**Title**

12 kinds of Chinese medicine injections for acute cerebral infarction: protocol for a

systematic review and network meta-analysis

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**Abstract**

**Introduction**

Chinese medicine injections (CMIs) are widely applied to the treatment of acute cerebral infarction (ACI) in China. However, there are very few head-to-head comparative trials to determine the relative efficacy between different CMIs. It is reported that 20 kinds of CMIs are often used for treating cerebral infarction. Due to the fact that various CMIs are used in clinic, it’s difficult for clinicians to choose the optimal CMIs for patients with ACI. We plan to conduct a network meta-analysis (NMA) to compare the efficacy of 12 kinds of different CMIs, including direct and indirect comparisons between CMIs, aiming to provide the best currently available evidence base to guide the choice about CMIs treatment for patients with ACI.

**Methods**

A systematic and comprehensive search will be performed from inception to August 2018 in both English and Chinese databases, involving PubMed ,Cochrane Library, Embase, China National Knowledge Infrastructure Database (CNKI), Wanfang Database, Chongqing VIP information (CQVIP), and SinoMed. Randomized controlled trial (RCT) related to CMIs in the treatment of ACI will be included. Quality of included literature will be assessed 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 13.1.

**Results**

This systematic review and NMA is to summarise the direct and indirect evidence for 12 kinds of different CMIs to manage ACI, and to rank these CMIs for CMIs treatment of patients with ACI. The findings of this NMA will be reported according to PRISMA-NMA statement.

**Conclusion**

This study will offer helpful and informative evaluations of current CMIs for ACI. The results will inform clinicians, provide optimal CMI, establish evidence gaps, and identify promising CMIs for evaluation in future trials.

**Keywords**

Chinese medicine injections, acute cerebral infarction, network meta-analysis, protocol

**Protocol registration number:**CRD42018109188

**1.Introduction**

Cerebral infarction refers to the formation of an area of necrosis in the cerebrum caused by an insufficiency of arterial or venous blood flow according to the definition of Mesh Terms of Pubmed(https://www.ncbi.nlm.nih.gov/pubmed). Acute cerebral infarction is a clinical classification of cerebral infarction and the acute phase of ACI generally refers to 2 weeks after the onset of disease [1]. As one of the major public health problems and the third costliest health condition in developed countries, ACI has a high disability, mortality and recurrence rate and usually leads to serious damage of central nervous system[2].There is a study shows that the brain loses 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated nerve fibres every minute in a typical acute ischemic stroke[3]. According to the top 10 causes of death provided by World Health Organisation(WHO), ischaemic heart disease and stroke are the world’s biggest killers, and have remained the leading causes of death globally in the last 15 years (http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death). In China, cerebrovascular disease is the second large cause of death( http://www.docin.com/p-6587220.html). In addition, ACI has the characteristic of sudden onset and rapid progress. For above reasons, early detection and rapid intervention are advised in terms of ACI. In other words, for ACI , quick selection of appropriate treatments among the therapies available is of crucial importance.

Currently, conventional treatment recommended by the clinical practice guideline mainly includes thrombolytics, antithrombotics and anticoagulants[4]. Although these medications offer certain help for patients with ACI, side effects and drug resistance have been seen with their use in practice. Thus, CMIs are increasingly widely used as a complementary therapeutic approach for patients with ACI in China due to its remarkable effectiveness, rapid action, and high bioavailability [5]. According to Traditional Chinese Medicine (TCM) theory, cerebral infarction pertains to “apoplexy,” primarily due to blood stasis syndrome, and the therapeutic principle is promoting blood circulation to remove blood stasis [6]. At present, it is reported that 20 class for invigorating blood circulation CMIs are often used in the treatment of cerebral infarction [7]. Both of CMIs above can dilate blood vessels, improve blood circulation and increase blood flow to the brain arteries. Since various CMIs are used in clinical, it poses a challenge for clinicians to choose the optimal CMIs for patients with ACI.

