Comparative efficacy of oral traditional Chinese patent medicine for acute cerebral infarction: protocol for network meta-analysis of randomized controlled trials

**Abstract**

**Background:** Acute cerebral infarction (ACI) is one of the most common cerebral vascular diseases. Traditional Chinese patent medicines (TCPMs) are widely used in the treatment of ACI in China. However, rarely have randomized controlled trials (RCT) have been performed to directly compare the efficacy of different regimens of TCPMs. There is no evidence to demonstrate which of TCPMs more effective for clinicians. Therefore, we plan to conduct a systematic review and network meta-analysis (NMA) to compare the efficacy of different regimens of oral TCPMs for ACI. The aim is to provide the best currently available evidence base to guide the selection of oral TCPMs.

**Methods:** Electronic search strategies were developed by an experienced medical information specialist in consultation with our team. A systematic and comprehensive search will be performed from inception to July 2018 in both English and Chinese databases, involving Medline, Cochrane Library, Embase, China National Knowledge Infrastructure Database (CNKI), Wanfang Database, Chongqing VIP information (CQVIP), and SinoMed. Randomized controlled trials (RCTs) related to oral TCPMs in the treatment of ACI will be included. Two reviewers will independently screen the literature using pre-specified eligibility criteria, and assess the quality of included studies according to the risk of bias tool of Cochrane Handbook 5.1.0. The GRADE approach will be used to rate the quality of evidence of estimates derived from NMA. Data analysis will be conducted by using STATA 13.0 and WinBUGS 1.4.3 software.

**Discussion**: This NMA will offer new and informative evaluations of current oral TCPMs for ACI. The findings of this NMA will be reported according to PRISMA-NMA statement. The results will inform clinicians, provide optimal clinical treatment strategies to establish evidence gaps, and identify promising oral TCPMs for evaluation in future trials.

**Ethics and dissemination:** Since this study belongs to literature analysis based on published articles, it does not require ethics approval and patient consent.

**Protocol registration number:**

**Keywords:** oral traditional Chinese patent medicine, acute cerebral infarction, network meta-analysis

**1.Introduction**

Cerebral infarction (CI) is an area of necrotic tissue in the brain resulting from a blockage or narrowing in the arteries supplying blood and oxygen to the brain. The restricted oxygen due to the restricted blood supply causes an ischemic stroke that can result in an infarction if the blood flow is not restored within a relatively short period of time[1]. CI is the second largest cause of death, and stroke from all causes has high morbidity and mortality[2]. Annually, 15 million people suffer from cerebral infarction[3]. Acute cerebral infarction (ACI) is a clinical classification of cerebral infarction and the acute phase of ACI generally refers to 2 weeks after the onset of disease[4]. ACI is a major disease leading to serious damage of central nervous system or death[5]. It was estimated that ACI cause 6.2 million mortalities annually worldwide[6]. ACI is one of the major public health problems that needs to be solved. It has a high recurrence rate, complication rate, disability rate and mortality[7].

Currently, conventional treatment recommended by the clinical practice guideline mainly includes thrombolytics, antithrombotics and anticoagulants[8]. Although these drugs can improve the patient's condition, there are still many problems in the clinic, such as drug side effects and drug resistance.

In traditional Chinese medicine (TCM) theories, cerebral infarction is a "stroke" mainly due to blood stasis syndrome, and the principle of treatment is to promote blood circulation to eliminate blood stasis[9]. TCM has been historically used for stroke treatment[10]. At present, traditional Chinese medicine is widely used as a complementary and replacement therapy for Chinese patients with ACI. Oral Traditional Chinese patent medicine (TCPM) is an important component of TCM, which has several characteristics, including natural medicine, complex composition, and multifunction. Oral TCPMs for stroke treatment are generally a mixture of different plant and animal extracts[11]. Different drugs have anti-inflammatory or antioxidant properties, cause vasodilation, increase cerebral blood flow velocity, inhibit platelet aggregation, protect against reperfusion injury, and increase tissue tolerance to hypoxia[12].

Although the existence of a large number of related studies, including numerous randomized controlled trials (RCTs) and systematic reviews assessed the effect of traditional Chinese medicines for ACI，researchers are more concerned about Chinese medicine injections. Oral TCPM is also an effective measure for the treatment of ACI. Due to the lack of direct comparisons of oral TCPM clinical trials, it is difficult to evaluate the effectiveness of multiple oral TCPMs. Therefore, we plan to compare the efficacy of a variety of oral TCPMs through systematic reviews and network meta-analysis, and rank their benefits relative to each other. We hope that the results of this study will contribute to the management and application of oral TCPMs in ACI treatment.

