Meta-Analysis and Systematic Review

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Comparative study of xuesaitong injection and compound *salvia miltiorrhizae* injection in the treatment of acute cerebral infarction: a meta-analysis

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Abstract

Objective: This study was conducted to systematically evaluate the clinical effectiveness of xuesaitong injection (XST) and compound *salvia miltiorrhizae* injection (CSM) in the treatment of acute cerebral infarction (ACI).

Methods: We searched several databases for randomized controlled trials (RCTs) using XST and CSM for the treatment of ACI. Two researchers independently selected the RCTs and extracted information. The quality of included RCTs was evaluated, and then data were analyzed using RevMan5.3 and STATA 12.0 software.

Results: Twenty-three RCTs that enrolled 2101 participants were included in this study. A meta-analysis showed that XST with routine Western medicine (WM) can achieve a better effect than CSM with WM for the total effective rate (*RR* = 1.22, 95%*CI*: 1.18–1.27). In addition, XST combined with WM could improve neurological impairment (*MD* = −4.65, 95%*CI*: −7.85 – −1.44) and hemorheological parameters. XST decreased the whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, and plasma fibrinogen.

Conclusions: For treating ACI, XST combined with WM was more effective than CSM with WM. However, more evidence is needed to support the safety of XST and CSM.

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Xuesaitong injection, compound *salvia miltiorrhizae* injection, acute cerebral infarction, systematic review, meta-analysis, randomized controlled trial

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Introduction

Acute cerebral infarction (ACI), also known as acute ischemic stroke, is defined as infarction of the brain, spinal cord, or retina and it represents the majority (70%) of strokes globally. The main ACI subtypes are atherothrombotic, cardioembolic, and lacunar infarcts. ACI manifests as ischemia and hypoxia of the brain, neurological impairment (NI) and other symptoms.[1,2] ACI is associated with increasing morbidity and mortality, accounting for 60% to 80% of all strokes, which are harmful to physical and mental health.[3,4] ACI is also the primary cause of adult disability in China and it has become a major event for public security in low- and middle-income countries.[5,6] Although routine Western medicine (WM) has achieved a certain effect, there are still some problems, such as time windows and treatment costs that impact its effectiveness.[7] As recognition of traditional Chinese Medicine (TCM) increases, combination of TCM and WM to treat diseases is another method and solve these problems. In the TCM theory, ACI belongs to the category of "stroke" with a common symptom of blood stasis.[8] Therefore, promoting blood circulation to remove blood stasis could be used to treat ACI.

Xuesaitong injection (XST) and compound *salvia miltiorrhizae* injection (CSM), which are well-known Chinese patent medicines, are commonly administered to promote blood circulation and remove blood stasis, and they are useful for clinical treatment of ACI. Both medicines were authorized by the China Food and Drug Administration. XST is composed of notoginseng total saponins with the effects of promoting blood circulation, removing blood stasis, and freeing network vessels. The notoginseng total saponins that made up XST were sourced from *Panax notoginseng (Burk.) F.H.Chen*. Quality control was reported, and chemical analysis of the material was included. XST can, for example, dilate blood vessels, inhibit platelet aggregation, and reduce plasma viscosity. Moreover, saponins, the active ingredients in XST, have a significant antithrombotic effect.[9] Therefore, saponins are frequently used to treat blood stasis syndrome.[10] CSM is an injection of extracted ingredients from the root or rhizome of *Salvia miltiorrhiza* Bunge and lignum of *Dalbergia odorifera* T.C.Chen. Each milliliter of CSM is equivalent to 1 g of *Salvia miltiorrhiza* Bunge and 1 g of *Dalbergia odorifera* T.C.Chen. CSM was processed in accordance with the China Food and Drug Administration standards. The authenticity of CSM was verified. Quality control was reported, and a chemical analysis of the material was included. Tanshinone, phenols, and volatile oil were the main components in CSM. CSM has functions in, for example, expanding coronary arteries, lowering blood fat, and lowering blood pressure. CSM is widely used to treat cerebral infarction, coronary heart disease, and angina pectoris.[11]

Both XST and CSM can be used to treat ACI, and both have been shown to be effective interventions for ACI.[12–14] Therefore, it is necessary to verify which one is better using systematic reviews of clinical randomized controlled trials (RCTs). To provide evidence-based information for clinical practice, we performed a meta-analysis to

evaluate the effectiveness of XST and CSM in the treatment of ACI by extensively collecting existing clinical research data.