Despite the existence of several relevant research, including numerous randomised controlled trials (RCTs) and systematic reviews assessed the effect of various CMIs for ACI, there remains uncertainty regarding the comparative efficacy of these CMIs cause most of them were designed in comparison with conventional western medicine. Thus, we plan to use the method of systematic review and network meta-analysis to compare the efficacy of 12 different CMIs and rank their benefits relative to each other. We do hope that the findings of this study would be facilitating the management and application of CMIs in the treatment of ACI.

**2. Methods**

**2.1 Study registration and reporting**

The study protocol has been registered on PROSPERO (International Prospective Register of Systematic Reviews) (CRD42018109188). This protocol is developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) [8]. 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[9].

**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**

Regardless of whether or not blinding is used, randomized controlled trials (RCTs) related to CMIs in the treatment of ACI will be included for analysis. RCTs from the same population (duplicate studies) and not reporting effect estimates or with insufficient information to compute effect estimates will be excluded. No language or other restrictions were applied.

**2.2.2 Population**

Cerebrovascular disease was diagnosed according to the standards revised by the Fourth National Conference on Cerebrovascular Disease by the Chinese Medical Association in 1995[10].The acute phase of ACI generally refers to 2 weeks after the onset of disease. Patients who are not in the acute phase of the disease are excluded. In addition, studies involving patients who had a severe cognitive disorder, hemorrhagic tendency, or serious complications, such as

atrial fibrillation, severe heart failure, severe liver and kidney diseases, undergoing surgery or other physical therapy are not taken into consideration as well. There are no limits on age, gender, race or nationality.

**2.2.3 Interventions/Comparators**

We have completed a preliminary analysis of the relevant literature on the treatment of acute cerebral infarction with CMIs, and found that 12 kinds of CMIs are commonly used to treat acute cerebral infarction. All of these 12 kinds of CMIs can dilate blood vessels, improve blood circulation and increase blood flow to the brain arteries. The basic information of the 12 kinds of CMIs is listed in Table 1. To facilitate data analysis, we define conventional treatment as thrombolytic therapy, anticoagulant therapy and antiplatelet aggregation therapy[5]. 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) CMI a + conventional treatment versus CMI b + conventional treatment; 2) CMI + conventional treatment versus conventional treatment. Considering that western medicine is updated quickly and some drugs are withdrawn from the market, studies of CMIs combined with a specific non-common western medicine will be excluded. No limitations on drug dosages or treatment courses exist.

**2.4 Outcome measures**

Reviewing clinical trials of ACI published in international journals, we found that outcomes reported more are imaging surrogate markers, initial stroke severity, functional outcome, and short-term mortality in human AIS [11]. However, in Chinese studies, the markedly effective rate which depends predominantly on the change of neurological deficit score is commonly used[10]. Thus we adopted the following standard of outcomes. The primary outcome of interest includes mortality and the rate of cerebrovascular event including recurrence event. The secondary outcome of interest includes National Institutes of Health Stroke Scale (NIHSS) and adverse drug events. Any RCT with outcome measures other than outcome of interest is excluded.

**2.3 Data sources and search strategy**

The literature search will be conducted in three English databases (PubMed, Cochrane Library and Embase) and four Chinese databases (China National Knowledge Infrastructure Database, Wanfang Database, Chongqing VIP information and Sinomed) from inception to August 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 Clinical Trials.gov and the International Clinical Trials Registry Platform search portal to identify in-progress and completed trials. In addition, we searched 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 were collected.

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" or "Chinese heral injection" or "Chinese medicine injection"))

#3 Search ("Injections"[Mesh]) OR (("Injection" or "Injectables" or "Injectable"))

#4 #2 AND #3

#5 Search (("Shuxuening injecton " or " Xiangdan injection " or " Danshen injection " or " Mailuoning injection " or " Shuxuetong injection " or " Kudiezi injection " or " Xuesaitong injection " or " Xueshuantong injection " or " Danhong injection " or " Xingnaojing injection " or " Dengzhanhuasu injection " or " Dengzhanxixin injection "))

#6 #4 OR #5

#7 #1 AND #6

**2.4 Study selection and data extraction**

Records downloaded from seven databases will be managed by NoteExpress software. Two researchers 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 included. The screening process will be presented with reference to the PRISMA statement as figure 1.Microsoft Excel 2010 will be used to extract data and collect relevant information. The main components of the extracted information are classified as five parts: a. publication information: first author, publication year, journal and publication country ; b. general characteristics of patients : disease name, sample size, gender, age, eligibility criteria, baseline condition and numbers of dropouts; c. details of intervention and control therapy: drug names, dosages and treatment; d. 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. e. bias risk assessment information: quality of included studies and research sites.

