Hospital, Shenzhen, China.
[2]Nanjing University of Chinese Medicine, Nanjing, China.

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