Systematic Review and Meta-Analysis

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Chinese herbal injections combined with rt-PA intravenous thrombolysis for acute ischemic stroke

A systematic review and meta-analysis protocol

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Abstract

Background: Acute ischemic stroke (AIS) is an important factor leading to adult death and disability globally. For AIS patients who meet certain conditions, recombinant tissue plasminogen activator (rt-PA) intravenous thrombolysis is an important method recommended by national guidelines to achieve vascular recanalization. However, complications such as hemorrhagic transformation and vascular reocclusion after thrombolysis are still unsolved problems in clinical. Several systematic reviews of clinical randomized controlled trials (RCTs) in the past have shown that Chinese herbal injections (CHIs) can improve the neurological function of patients, increase the tolerance of ischemic tissues to hypoxia, and inhibit platelet aggregation. Therefore, this study conducted a meta-analysis of AIS treatment with intravenous thrombolysis alone and compared it with the combined application of CHIs. To evaluate whether CHIs have a synergistic effect on thrombolytic therapy and provide a basis for clinical application.

Methods: The following databases will be searched until September 2020: ①English databases: PubMed, Cochrane Library, Embase; ②Chinese databases: CNKI, Wanfang database, Weipu database, SinoMed. RCTs will be included to compare the efficacy of thrombolysis combined with CHIs and thrombolysis alone in the treatment of AIS. Data extraction and risk of bias assessments will be carried out by 2 verifiers independently. The risk of bias will be evaluated through the Cochrane risk of bias tool. Review Manager software 5.3 will be used for statistical analysis.

Results: This study will provide comprehensive evidence for the treatment of AIS by CHIs combined with intravenous thrombolysis from multiple aspects.

Conclusion: The conclusion of the meta-analysis will provide a basis for judging whether CHIs combined with intravenous thrombolysis is an effective measure for the treatment of AIS.

Ethics and dissemination: Ethical approval is not needed because this study will be based on data that already published. We will publish the findings of this study in a peer-reviewed journal and related conferences.

PROSPERO registration number: CRD42020215546.

Abbreviations: AIS = acute ischemic stroke, CHIs = Chinese herbal injections, NIHSS = National Institute of Health stroke scale, RCTs = randomized controlled trials, rt-PA = recombinant tissue plasminogen activator.

Keywords: acute ischemic stroke, Chinese herbal injections, intravenous thrombolysis, meta-analysis

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Stroke is a major factor leading to adult death and disability globally.[1] Among them, AIS accounts for about 69.6% to 70.8% of stroke types,[2] which seriously threatens people's health. In recent years, the continuous advancement of AIS treatment methods has significantly reduced the mortality of patients and improved the prognosis. In particular, reperfusion therapy, such as intravenous thrombolysis and endovascular therapy, has significant effects on patients.[3,4] Among them, for AIS patients who meet certain conditions, recombinant tissue plasminogen activator (rt-PA) intravenous thrombolysis is an important method recommended by national guidelines to achieve vascular recanalization (level I recommend, level A evidence).[5,6] However, complications such as hemorrhagic transformation, vascular reocclusion, reperfusion injury, and cerebral edema after thrombolysis are still unsolved problems in clinical.[7,8]

In China, various traditional Chinese medicines and acupuncture therapies are commonly used in the acute and convalescent stages of stroke. No matter in traditional Chinese medicine hospitals or Western hospitals, acupuncture therapy or at least 1 Chinese patent medicine is commonly used for stroke patients, a meta-analysis that included 191 clinical trials showed that Traditional Chinese Patent Medicine could significantly improve neurological impairment in patients, and appeared potentially beneficial and nontoxic.[9] Among them, CHIs has the advantages of production line standard and high bioavailability[10] and has been approved by the State Food and Drug Administration of China for more than 40 years. Chinese Guidelines for the Diagnosis and Treatment of Cerebral Infarction with Integrated Traditional Chinese and Western Medicine also recommend the clinical use of integrated traditional Chinese and western medicine,[11] using injections such as Danshen preparations, safflower preparations, and ginkgo biloba preparations. Therefore, clinically, for patients who meet the conditions for intravenous thrombolysis, CHIs are generally given for treatment after thrombolysis.