**2.5 Quality assessment**

The Risk of Bias Tool (ROB) in Cochrane Handbook 5.1.0 [12] is used to assess the methodological quality of included studies by two independent reviewer (DDY and RZC). Disagreements will be resolved by discussion with a third reviewer (XL).Seven items are included in the Cochrane collaboration’s risk of bias tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Judgment of each item is divided into three levels: low risk of bias, high risk of bias and unclear risk of bias.

In addition, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework will be used to assess the certainty of evidence contributing to network estimates of the primary outcome[13]. 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.

**2.6 Statistical analysis**

**2.6.1 Pairwise meta-analysis**

The conventional pairwise meta-analysis will be performed by using Stata 13.1 software. The pooled odds ratios (ORs) with 95% confidence interval(95%CI) are calculated for dichotomous data(mortality and the rate of cerebrovascular event including recurrence event) and mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval(95%CI) are calculated for continuous data(NIHSS). The χ2 test and I2 test will be conducted to detect the potential heterogeneity across the included studies. If I2 <50% and P>0.1, it suggests that heterogeneity is not important and the Mantel–Haenszel fixed model will be employed for meta-analysis. If I2≥50% and P≤0.1, it manifests that heterogeneity needs to be analyzed. Heterogeneity is divided into three types—statistical heterogeneity, clinical heterogeneity and methodological heterogeneity[12]. Random-effects model will be used for statistical heterogeneity. Subgroup analysis or meta-regression will be conducted if clinical and methodological heterogeneity exists. In addition, if the source of heterogeneity is unknown, we will give up synthetic analysis and adopt descriptive analysis instead. Sensitivity analysis will be employed for the robustness of results of the included studies. Begg’s or Egger’s funnel plot method will be performed to distinguish publication bias, if at least 10 studies are available[14,15].

**2.6.2 Network meta-analysis**

The network meta-analysis will be conducted using the network command in STATA[16-19].To rank probabilities of treatments, surface under the cumulative ranking (SUCRA) will be used to summarize the probability values. A SUCRA value of 100% is assigned to the best treatment and 0% for the worst treatment[20].We will employ the inconsistency factor (IF) to evaluate heterogeneity among the included studies if a closed loop exists. If the 95% CIs of the IF values are truncated at zero, it indicates that direct and indirect evidences are in agreement [20]. A comparison-adjusted funnel plot will be conducted to assess the presence of small-study effect[21]. All analyses will be performed using Stata sofware version 13.1.

**2.7Patient and Public Involvement**

This part is not covered in this study.

**3.** **Discussion**

During the process of retrieving literature, two NMAs about Chinese herbal injections(CHIs) for cerebral infarction were detected[22,23].Chinese herbal injections (CHIs) are prepared by extracting and purifying effective substances from herbs (or decoction pieces) using modern scientific techniques and methods. Chinese medicine injections (CMIs) have a wider range of sources, for it can not only be made from plants or herbs, but also from animals. To better demonstrate the merits of the NMA, we make a comparison between the current NMA and the other 2 NMAs. The details of the comparison can be seen in Table 2.

From the comparison shown in table 2, the current NMA will have a updated literature searching and focus on ACI treating by two different kinds of interventions. With GRADE evaluation, the certainty of evidence in the main results of the current NMA will be incorporated to highlight the most robust findings for further use in making a clinical judgment.

