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Protocol

Comparative efficacy of oral traditional Chinese patent medicines for acute cerebral infarction: A protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction: Traditional Chinese patent medicines (TCPMs) are widely used in the treatment of acute cerebral infarction (ACI) in China. Many oral traditional Chinese patent medicines have been reported to be effective for ACI. However, a comparison of randomized controlled trials (RCTs) to directly compare the efficacy of the different oral TCPMs has not been performed. There is no evidence to demonstrate which of oral TCPMs are more effective for clinicians. Therefore, we plan to conduct a systematic review and network meta-analysis (NMA) to compare the efficacy of 10 kinds of oral TCPMs for ACI. The aim is to provide the best currently available evidence base to guide the selection of oral TCPMs.

Methods: A systematic and comprehensive search will be performed from inception to July 2019 in both English and Chinese databases, involving Medline, Cochrane Library, Embase, China National Knowledge Infrastructure Database, Wanfang Database, Chongqing VIP information, and SinoMed. All RCTs related to TCPMs in the treatment of ACI will be included. The primary outcomes are mortality, as well as the the rate of cerebrovascular event including a recurrence event. The secondary outcomes include National Institutes of Health Stroke Scale and adverse drug reactions/adverse drug events. Two reviewers will independently screen the literature by 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 STATA13.0 and WinBUGS1.4.3.

Results: This systematic review and NMA aims to summarize the direct and indirect evidence for 10 kinds of oral TCPMs and to rank these TCPMs. The findings of this NMA will be reported according to PRISMA-NMA statement. The results of the NMA will be submitted to a peer-reviewed journal once completed.

Conclusion: Using NMA, this study will offer new and informative evaluations of current TCPMs for ACI. The results will inform clinicians, provide optimal clinical treatment strategies, bridge the evidence gaps, and identify promising TCPMs for evaluation in future trials.

The protocol has been registered on PROSPERO (International Prospective Register of Systematic Reviews) (CRD42018110307).

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. CI is commonly referred to as a stroke or ischemic stroke which is the most common form of all stroke cases. Oxygen deficiency due to insufficient 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 in China [4]. ACI is a major disease

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leading to serious damage of central nervous system or death [5]. It was estimated that ACI causes 6.2 million mortalities annually worldwide [6]. ACI is one of the major public health problems which has a high recurrence rate, complication rate, disability rate and mortality [7].

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

According to traditional Chinese medicine (TCM) theories, cerebral infarction is defined as apoplexy mainly due to the disorder of blood and *Qi*, and the principle of treatment is to promote blood circulation to eliminate blood stasis [9]. TCM therapies have been historically used for ACI treatment [10]. At present, TCM is widely used as a complementary and alternative therapy for Chinese patients with ACI. Traditional Chinese patent medicines (TCPMs) is an important part of TCM. It has the characteristics of being a natural medicine, and has complex ingredients and multiple functions.. TCPMs for ACI treatment are generally a mixture of different plant and animal extracts [11]. It has been reported that TCPMs exhibit the effects of anti-inflammatory or antioxidant properties, dilating tissue and vessels, increasing cerebral blood flow velocity, inhibiting platelet aggregation, protecting against reperfusion injury, and increasing tissue tolerance to hypoxia [12]. There are three main forms of delivery for TCPMs such as oral, injection and topical (external) application. Oral TCPMs are especially common in the treatment of ACI.

There are a large number of related studies, including numerous randomized controlled trials (RCTs) and systematic reviews assessing the effect of TCPMs for ACI [13,14]. Researchers have been more concerned about Chinese medicine injections, however oral TCPM is also effective for the treatment of ACI. Direct comparisons on efficacy between oral TCPMs from existing clinical trials are based on insufficient or deficient design. Moreover, there are no comprehensive comparisons between different TCPMs. Therefore, we plan to compare the efficacy of 10 common oral TCPMs using 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) (CRD42018110307). This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) [15]. 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 [16].

2.2. Eligibility criteria

The PICOS (Population-Intervention-Comparators-Outcomes-Study design)

framework was adopted as the eligibility criteria for the review as following.

2.2.1. Study design

Only randomized controlled trials (RCTs) related to TCPMs in the treatment of ACI will be included, whether or not blinded. There will be no language or other restrictions.