Several systematic reviews of clinical randomized controlled trials in the past have shown that CHIs can improve the neurological function of patients, increase the tolerance of ischemic tissues to hypoxia, inhibit platelet aggregation, improve blood circulation, and reduce reperfusion injury.[12,13] There are also clinical trials showing that CHIs combined with intravenous thrombolysis has significant clinical effects. For example, in patients with rt-PA thrombolysis combined with Danshen injection for 3 weeks, the National Institute of Health stroke scale (NIHSS) score was significantly lower than that of patients with simple intravenous thrombolysis(7.26 ± 1.65 vs 10.23 ± 2.01);[14] after 14 days of rt-PA combined with Shuxuetong injection, the NIHSS score was significantly lower than that of the patients with intravenous thrombolysis alone(9.63 ± 2.14 vs 14.52 ± 2.58), and the prognosis was better.[15] However, due to CHIs are clinically applied to stroke patients with different pathological types and different pathological periods, for example, CHIs are given in both the acute phase and the recovery phase of the disease and medications under different conditions have a greater impact on the treatment effect, it is impossible to specifically evaluate the efficacy of CHIs under different conditions of use.

At present, there has been no analysis of the efficacy and safety of using CHIs after thrombolysis. Therefore, this study conducted a meta-analysis of AIS treatment with intravenous thrombolysis alone and compared it with the combined application of CHIs. To evaluate whether CHIs have a synergistic effect on thrombolytic therapy and provide a basis for clinical application.

2. Materials and methods

2.1. Inclusion criteria

2.1.1. Types of studies. Only RCTs that provide AIS patients with rt-PA intravenous thrombolysis and CHIs treatment after thrombolysis will be included. Thrombolytic therapy should be standardized treatment within the time window recommended by the guidelines, and CHIs should be an intravenous drip. Besides, non-randomized controlled trials, animal experiments, experience reports, and comments will not be included.

2.1.2. Study population. AIS patients are eligible for rt-PA intravenous thrombolytic therapy.

2.1.3. Interventions. Control group: rt-PA intravenous thrombolysis

Test group: After rt-PA intravenous thrombolysis, use CHIs intravenously.

In addition to the above treatment, both groups can receive the same basic treatment, such as oxygen absorption, blood pressure control, intracranial pressure reduction, and maintenance of water and electrolyte balance. For specific treatment methods, refer to the Guidelines for the Early Management of Patients With Acute Stroke given by the American Heart Association/American Stroke Association.[5]

2.1.4. Outcome indicators. The main outcome evaluation indicators should include treatment response rate, NIHSS score and death, while the secondary evaluation indicators include short-term or long-term prognosis, quality of life evaluation, cerebral infarction volume, and peripheral blood biological indicators.

2.1.5. Exclusion criteria.

1. Patients with thrombolysis beyond the time window.
2. The dose or manner of rt-PA use was not recommended in accordance with the guidelines.
3. In addition to the CHIs studied, other traditional Chinese medicine or acupuncture were also used.

2.2. Retrieval strategy

2.2.1. Searching Scope. PubMed, the Cochrane Library, EMBASE, CNKI, WanFang Data, VIP, and SinoMed databases will be electronically searched. The search time limit is to build the database until September 26, 2020, and the language is set to English and Chinese.

2.2.2. Searching keywords. Keywords include: stroke, cerebrovascular stroke, cerebral stroke, acute stroke, acute ischemic stroke, brain ischemia, brain infarction, cerebral infarction, cerebral ischemia, cerebrovascular disorders, cerebrovascular disease, cerebrovascular accident, cerebral artery disease, brain Vascular accident, apoplexy, cerebrovascular apoplexy, thrombolytic therapy, intravenous thrombolysis, thrombolysis, thrombolytic, fibrinolytic therapy, fibrinolytic therapies, therapeutic thrombolysis, tissue plasminogen activator, tPA, rt-PA, alteplase, T plasminogen activator, injections, injection, injectables, injectable. Using the combination of subject words and free words, keyword search and RCT document screening are carried

Table 1

Search strategy for the PubMed database.