**2. Methods**

**2.1 Study registration and reporting**

The protocol has been registered on PROSPERO (International Prospective Register of Systematic Reviews) (CRD ). This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P)[13]. Any protocol modifications made during the performing of the review will be recorded in the publication of the final report. The PRISMA Extension Statement to ensure all aspects of methods and findings are reported[14].

**2.2 Eligibility criteria**

**2.2.1** **Study design**

Randomized controlled trials (RCTs) related to oral TCPMs in the treatment of ACI will be included, whether or not blinding. No languages or other restrictions exist.

**2.2.2 Population**

Regardless the race, age, gender and nationality, people who have been clinically diagnosed with acute cerebral infarction will be enrolled[15]. The acute phase of ACI generally refers to 2 weeks after the onset of disease. Thus, this NMA enrolled patients with the course of disease within 2 weeks. In addition, studies involving patients who had a severe cognitive disorder, hemorrhagic tendency, or serious complications, such as atrial fibrillation, severe liver and kidney diseases, severe heart failure, undergoing surgery or other physical therapy are excluded.

**2.2.3 Interventions/Comparators**

The listed oral TCPMs for ACI approved by the China Food and Drug Administration (CFDA) are included. To facilitate data analysis, we define conventional treatment as thrombolytic therapy, anticoagulant therapy and antiplatelet aggregation therapy. In addition, some symptomatic supportive treatments, such as control of blood pressure and adjustment of blood lipids are included as well. Eligible comparisons are as follows: 1) oral TCPM a + conventional treatment versus oral TCPM b + conventional treatment; 2) oral TCPM+ conventional treatment versus conventional treatment. Considering that western medicine is updated quickly and some drugs are withdrawn from the market, studies of oral TCPMs combined with a specific non-common western medicine will be excluded. No limitations on drug dosages or treatment courses exist.

**2.2.4 Outcome measures**

The primary outcome of interest is the markedly effective rate, which depends predominantly on the change of neurological deficit score（National Institutes of Health Stroke Scale or Chinese Stroke Scale）. According to reduction of the neurological deficit score, the efficacy criteria could be divided into six grades: basic recovery, significant progress, progress, no change, deterioration and death. Basic recovery, significant progress, progress, no change, and deterioration are determined when the neurological deficit score decreased from 91% to 100%, from 46% to 90%, from 18% to 45%, by 17%, and increased respectively. The markedly effective rate (%) = (number of basic recovered patients + number of patients with significant progress+ number of patients with progress) / total number \*100%[16].

The secondary outcomes of interest include improvement of neurological impairment (NIHSS or CSS), activities of daily living function（Barthel Index）, adverse drug reactions / adverse drug events (ADRs/ADEs) and number of death within the treatment and during the entire follow-up period.

**2.3 Data sources and search strategy**

Electronic search strategies were developed by an experienced medical information specialist in consultation with our team. The literature search will be conducted in three English databases (Medline, Cochrane Library and Embase) and four Chinese databases (China National Knowledge Infrastructure Database, Wanfang Database, Chongqing VIP information and Sinomed) from inception to July 2018. A separate search for systematic reviews will be performed to compare the list of included studies from existing reviews against those retrieved from the core RCT searches. We will also undertake a targeted gray literature search of ClinicalTrials.gov and the International Clinical Trials Registry Platform search portal to identify in-progress and completed trials.

Search strategy of PubMed is as follows:

#1 Search ("Cerebral Infarction"[Mesh]) OR (("Cerebral Infarctions" or "Infarctions, Cerebral" or "Infarction, Cerebral" or "Cerebral Infarction, Left Hemisphere" or "Left Hemisphere, Infarction, Cerebral" or "Infarction, Left Hemisphere, Cerebral" or "Left Hemisphere, Cerebral Infarction" or "Cerebral, Left Hemisphere, Infarction" or "Infarction, Cerebral, Left Hemisphere" or "Subcortical Infarction" or "Infarction, Subcortical" or "Infarctions, Subcortical" or "Subcortical Infarctions" or "Posterior Choroidal Artery Infarction" or "Anterior Choroidal Artery Infarction" or "Cerebral Infarction, Right Hemisphere" or "Infarction, Right Hemisphere, Cerebral" or "Infarction, Cerebral, Right Hemisphere" or "Cerebral, Right Hemisphere, Infarction" or "Right Hemisphere, Infarction, Cerebral" or "Right Hemisphere, Cerebral Infarction"))