Methods

The conduct of this study was based on the PRISMA 2009 Checklist.[15] The design idea and concise workflow are presented in Figure 1.

Inclusion and exclusion criteria

Studies that were included in this meta-analysis met the following criteria: (1) RCTs using XST and CSM to treat ACI regardless of blinding and language; (2) All patients were diagnosed with ACI and conformed to "various types of cerebrovascular disease diagnosis points" revised by the Fourth National Conference on cerebrovascular diseases of the China National Medical Association,[16] which was confirmed by head CT or MRI, regardless of age, sex, race, and disease severity; (3) All patients were given WM, which included lowering intracranial pressure, antiplatelet aggregation, and brain protection. The commonly used drugs include calcium antagonists, mannitol, cell two-choline phosphate, and aspirin. The control group was treated by WM and CSM, and the experimental group was given WM and XST. Dosage and course of treatment were not limited. Other complications would be given corresponding treatment. The intervention was XST + WM versus CSM + WM; and (4) Clinical effectiveness was judged by the clinical neurologic impairment score.[17]

The primary outcome was the total effective rate (TER), which was calculated as follows:

TER = (the number of patients cured + the number of patients with significant progress + the number of patients with progress)/total number of patients × 100%.

When the NI score was reduced by 91% to 100%, patients were considered to be cured. Patients with NI scores reduced by 46% to 90% were considered to have significant progress. When NI scores were reduced by 18% to 45%, patients were regarded as making progress. The patients were regarded as invalid when NI scores were reduced by 0% to 17%. The patients were regarded as deteriorating when the NI score was < 0. The secondary outcomes were NI, hemorheological parameters (HP), which included whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, and plasma fibrinogen, and adverse drug reactions (ADRs)/adverse drug events (ADEs).

Exclusion criteria were as follows: articles in which diagnostic criteria or efficacy evaluation criteria were not clear or

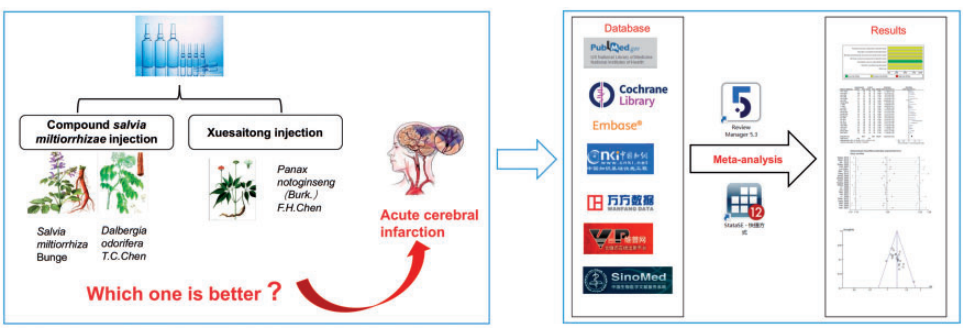

Figure 1. Graphical abstract.

did not meet the inclusion criteria; the randomization method was wrong, such as random grouping according to admission order; patients were given traditional Chinese herbs, surgery, and acupuncture; and articles without access to full text.

Literature search

We retrieved RCTs that compared XST with CSM to treat ACI in the China National Knowledge Infrastructure Database (CNKI), Chinese Scientific Journals Database (VIP), Wanfang Database, PubMed, Cochrane Library, SinoMed, and Embase up to October 10, 2018. Additionally, the references of related literature were searched by hand. An example of the retrieval strategy using PubMed:

#1: "Brain infarction" [Mesh]
#2: "Cerebral infarction" [Title/Abstract] OR "Stroke" [Title/Abstract]) OR "Brain embolism" [Title/Abstract] OR "Ischaemic stroke" [Title/Abstract]) OR "Cerebrovascular disorders" [Title/Abstract]
#3: #1 OR #2
#4: "Compound danshen injection" [Title/Abstract]) OR "Composite *salvia miltiorrhiza* injection" [Title/Abstract]) OR "Fufang Danshen injection" [Title/Abstract]) OR "Fufang Danshen zhusheye" [Title/Abstract]
#5: "Xuesaitong injection" [Title/Abstract]) OR "Xuesaitong zhusheye" [Title/Abstract]
#6: #3 AND #4 AND #5