Number	Search items
#1	"Stroke"[Mesh]
#2	((((((((((((Cerebrovascular Stroke[Title/Abstract]) OR (Cerebral Stroke[Title/Abstract])) OR (Acute Stroke[Title/Abstract])) OR (acute ischemic stroke[Title/Abstract])) OR (brain ischemia[Title/Abstract])) OR (brain infarction[Title/Abstract])) OR (cerebral infarction[Title/Abstract])) OR (cerebral ischemia[Title/Abstract])) OR (cerebrovascular disorders[Title/Abstract])) OR (cerebrovascular disease[Title/Abstract])) OR (cerebrovascular accident[Title/Abstract])) OR (cerebralartery disease [Title/Abstract])) OR (Brain Vascular Accident[Title/Abstract])) OR (Apoplexy[Title/Abstract])) OR (Cerebrovascular Apoplexy[Title/Abstract])
#3	#1 OR #2
#4	"Thrombolytic Therapy"[Mesh]
#5	(((((Intravenous thrombolysis[Title/Abstract]) OR (thrombolysis[Title/Abstract])) OR (thrombolytic[Title/Abstract])) OR (Fibrinolytic Therapy[Title/Abstract])) OR (Fibrinolytic Therapies[Title/Abstract])) OR (Therapeutic Thrombolyses[Title/Abstract])
#6	# 4 OR #5
#7	"Tissue Plasminogen Activator"[Mesh]
#8	(((tPA[Title/Abstract]) OR (rtPA[Title/Abstract])) OR (alteplase[Title/Abstract])) OR (T Plasminogen Activator[Title/Abstract])
#9	#7 OR #8
#10	"Injections"[Mesh]
#11	((Injection[Title/Abstract]) OR (Injectables[Title/Abstract])) OR (Injectable[Title/Abstract])
#12	#10 OR #11
#13	#3 AND #6 AND # 9 AND #12

out according to the characteristics of each database. The detailed PubMed searching strategy is listed in Table 1.

2.3. Literature selection

Import all the retrieved documents into EndNote software, firstly filter out duplicate documents, Then, 2 researchers will read the title and abstract of the article initially, filter out irrelevant documents, and finally read the full text of the article to filter out documents that do not meet the inclusion criteria. The literature screening process is carried out independently by 2 researchers. If there is any disagreement, it can be resolved through negotiation, or a third party can make a joint decision. The literature screening process is shown in Figure 1.

2.4. Data extraction and management

After reading the literature, the 2 researchers performed literature screening and information extraction independently. The information extraction included:

1. General information: author names and publication data;
2. Patient information: median age, number of patients, gender;
3. Intervention: names, dosages, duration of treatment;
4. Outcomes: the effective rate, improvement of neurological deficit, activities of daily living function, death and complications, and adverse drug events within the treatment.

Checking whether the information extracted by the 2 researchers is consistent. In case of disagreement, it can be resolved through negotiation, or a third-party researcher can make a joint decision.

2.5. Risk of bias assessment

The 2 researchers will use the RCT bias risk evaluation criteria of the Cochrane Systematic Review Manual Version 5.2 to evaluate the quality of the literature independently. Evaluation content includes random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. Each item is divided into "low risk," "high risk," or "unclear risk." If there is any disagreement, the 2 researchers can decide through consultation.

2.6. Statistical analysis

Statistical analysis will be performed with Review Manager software 5.3. Relative risk (RR) is used to evaluate the effect size for binary variables, and the mean difference (MD) is used as the efficacy analysis statistic for continuous variables. The 95% confidence interval is utilized to represent the interval estimation. The random-effects model is used to analyze the results. Judge the size of the statistical heterogeneity included in the literature by the value of P and I^2, $P > .1$ and $I^2 < 50\%$ indicate small heterogeneity; $P < .1$ and $I^2 \geq 50\%$ indicate high heterogeneity.

2.7. Subgroup analysis

If the results to be analyzed are heterogeneous, analyze the source of the heterogeneity, and perform subgroup analysis according to the patient's age, the severity of illness, treatment course, or medication dosage.

2.8. Sensitivity analysis

If necessary, sensitivity analysis will be performed to investigate the asymmetry of funnel plots to exclude low-quality studies. Evaluate whether the results of the meta-analysis are stable and reliable.