#2 Search ("Medicine, Chinese Traditional"[Mesh]) OR (("Traditional Chinese Medicine" or "Chung I Hsueh" or "Hsueh, Chung I" or "Traditional Medicine, Chinese" or "Zhong Yi Xue" or "Chinese Traditional Medicine" or "Chinese Medicine, Traditional" or " Chinese patent medicine" or "Chinese patent drug" or "proprietary Chinese medicine" or "proprietary Chinese drug"))

#3 #1 AND #2

**2.4 Study selection and data extraction**

Two reviewers independently screen the included literature, extract data, evaluate quality of included studies and cross-check each other according to the established selection criteria. Disagreements will be resolved by discussion or consultation with a third author (XL). First, preliminary screening will be performed by reading the title and abstract of the obtained literature and studies that fails to meet the eligibility criteria will be excluded. Then full text of the articles will be retrieved to further determine whether they are eligible. The screening process will be presented with reference to the PRISMA statement as figure 1.

The data of interest from each included RCTs will be collected using a standard data abstraction form created in Microsoft Excel 2016. The main components of the extracted information are classified as five parts: (1) publication information: first author, publication year, journal and publication country; (2) general characteristics of patients : disease name, sample size, gender, age, eligibility criteria, baseline condition and numbers of dropouts; (3) details of intervention and control therapy: drug names, dosages and treatment; (4) details of outcomes: the markedly effective rate, improvement of neurological impairment, activities of daily living function, adverse drug events and number of death within the treatment and during the entire follow-up period; (5) bias risk assessment information: quality of included studies and research sites.

Records retrieved from each database (n= )

Records obtained from other sources (n= )

Records after duplicates removed (n= )

Records screened (n= )

Records

excluded (n= )

Full-text articles assessed for eligibility (n= )

Records

excluded after full-text articles (n= )

Studies included for qualitative analysis (n= )

Studies included for quantitative analysis (meta-analysis and network meta-analysis) (n= )

Figure 1 Flow chart of searching and screening studies.

**2.5 Assessment of risk of bias in included studies**

The methodological quality of each included studies will be evaluated using The Risk of Bias Tool (ROB) in Cochrane Handbook 5.1.0[17]by two independent reviewers (DDY and RZC). Disagreements will be resolved by discussion with a third reviewer (XL). The judgment of each item is divided into three grades: “high”, “unclear”, and “low”.

The following domains are assessed according to this tool:

(1). Sequence generation (selection bias)

(2). Allocation concealment (selection bias)

(3). Blinding of participants and personnel (performance bias)

(4). Blinding of outcome assessment (detection bias)

(5). Incomplete outcome data (attrition bias)

(6). Selective outcome reporting (reporting bias)

(7). Other potential sources of bias (including for-profit bias)

**2.6 Assessment of the quality of evidence**

The certainty of evidence contributing to network estimates of the primary outcome will be assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework[18]. Based on five key domains (risk of bias, indirectness, inconsistency, imprecision and publication bias), the quality of evidence will be classified in one of four levels—high, moderate, low and very low.

**3** **Statistical analysis**

**3.1 Measures of treatment effect**

For dichotomous outcomes, we will calculate the odds ratio (OR) with a 95% credible interval (the markedly effective rate, ADRs/ADEs). For continuous outcomes, we will calculate the mean difference (MD) with a 95% credible interval (improvement of neurological impairment, activities of daily living function). For multi-arm studies, we will use the data from all reported comparisons.

**3.2 Network geometry**

Qualitative description of network geometry will be provided and accompanied by a network plot[19]. We will obtain a network plot to assess if the trial treatments are connected. Nodes in network geometry represent different interventions and edges represent head to head comparisons. The size of nodes and thickness of edges are associated with sample sizes and numbers of RCTs, respectively.

**3.3 Assessment of heterogeneity**

We will assess clinical and methodological heterogeneity through examination of the characteristics of the included trials. Heterogeneity across trials will be assessed by χ2 test and I2 statistics. If I2<50% and P>0.1, which suggests there is no statistical heterogeneity, then the Mantel–Haenszel fixed eﬀects model will be employed. If I2≥50% and P≤0.1, it manifests that heterogeneity needs to be analyzed. we will explore sources of heterogeneity by subgroup analysis or meta-regression.

**3.4 Assessment of transitivity across treatment comparisons**

We will assess the assumption of transitivity by comparing the distribution of the potential effect modifiers (which include (1) baseline frailty level, (2) age, (3) gender, (4) trials with low risk of bias compared to trials with high risk of bias, across the different pairwise comparisons) to ensure that they are on average balanced. Control groups (conventional treatment) will be assessed for their similarity across treatment comparisons[20].