Data extraction and quality assessment

Two researchers (XD and DZ) read the titles and abstracts independently to screen out the irrelevant articles, reviews, and pharmacological experiments. If the article was an RCT, the full text was read to determine whether it met the inclusion criteria. Data were extracted from the included studies. Disagreements were resolved by group consensus or by obtaining another opinion (JW). The main contents of the extracted information included basic information on the studies, such as first author's name and year of publication; basic characteristics of the study, including the number of experimental groups and control groups, sex, average age, intervention, and other details; outcomes and measurement data; and the key factors of bias risk assessment. All studies were managed using Note Express software (Wuhan University Library, Wuhan, China).

Two researchers (XD and SL) evaluated the quality of the included RCTs using the Cochrane Risk of Bisk Assessment Tool.[18] The evaluation items included sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias); and other sources of bias (other bias). Each aspect had three levels: "High", "Unclear", and "Low". "High" means that the outcomes were likely to be influenced by the information. "Low" means that the outcomes were less impacted by the information. "Unclear" means that there was insufficient information to assess bias.

Ethics approval was not necessary because the data were from electronic databases, and the patients' primary information was not involved.

Statistical analysis

The data were analyzed using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK) and STATA 12.0 software (StataCorp LP, College Station, TX, USA). Dichotomous outcomes were measured by the relative risk (*RR*), continuous variables were measured

by the mean difference (MD), and both were calculated with 95% confidence intervals ($95\%CIs$). The χ^2 test and inconsistency index (I^2) were used to assess heterogeneity among the studies. When $P > 0.1$ and $I^2 < 50\%$,[19] the fixed-effects model was used to analyze the data. Otherwise, the random-effects model was used. A funnel plot was used to analyze the potential publication bias. STATA 12.0 software (StataCorp LP) was used to analyze the sensitivity to test the stability of the results.

Results

Search results

Electronic databases and references were searched, and 265 studies were initially retrieved. After duplicates were removed, 174 studies remained. Excluded studies (n = 66) included reviews (n = 5), animal experiments (n = 8), and unrelated articles (n = 53). We read the full text of the remaining 108 studies. Additional studies were then excluded, including articles in which the intervention (n = 68), diagnostic criteria (n = 4), or efficacy evaluation criteria (n = 4) did not meet the inclusion criteria; incorrect randomization method (n = 7); case reports (n = 1); and no access to full text (n = 1). Finally, there were 23 studies that were included in the analysis (Figure 2). All included studies were published in China from 2004 to 2012.

Characteristics of the included studies

Twenty-three studies with 2101 patients were included. Among them, 1074 patients were in the experimental group and 1027 were in the control group. Male patients accounted for 64.01% (1345/2101) of all patients. Most patients were middle-aged and elderly with an average age of 61.07 years. The control group and the experimental group were treated with the same WM. The experimental group included XST and the control group included CSM. The basic characteristics of the included studies are summarized in Table 1.

Quality assessment

A Cochrane risk assessment table was completed to evaluate the quality of the included RCTs. The 23 studies only mentioned "random", and the selection biases were unclear. The performance bias and detection bias were unclear because none of the studies mentioned a blinding method. There was no incomplete outcome data among the included RCTs. Thus, attrition bias was deemed to be a low risk. Because all of the studies were not registered and did not include access to the scheme design and whether there was any unreported information, the reporting bias was unclear. Other bias was unclear because there was insufficient information to assess whether there was an important risk of bias. Therefore, the quality of included studies was general (Figure 3).

Total effective rate

Twenty-three studies reported the TER of the ACI.[20–42] The heterogeneity was small ($P = 0.44$, $I^2 = 1\% < 50\%$), so the fixed-effects model was used. The meta-analysis results showed that the TER of XST combined with WM in the treatment of ACI was better than CSM combined with WM. The TER increased by 22%, and there were significant differences between the two groups ($RR = 1.22$, $95\%CI$: 1.18–1.27, $P < 0.00001$, Figure 4).