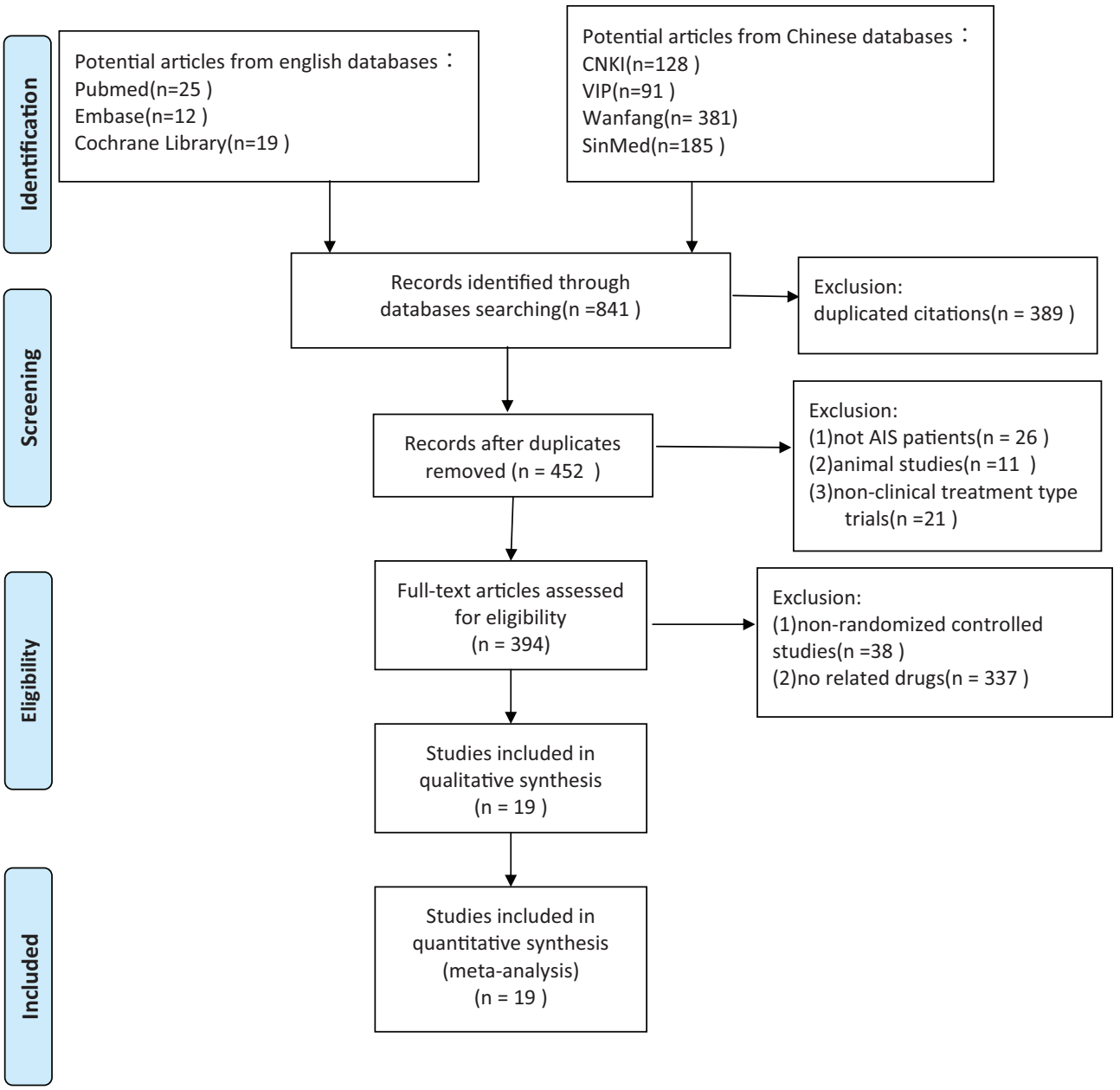

Figure 1. Document screening flow chart.

2.9. Reporting bias

When the number of references is ≥9, an inverted funnel plot will be drawn to judge the publication bias of the included studies. Egger tests will be performed to analyze potential causes if the asymmetry exists in the funnel plots.

2.10. Dealing with missing data

When data from included studies are incomplete, the researcher will try to contact the authors of the literature to obtain complete data. When the author cannot be contacted, the current data will be analyzed and the possible impact of missing data on the results will be assessed.

2.11. Quality of evidence

Two researchers will separately evaluate the quality of the review based on the Grading of Recommendations Assessment Development and Evaluation (GRADE).

3. Discussion

This is the first comprehensive review of the application of CHIs after thrombolysis. In recent years, significant progress has been made in the treatment of intravenous thrombolytic therapy. Not only has the time window gradually expanded, but also for patients after awakening and with unknown onset time, thrombolytic therapy can be performed under conditions of

MRI-DWI positive and FLAIR negative.[5] However, the recanalization rate and complications of thrombolysis have always been problems that cannot be ignored. Whether an effectual method of combined application can be found to improve the therapeutic effect of intravenous thrombolysis and reduce its adverse reactions has always been a difficult problem to be solved.