**3.5 Network meta-analysis**

We will conduct network meta-analyses to compare multiple interventions simultaneously for each of the primary and secondary outcomes. The network meta analyses will be conducted in a Bayesian hierarchical framework by WinBUGS 1.4.3 software and all the result figures will be generated using Stata 13.0 software[21,22]. The Markov Chains Monte Carlo (MCMC) sampler will be used to generate samples. Model convergence will be assessed using Brooks–Gelman–Rubin plots method[23]. To ensure convergence, the previous 5000 samples will be abandoned and described as ‘burn in’, and posterior summaries will be based on 100000 subsequent simulations. Deviance information criterion (DIC) will be used for judging the model fitness by comparing the fixed and random effects model[24]. When the difference between two DIC is less than 3 or 5, it indicates that the two models are consistent. If the difference between two DIC is more than 3 or 5, the lower DIC will be preferred. We will also estimate the ranking probabilities for all treatments at each possible rank for each intervention. Then, we will obtain the treatment hierarchy using the surface under the cumulative ranking (SUCRA) curve and mean ranks. SUCRA value of 100% is assigned to the best treatment and 0% for the worst treatment[25]. We will also try to use the frequentist approach to compare stability if necessary[26].

**4 Assessment of inconsistency**

To check the assumption of consistency in the entire network, we will use the design-by-treatment interaction model[27]. This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results and when there is disagreement between direct and indirect evidence. Using this approach, we will make inferences about the presence of inconsistency from any source in the entire network based on a chi2 test. If the design-by-treatment interaction model shows evidence of inconsistency, we will use the loop-specific approach (if we have a network with at least one closed loop) to detect the paths of the network that are responsible of inconsistency locally[28]. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop. Then, the magnitude of the inconsistency factors and their 95% CIs can be used to make inferences about inconsistency in each loop and its statistical significance.

**5 Subgroup and meta-regression analysis**

If sufficient studies are available, we will perform subgroup analyses using possible sources of inconsistency or heterogeneity between studies such as age, gender, and duration of drug. We will conduct additional meta-regression analyses using random-effects network meta-regression models to examine potential effect moderators such as the mean age of participants, baseline frailty level, and adherence level to treatment.

**6 Sensitivity analysis**

If sufficient studies are available, we will assess the effect of excluding (1) studies with high risk of bias, (2) studies with missing data, and (3) studies with imputed data (to ensure that our imputations do not bias our network meta-analysis results) from the analyses.

**7. Assessment of publication biases**

For each treatment comparison, we will visually assess publication bias and using funnel plots. In the network, we will use a comparison-adjusted funnel plot to assess network-wide publication bias[29]. Funnel plots will be drawn only when the number of studies is ≥10. Funnel plot asymmetry might be due to publication bias but other reasons such as true heterogeneity are also possible.

**8. Discussion**

A variety of Chinese Medicines have been used in treating ACI. Chinese medicine injections（CMIs）and oral TCPMs are the two main categories. There are Several Traditional systematic reviews and NMAs in CMIs. however, only few Traditional systematic reviews in oral TCPMs，no NMAs enabling comparison of the multiplicity of interventions in a unified synthesis and making use of direct and indirect evidence have been performed. NMA enables researchers to address more clinically relevant questions by considering all clinically relevant comparators and incorporating all available direct and indirect evidence. This review incorporating NMA will offer new and informative evaluations of current oral TCPMs for ACI and enhance insights into the relative benefits of the available interventions for managing this difficult condition.

There are several caveats for this study. Firstly, it is well known that in most studies published in Chinese journals, specific methods of randomization have not been reported. Therefore, the randomized study is considered as a randomized controlled trial (RCT) in this study. This approach may reduce methodological rigor by increasing bias.

Secondly, this study is indirect comparative study. The relative efficacy between oral TCPMs will be estimated from a common comparator indirectly using a network meta-analysis. we will use Bayes Statistics to improve the accuracy of the estimate. However, we cannot guarantee that the relative efficacy of the difference between oral TCPMs is a 100% true value. Further direct comparison may still be required to confirm the results.

Thirdly, heterogeneity is an inherent problem in meta analyses because of the diversity in clinical and methodological characteristics. Transitivity is also a very important factor in NMA. Variations between studies would affect the estimate. Therefore, we will focus on identifying the reason for the heterogeneity or degree of transitivity by performing sensitivity analyses and subgroup analyses. By doing this, we will be grouping studies that are more homogenous together to synthesise a more precise summary of effect.

This protocol is designed in accordance with guidelines for NMA protocols and will be conducted and reported according to the PRISMA extension statement for NMA[14].

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