Neurological impairment

NI was reported in seven studies.[26,28,33,34,40–42] The seven studies had high statistical heterogeneity ($P < 0.00001$, $I^2 = 95\% > 50\%$), so the data were analyzed using the random-effects model. The results showed that WM plus

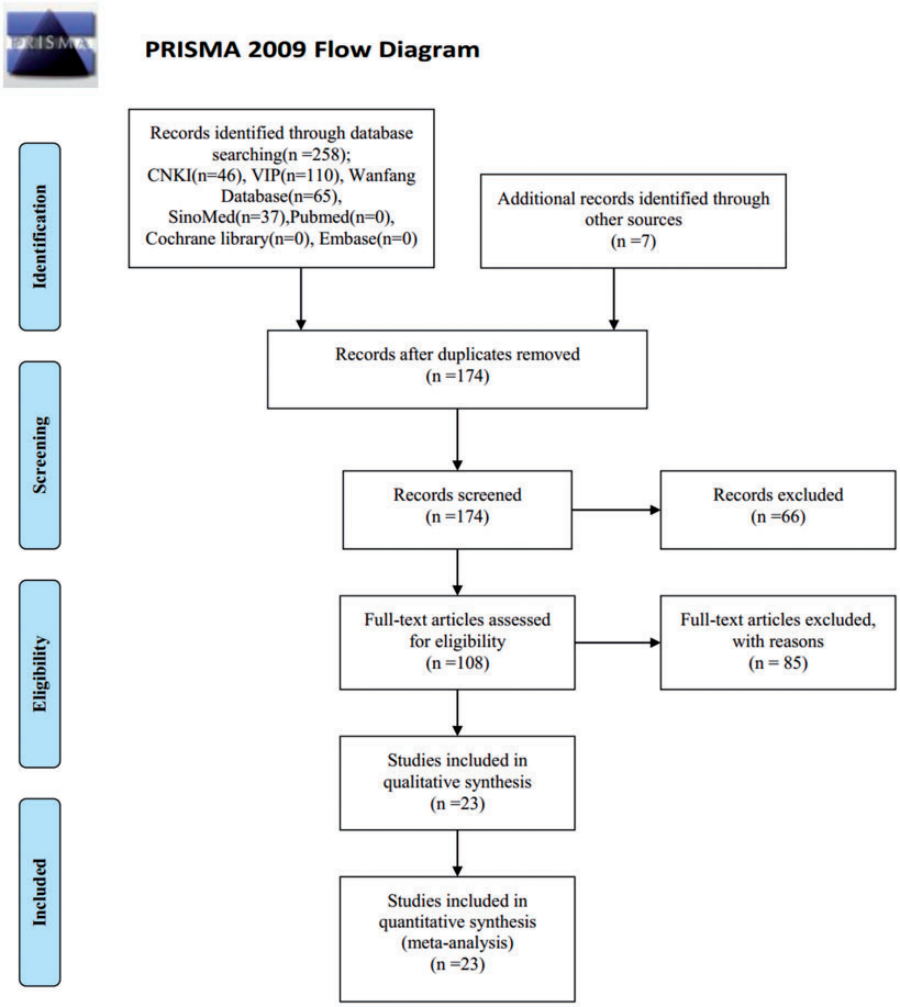

Figure 2. Flow chart of literature search.
Note: n, number; CNKI, China National Knowledge Infrastructure Database; VIP, Chinese Scientific Journals Database.

XST better improved the patients' degree of NI compared with WM plus CSM. The difference between groups was statistically significant ($MD = -4.65$, $95\%CI$: -7.85–-1.44, $P = 0.005$, Figure 5).

Hemorheological parameters

The hemorheological parameters in this study comprised whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, and plasma fibrinogen. There were five studies[20,28,33,36,39] that compared whole blood high shear viscosity, five studies[20,28,33,36,39] that compared whole blood low shear viscosity, six studies[20,23,32,33,36,39] that compared plasma viscosity, and six studies[20,23,32,33,36,39] that compared plasma fibrinogen. As shown in Table 2, XST assisted WM in significantly reducing whole blood high shear viscosity, whole blood low shear

Table 1. Basic characteristics of included studies.