Despite availability of some randomized controlled trials (RCTs) and systematic reviews about CMIs treatment for ACI, it is still a challenge for clinicians to choose the optimal CMIs when it comes to the management of ACI since head-to-head comparisons between CMIs for ACI is insufficient. In the process of retrieving literature, we found two NMAs concerning to CHIs for cerebral infarction[22,23].However, the literature retrieval time for both studies is until June of 2016. In addition, both of the two studies included chemicals containing traditional Chinese medicine ingredients, such as salviae miltiorrhizae,ligustrazine hydrochloride injection, ginkgo leaf extract and dipyridamole injection and et.al. Injections mentioned above are not part of CHIs. And none of studies performed the GRADE to report the quality of the evidence. For the above reason, we will update the search strategy and make some adjustments based on the above two studies to perform a comprehensive comparative appraisal of the efficacy of CMIs used in the management of ACI by using the approach of NMA. We are confident that our network meta-analysis results have the potential to influence a large proportion of the population since China has the second largest population in the world. And our results will make full use of potential CMIs treatment options for ACI and strengthen evidence base by analysing both direct and indirect evidence.

Several points need to be paid attention for this study. Firstly, it is common that randomization fails to be correctly used in most research published in Chinese journals. Therefore, research referred to random is regarded as randomized controlled trial(RCT) in this study. This kind of practice may cause bias. Secondly, this study is not a direct head to head comparative study. The relative efficacy between CMIs will be estimated from a common comparator indirectly using a network meta-analysis. The presence of heterogeneity is an inherent problem in meta-analysis because of the diversity in clinical and methodological characteristics, and variations between studies would affect the estimate. Thirdly, as an emerging statistical method, some limitations remain in the use of NMA.NMA depends on three conditions—network connectivity, similarity of trials with respect to study design and populations, and network consistency. It is imperative that these conditions be assessed and appropriate adjustments be taken when they are not met, such as meta-regression. Thus, we cannot guarantee that the relative efficacy of the difference between CMIs is a 100% true value. Moreover, further head to head comparison may still be required to confirm the results.

As this study is secondary research based on literature, ethics approval and patient consent is not necessary .This protocol is designed in accordance with guidelines for NMA protocols [8] and will be conducted and reported according to the PRISMA extension statement for NMA [9]. The results of this NMA will be submitted to a peer-reviewed journal once completed.

**4.Conclusion**

This study will offer helpful and informative evaluations of current CMIs for ACI. The results will inform clinicians, provide optimal CMI, establish evidence gaps, and identify promising CMIs for evaluation in future trials.

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# Conflict of Interests   The authors have declared no conflict of interest.

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Records obtained from other sources(n=)

Records retrieved from each database(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

Table 1 Basic information on 12 kinds of CMIs

|  |  |  |  |
| --- | --- | --- | --- |
| Number | Generic name | Chemical composition | Botanical/Animal name |
| 1 | Shuxuening injection | Ginkgo biloba leaves are extracted from a sterile aqueous solution.;excipients are sorbitol, 95% ethanol, methyl sulfide | Ginkgo biloba extract |
| 2 | Xiangdan injection | salvia, fragrant, excipient is polysorbate 80 | salvia miltiorrhiza bunge,dalbergia odorifera |
| 3 | Shuxuetong injection | hirudo, pheretima | hirudo nipponica whitman, pheretima aspergillum |
| 4 | Kudiezi injection | ixeris sonchifolia | ixeris sonchifolia |
| 5 | Xuesaitong injection | panax notoginsenosides, excipient is sodium chloride | panax notoginseng extract |
| 6 | Xueshuantong injection | panax notoginsenosides, excipient is sodium chloride and sodium citrate | panax notoginseng extract |
| 7 | Dengzhanhuasu injection | breviscapine, excipient is ethylenediamine tetraacetic acid disodium | erigeron breviscapus |
| 8 | Danhong injection | salvia miltiorrhiza, safflower, water for injection | salvia miltiorrhiza bunge, carthamus tinctorius |
| 9 | Dengzhanxixin injection | wild baicalin (C21H18O12) and total caffeate,excipients: sodium chloride | erigeron breviscapus extract |
| 10 | Danshen injection | salvia miltiorrhiza | salvia miltiorrhiza bunge |
| 11 | Mailuoning injection | honeysuckle, achyranthes, dendrobium, scrophularia and excipient is polysorbate 80 | lonicera japonica, achyranthes bidentata blume, dendrobium nobile, scrophularia ningpoensis hemsl |
| 12 | Xingnaojing injection | artificial musk, gardenia, turmeric, borneol and accessories for poly yamanashi ester 80, sodium chloride | moschus,gardenia jasminoides ellis, curcumakwangsiensis |