2.2.2. Population

Cerebrovascular disease is diagnosed according to any well known standards [4,8,17,18]. Regardless of the race, age, gender and nationality, patients who have been clinically diagnosed with acute cerebral infarction will be enrolled. The acute phase of ACI generally refers to 2 weeks after the onset of disease. Thus, this NMA will evaluate studies in which patients had their disease onset within 2 weeks of enrolment into the study. 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 therapies will be excluded.

2.2.3. Interventions/Comparators

The listed oral TCPMs for ACI approved by National Medical Products Administration (NMPA) will be included. In our preliminary analysis of relevant literature, we found that no less than 30 kinds of oral TCPMs were used to treat ACI. Some of these medicines have only one or two published articles. In view of this situation, the top 10 oral TCPMs with the largest number of published articles will eventually be 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 will also be included. In the treatment of thrombolytic therapy, only intravenous thrombolysis will be included. Ultrasound thrombolysis, mechanical thrombectomy and arterial thrombolysis will be excluded. The drugs will mainly include alteplase, tenecteplase, urokinase, and recombinant tissue plasminogen activators. For anticoagulant therapy, drugs will be mainly dabigatran, rivaroxaban, apixaban, edoxaban and thrombin inhibitors. For antiplatelet aggregation therapy, drugs will be mainly aspirin and clopidogrel [8,18]. Eligible comparisons will be as follows: 1) TCPM a + conventional treatment versus TCPM b + conventional treatment; 2) TCPM + conventional treatment versus conventional treatment; 3) TCPM + conventional treatment versus placebo + conventional treatment. Considering that western medicine is updated quickly and some drugs are withdrawn from the market, studies of TCPMs combined with a specific non-common western medicine will be excluded. There will be no limitations on drug dosages or treatment duration.

2.2.4. Outcome measures

The primary outcomes of interest will include: mortality and the rate of cerebrovascular events including any recurrence event. The secondary outcomes of interest will include National Institutes of Health Stroke Scale (NIHSS) and adverse drug reactions/adverse drug events (ADRs/ADEs).

2.3. Data sources and search strategy

Electronic search strategies were developed by an experienced specialist of medical information 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 2019. A separate literature search will be performed to compare the list of included studies from the current systematic reviews against those retrieved from some published systematic reviews . 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. In addition, we will search Google Scholar, CINHAL, Web of Science, and Baidu Scholar to identify trial protocols and other literature; and relevant articles from the reference lists of retrieved review articles will be collected.

Search strategy of Medline 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

#4 Search ("randomized controlled trial "[All Fields]) OR (("RCT" or " randomized " or " randomised "or "randomly"))

#5 #3 AND #4

2.4. Study selection and data extraction

Two reviewers (DDY and RZC) will independently screen the included literature, extract data, evaluate quality of included studies and cross-check with 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. Studies that fail 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-NMA (see Fig. 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 will be classified into 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: number of deaths during treatment, cerebrovascular event including a recurrence event, NIHSS and ADRs/ADEs; (5) risk of bias assessment information: quality of included studies and research sites.

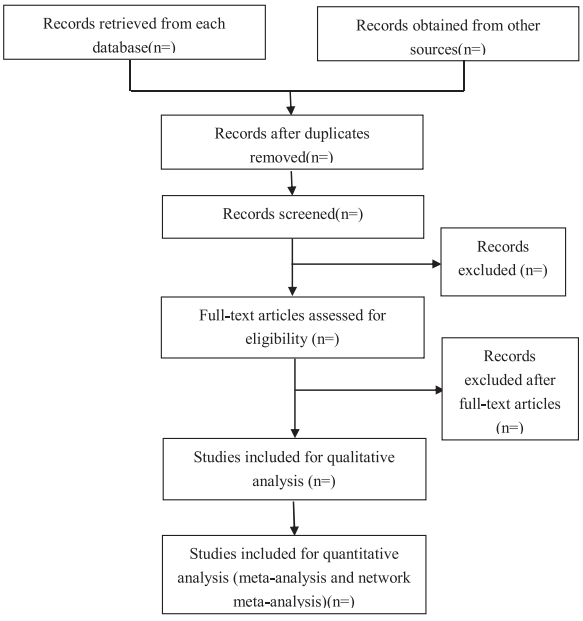

Fig. 1. Flow chart of searching and screening studies.