Study	N, E/C	Sex, M/F	Age	Therapy of EG	Therapy of CG	Course	Outcome
Wang 2010[20]	40/40	51/29	E: 61 C: 60.5	XST 20 mL + WM	CSM 20 mL + WM	15 d	TER, HP
Zhou 2010[21]	40/40	55/25	E: 60.4 C: 61.2	XST 400 mg + WM	CSM 250 mL + WM	14 d	TER
Xie 2010[22]	30/30	38/22	E: 61 C: 60	XST 400 mg + WM	CSM 10 mL + WM	15 d	TER
Wang 2005[23]	51/51	59/43	E: 67 C: 66.5	XST 10 mL + WM	CSM 20 mL + WM	14 d	TER, HP, ADR/ADE
Han 2007[24]	64/32	57/39	E: 66.3 ± 9.5 C: 67.8 ± 10.6	XST 500 mg + WM	CSM 20 mL + WM	14 d	TER
Yao 2007[25]	50/50	64/36	E: 65.2 C: 64.3	XST 500 mg + WM	CSM 16 mL + WM	15 d	TER, ADR/ADE
Luo 2004[26]	32/32	34/30	E: 59.2 C: 59.8	XST 500 mg + WM	CSM 30 mL + WM	14 d	TER, NI
Ren 2012[27]	30/30	32/28	39–77 59.5 ± 3.13	XST 400 mg + WM	CSM 20 mL + WM	14 d	TER
Yang 2012[28]	65/65	87/43	48-75 63.27 ± 5.01	XST 400 mg + WM	CSM 250 mL + WM	14 d	TER, NI, HP
Gong 2006[29]	42/40	55/27	E: 44–78 C: 51–76	XST 400 mg + WM	CSM 20 mL + WM	14 d	TER, ADR/ADE
Zheng 2005[30]	65/62	92/35	E: 51 C: 59	XST 500 mg + WM	CSM 10 mL + WM	14 d	TER, ADR/ADE
Chen 2009[31]	34/34	38/30	E: 62.5 C: 63	XST 800 mg + WM	CSM 30 mL + WM	15 d	TER, ADR/ADE
Huang 2009[32]	45/45	52/38	E: 61.32 ± 4.35 C: 61.08 ± 4.27	XST 300–400 mg + WM	CSM 16 mL + WM	14 d	TER, ADR/ADE
Wang 2008[33]	60/55	63/52	43–85 56.5 ± 17.63	XST 400 mg + WM	CSM 20 mL + WM	15 d	TER, NI, HP
Li 2008[34]	30/30	35/25	E: 57.1 C: 57.0	XST 20 mL + WM	CSM 20 mL + WM	15 d	TER, NI, ADR/ADE
Wu 2008[35]	46/46	58/34	E: 60.2 C: 62.6	XST 400 mg + WM	CSM 25 mL + WM	14 d	TER, ADR/ADE
Gao 2002[36]	45/45	71/19	E: 66.22 C: 65.21	XST 400 mg + WM	CSM 20 mL + WM	15 d	TER, HP, ADR/ADE
Xie 2007[37]	50/50	74/26	E: 50–68 C: 52–69	XST 400 mg + WM	CSM 20 mL + WM	14 d	TER, ADR/ADE
Li 2009[38]	32/31	41/22	E: 66.5 C: 64.7	XST 500 mg + WM	CSM 20 mL + WM	14 d	TER
Chen 2012[39]	78/74	88/64	E: 48.8 C: 49.1	XST 400 mg + WM	CSM 30 mL + WM	30 d	TER, HP, ADR/ADE
Yang 2005[40]	48/48	57/39	E: 59.9 ± 10.9 C: 62.5 ± 8.5	XST 500 mg + WM	CSM 20 mL + WM	10–20 d	TER, NI
Gan 2009[41]	47/47	58/36	E: 63 C: 60	XST 400 mg + WM	CSM 250 mL + WM	14 d	TER, NI
Yan 2005[42]	50/50	86/14	E: 61.6 C: 60.2	XST 400 mg + WM	CSM 20 mL + WM	15 d	TER, NI

WM means routine western medicine, including lowering intracranial pressure, anti-platelet aggregation, and brain protection. The commonly used WM drugs were calcium antagonists, mannitol, cell two-choline phosphate, and aspirin.