Table 2 Comparison of basic information between this NMA and other 2 studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Study | Database | Retrieval time | Disease | Intervention VS control | Outcome | GRADE evaluation |
| Liu S2018[19] | PubMed,  Cochrane Library,  Embase,  CNKI,  Wanfang Database,  CBM. | inception to June 2016 | acute cerebral  infarction(ACI) | 1.CHIs①+AADN regimen VS AADN regimen  2. CHI a+AADN regimen VS CHI b+AADN regimen | 1.the markedly effective rate  2.improvement of  neurological impairment  3.activities of daily living function  4.death from all causes within the treatment and during the entire follow-up period | no |
| Xiang Y2017[20] | PubMed,  Cochrane Library,  Embase,  CNKI,  Wanfang Database,  CBM,  Chongqing VIP. | Inception to June 2016 | Stroke | 1.CMIs②+conventional treatment VS conventional treatment  2. CMIs +conventional treatment VS placebo  3.CMIs+ conventional treatment VS other CMIs  4.CMIs+ conventional treatment VS western medicine | 1. the markedly effective rate  2. neurological deficit score  3. daily activity ability score  4. adverse event incidence  5.mortality  6.cerebral hematoma changes  7.safety evaluation of adverse/reactive events  8.disability rate  9.quality of life. | no |
| the current NMA | PubMed,  Cochrane Library,  Embase,  CNKI,  Wanfang Database,  Sinomed ,  Chongqing VIP. | inception to July 2018 | acute cerebral  infarction(ACI) | 1.CMI③ a + conventional treatment VS CMI b + conventional treatment  2.CMI + conventional treatment VS conventional treatment. | 1. mortality  2. the rate of cerebrovascular event including recurrence event  3.improvement of neurological impairment  4.activities of daily living function  5.adverse drug events  6. the markedly effective rate | yes |

PS: 1.AADN inclide: aspirin + anticoagulants + dehydrant + neuroprotectant.

2. CHIs① include: Ligustrazine injection ,Xueshuantong injection, Xuesaitong injection, Shuxuening injection, Dengzhanxixin injection, Dengzhanhuasu injection, Shuxuetong injection, Danhong injection, Fufangdanshen injection, Ginkgo Leaf Extract and Dipyridamole Injection, Mailuoning injection, Honghuahuangsesu injection, Shenxiong glucose injection, salviae miltiorrhizae ,ligustrazine hydrochloride injection, Danshen injection.

3. CMIs② include: Fufangdanshen injection, Danhong injection, Ginkgo Leaf Extract and Dipyridamole Injection, Dengzhanxixin injection, Dengzhanhuasu injection, Shuxuetong injection, salviae miltiorrhizae ,ligustrazine hydrochloride injection, Shuxuening injection, Mailuoning injection,Gegensu injection, Kudiezi injection, Danshen injection,Danshen polyphenolate injection, Xueshuantong injection, Xuesaitong injection,Xinding injection, Extract of Ginkgo Biloba Leaves Injection.

4. CMI③ include: Shuxuening injection, Xiangdan injection,Shuxuetong injection, Kudiezi injection,Xuesaitong injection, Xueshuantong injection, Dengzhanhuasu injection, Danhong injection, Dengzhanxixin injection,Danshen injection, Mailuoning injection,Xingnaojing injection

5. conventional treatment include: thrombolytic therapy, anticoagulant therapy, antiplatelet aggregation therapy and some other symptomatic supportive treatments, such as control of blood pressure and adjustment of blood lipids.