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 [19] by two independent reviewers (RZC and DDY). 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 (e.g. ethics approval, funding)

2.6. Assessment of the quality of evidence

The certainty of evidence contributing to network estimates of the primary outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework [20] by two reviewers (RZCand DDY). 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. The results of GRADE including evidence profile and summary of finding table will be generated using the GRADE pro software.

3. Statistical analysis

3.1. Measures of treatment effect

For dichotomous outcomes, we will calculate the odds ratio (OR) with a 95% CI (mortality, cerebrovascular event, ADRs/ADEs). For continuous outcomes, we will calculate the mean difference (MD) with a 95% CI (NIHSS). For multi-arm studies, we will use the data from all reported comparisons, and each group was analyzed as a single arm for data analysis.

3.2. Network geometry

Qualitative description of network geometry will be provided and accompanied by a network plot [21]. We will obtain a network plot to assess if the trial treatments are connected. Nodes in network geometry represent diff ;erent 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 $\chi 2$ test and I^2 statistics. If $I^2 < 50\%$ and $P > 0.1$, which suggests there is no statistical heterogeneity, then the Mantel–Haenszel fixed eff ;ects model will be employed. If $I^2 \geq 50\%$ and $P \leq 0.1$, 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: a. baseline frailty level, b. age, c. gender, d. 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 [22].

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 WinBUGS1.4.3 software and all the figures will be generated using Stata13.0 software [23,24]. The Markov Chains Monte Carlo (MCMC) sampler will be used to generate samples. Model convergence will be assessed using Brooks–Gelman–Rubin plots method [25]. To ensure convergence, the previous 5000 samples will be abandoned and described as 'burn in', and posterior summaries will be based on 100,000 subsequent simulations. Deviance information criterion (DIC) will be used for judging the model fitness by comparing the fixed and random effects model [26]. 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 [27]. We will also try to use the frequentist approach to compare stability if necessary [28].

4. Assessment of inconsistency

To check the assumption of consistency in the entire network, we will use the design-by-treatment interaction model [29]. 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 chi-squared 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 for inconsistency locally [30]. 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 [31]. Egger's test and funnel plots will be used to assess the publication bias of the included studies for outcome only when its 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 TCPMs have been used in treating ACI. Chinese medicine injections(CMIs) and oral TCPMs are the two main types of treatments. Comparing with CMIs, oral TCPMs have less ADRs and are easy to use in clinical practice. There are many traditional systematic reviews and NMAs about CMIs [32,33]. So far, few NMAs comparing different oral TCPMs head to head and making use of direct and indirect evidence have been performed to assess their comparative efficacy and acceptability. NMA enables researchers to address more clinically relevant questions by considering all clinically relevant comparators and incorporating all available direct and indirect evidence. Therefore, NMA is needed to determine the comparative effects of these TCPMs. 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 condition.

There may be several limitations to the current NMA. The relative efficacy among oral TCPMs will be estimated from a common comparator indirectly using a network meta-analysis. We will use Bayesian 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. Heterogeneity is an inherent problem for meta-analysis 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 synthesize a more precise summary of effect.

This protocol is designed in accordance with guidelines for NMA protocols. It will be conducted and reported according to the PRISMA extension statement for NMA [16]. On the basis of comparative effectiveness evidence and safety, the current NMA is expected to provide a ranking of these oral TCPMs for patients with ACI. The results of this NMA could help TCM practitioners and patients choose optimal treatment for ACI. Moreover, we also hope that the results of this study may provide clues to further clinical trials and evidence for clinical practice guidelines.

Contributors

XL conceptualized the study, XL and RZC designed the study and organized the team. RZC and XL designed the literature search, developed and refined the study protocol. RZC, JZ and DDY will undertake study selection, data extraction. RZC and HZ will undertake evidence quality with GRADE. RZC will undertake analysis, interpretation and report writing. RZC, NR and XL will draft the publication and all

authors will be asked to comment and revise. All authors have read and approved this manuscript.

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Declaration of Competing Interest

The authors have declared no conflict of interest.

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