N, number; EG, experimental group; C, control group; M, male; F, female; d, days; XST, xuesaitong injection; CSM, compound *salvia miltiorrhizae* injection; WM, Western medicine; ADRs, adverse drug reactions; ADEs, adverse drug events; TER, total effective rate; NI, neurologic impairment; HP, hemorheological parameters.

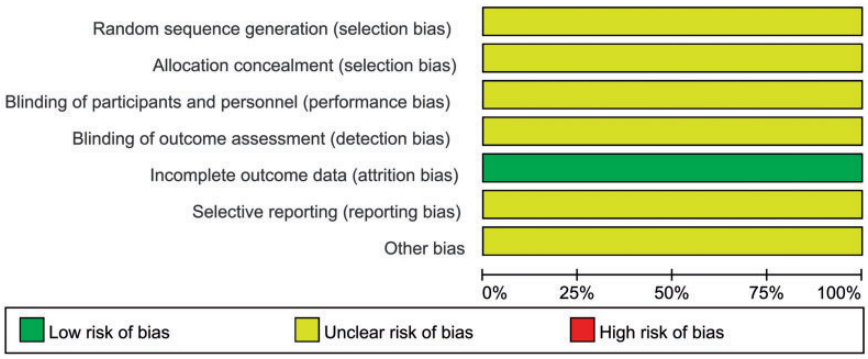

Figure 3. Risk of bias summary.

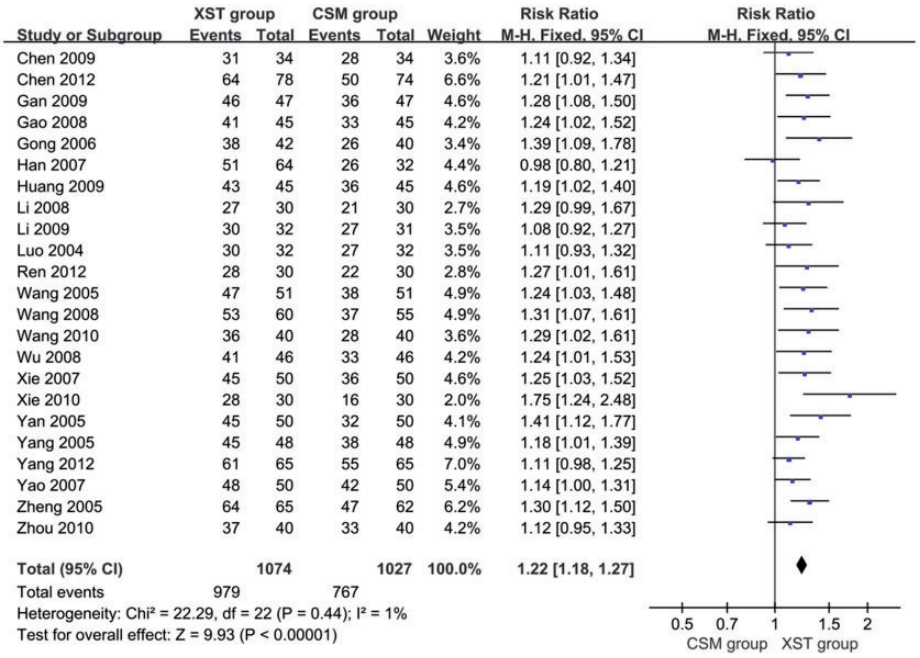

Figure 4. Meta-analysis for comparison of total effective rate of ACI between XST + WM and CSM + WM.

viscosity, plasma viscosity, and plasma fibrinogen between the groups. XST was significantly better compared with CSM-assisted WM.

Sensitivity analysis

Sensitivity analysis of TER was performed by excluding studies one by one. We excluded a study each time and analyzed the remaining studies to determine the stability of the results. The results showed that there was no qualitative change in the combined effect. Therefore, the results of this study had good stability (Figure 6).