Chinese patent medicine injection is widely used clinically in China and has shown a good curative effect, so it is also a research hotspot in recent years. Many ingredients of CHIs have been proved to be effective for AIS in basic and clinical trials. For example, the honghua injection is made from the traditional Chinese medicine honghua, the active ingredients mainly include neosafflorin, safflower yellow and safflower as well as safflower quinone glycosides, honghua has the effect of invigorating the circulation of blood stasis in the theory of traditional Chinese medicine. Modern pharmacological studies have shown that safflower yellow can significantly inhibit the decrease of APE/Ref-1 expression after brain injury, and significantly reduce nerve cell production, decrease the apoptosis of nerve cells, has a protective effect on the nervous system.[16] The clinical application of honghua injection can improve the hemodynamic levels of AIS patients' whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, and erythrocyte sedimentation rate, to achieve the effect of stabilizing the vascular intima, thereby reducing cerebral edema and neurological mediator metabolism disorders, and improving the recovery of patients' nerve function.[17]

The clinical effects of rt-PA intravenous thrombolysis and CHIs alone are conclusive. However, there has been no systematic review of intravenous thrombolysis combined with CHIs for the treatment of AIS. This study will evaluate the efficacy and safety of the combination of the 2 for the first time, which will provide clinicians with better guidance on medication.

Author contributions

Conceptualization: Jing Wu.
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Writing – original draft: Jing Wu, Jinmin Liu.
Writing – review & editing: Jing Wu, Jinmin Liu.

References

[1] Feigin Valery L, Norrving Bo, Mensah George A. Global burden of stroke. Circ Res 2017;120:439–48.
[2] Wang W, Jiang B, et al. Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480687 adults. Circulation 2017;135:759–71.
[3] Wardlaw Joanna M, Murray Veronica, Berge Eivind, et al. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2014; CD000213undefined.
[4] Goyal Mayank, Yu Amy YX, Menon Bijoy K, et al. Endovascular therapy in acute ischemic stroke: challenges and transition from trials to bedside. Stroke 2016;47:548–53.
[5] Powers William J, Rabinstein Alejandro A, Ackerson Teri, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49:e46–110.
[6] Peng B, Wu B. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. Chin J Neurol 2018;51:666–82.
[7] Mishra NK, Albers GW, Davis SM, et al. Mismatch-based delayed thrombolysis: a meta-analysis. Stroke 2010;41:e25.
[8] Zinkstok SM, Roos YB. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke:a randomised controlled trial. Lancet 2012;380:731–7.
[9] Wu B, Liu M, Liu H, et al. Meta-analysis of traditional Chinese patent medicine for ischemic stroke. Stroke 2007;38:1973–9.
[10] Xie YY, Xiao X, Luo JM, et al. Integrating qualitative and quantitative characterization of traditional Chinese medicine injection by high-performance liquid chromatography with diode array detection and tandem mass spectrometry. J Sep Sci 2014;37:1438–47.
[11] Gao CY, Wu CH, et al. Guidelines for diagnosis and treatment of cerebral infarction with integrated traditional Chinese and Western medicine in China (2017). Chin J Integr Tradit Western Med 2018; 38:136–44.
[12] Liu XT, Ren PW, Peng L, et al. Effectiveness and safety of ShenXiong glucose injection for acute ischemic stroke: a systematic review and GRADE approach. BMC Complement Altern Med 2016;16:68.
[13] Zhang X, Wu J, Zhang B. Xuesaitong injection as one adjuvant treatment of acute cerebral infarction: a systematic review and meta-analysis. BMC Complement Altern Med 2015;15:36.
[14] Wang J, Wang XM. The effect of Danshen injection combined with rt-PA intravenous thrombolysis on neurological deficit score and quality of life in patients with acute cerebral infarction. Heilongjiang J Tradit Chin Med 2020;49:143–4.
[15] Fang M. Clinical efficacy of recombinant tissue-type plasminogen activator combined with Shuxuetong injection in the treatment of acute cerebral infarction and its influence on patients' neurological function. Chin J Clin Ration Drug Use 2019;12:49–50.
[16] Qiu L, Huang XF, et al. Protective effect of safflor yellow on brain damage in newborn rats. Nei Mongol J Tradit Chin Med 2014;33:93.
[17] Zhang L. Effects of honghua injection on hemodynamics and neural function of patients with acute cerebral infarction. Henan Med Res 2020;29:3969–71.