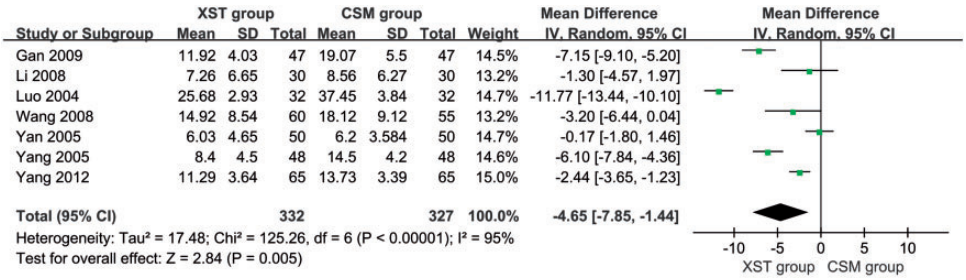

Figure 5. Meta-analysis for comparison of neurologic impairment between XST + WM and CSM + WM.

Table 2. Meta-analysis results of the comparison of hemorheological parameters between XST + WM and CSM + WM.

Outcomes	Number of studies	Effect model	*MD [95%CI]*	*P*
Whole blood high shear viscosity	5[20,28,33,36,39]	Random	−1.04 [−1.56, −0.51]	0.0001
Whole blood low shear viscosity	5[20,28,33,36,39]	Random	−1.66 [−2.39, −0.93]	<0.00001
Plasma viscosity	6[20,23,32,33,36,39]	Random	−0.38 [−0.60, −0.16]	0.0006
Plasma fibrinogen	6[20,23,32,33,36,39]	Random	−0.93 [−1.34, −0.53]	<0.00001

XST, xuesaitong injection; CSM, compound *salvia miltiorrhizae* injection; WM, Western medicine; 95%CIs, 95% confidence intervals; MD, mean difference.

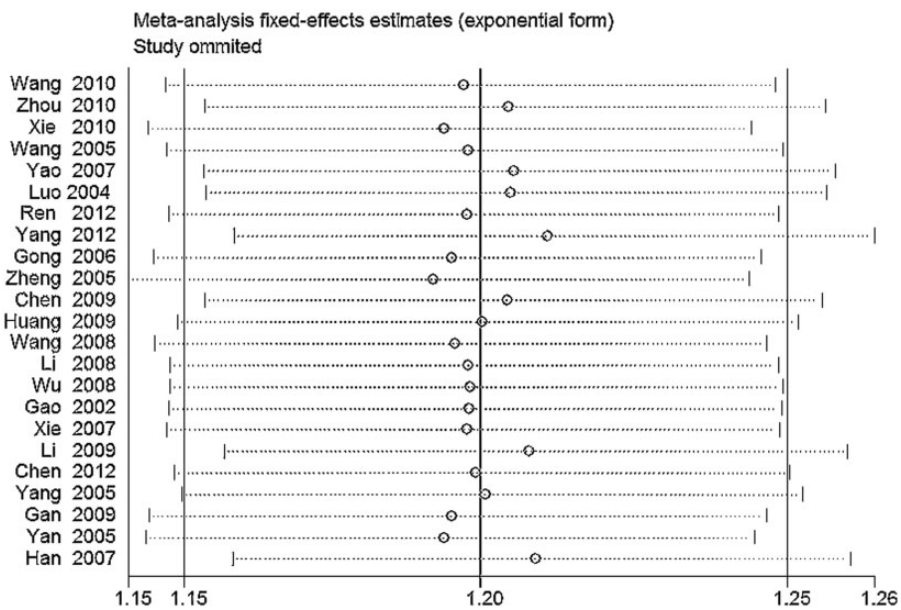

Figure 6. Sensitivity analysis of total effective rate.

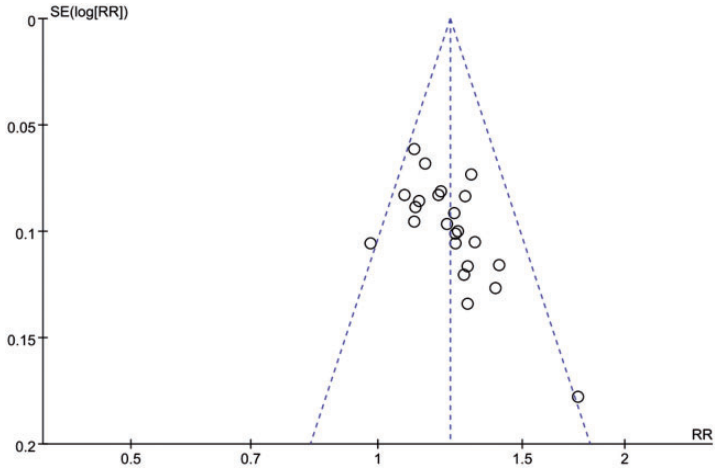

Figure 7. Funnel plot to evaluate the publication bias of TER.

Publication bias evaluation

An inverted funnel plot was used to evaluate the publication bias of TER. Figure 7 shows that the points in the plot were asymmetrical based on the midline. Therefore, there was a potential publication bias.

Safety evaluation

Among the 23 studies, six RCTs[30,31,34–36,39] did not describe obvious ADRs while six RCTs[23,25,29,32,33,37] described ADRs. In the XST group, there were four cases of mild skin rash, four cases of dizziness, heart palpitations, and blood pressure reduction, two cases of dry throat, two cases of facial flushing with mild dizziness, one case of mild skin itching, and one case of chills. In the CSM group, there was mild skin rash (four cases), mild skin itching (two cases), fever (two cases), and vomiting (one case). Neither group had adverse reactions such as liver and kidney damage. The other studies did not describe ADRs/ADEs. Therefore, the safety of XST and CSM in the treatment of patients with ACI requires further research.

Discussion

From the clinical observation data in the included studies, the results of our study showed that, compared with WM plus CSM, XST combined with WM may have some effects on treating ACI. XST can achieve a better effect in TER, NI, whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, and plasma fibrinogen. Moreover, the criteria for "acute phase" in our study was the course within 14 days or the patients were clearly defined as having ACI.

In our study, 12 RCTs mentioned ADRs. Twenty-three cases of ADRs were reported, 14 cases from the XST group and nine cases from the CSM group. The main adverse reaction of XST was skin allergy, including skin rash and skin itching, which was consistent with current research.[43] This reaction may result from the combination of the plasma protein *in vivo* and the half-antigen in the injection. Moreover, an injection drip that is too fast will cause a high blood concentration within a certain period. The main component of XST is the saponins of *panax notoginseng*. If the dosage is too large, there will

be ADRs, such as palpitation and arrhythmia.[44] Therefore, when XST is dripped too fast, the patients would feel heart palpitations. CSM's main adverse event was also skin allergy, which is the same as with XST. Because the composition of Chinese medicine is complex, there are many impurities in the Chinese herb injection. The impurities can easily form macromolecular antigens with plasma proteins.[11] Thus, the patient should be carefully monitored for ADRs/ADEs, especially skin allergic reactions, while using XST and CSM. Excessive doses and a fast fluid drip should also be avoided.

An article on XST compared with CSM for the treatment of ACI has been published.[45] The article was a paper based on a Master's thesis from Chengdu University of Traditional Chinese Medicine, which was published in 2014. The article's methodological quality was not high, and its retrieval strategy was not sufficiently comprehensive. There were 20 RCTs included in this article. Among them, the interventions in four RCTs were XST compared with danshen injection. WM in the experimental group in one RCT was not the same as that in the control group. Compared with the previous study, our study has the following advantages: 1) in our study, eight articles that met the inclusion criteria were included; 2) our study developed a more stringent inclusion and exclusion criteria. We only included the RCTs of XST with WM compared with CSM plus the same WM to compare the clinical efficacy of XST with CSM in the treatment of ACI; 3) the retrieval strategy and key words were more comprehensive; 4) our study analyzed the NI and HP of patients, which can comprehensively reflect their situation; and 5) our study conducted sensitivity analysis of the TER, which confirmed the stability of the results.

However, our study also had several limitations. First, the quality of the included RCTs was general. All of the RCTs only mentioned the word "random", and random sequence generation, allocation concealment, and blinding were all not mentioned, which greatly reduced the strength of the evidence in our results. Thus, more RCTs with large samples, multi-center recruitment, double-blind design, and a strict randomization method are required to evaluate the efficacy more accurately. Additionally, a new and larger multi-center comparative study comparing XST plus WM to CSM plus WM and to isolated WM is needed to verify the conclusions of this study. Second, all included RCTs were published Chinese articles from electronic databases. Thus, our study lacked the support of other languages, unpublished studies, and grey articles, which may cause a selection bias. Additionally, in our study, all patients were Asian, and we do not know whether the conclusions are generalizable to other races. Third, ACI has a high recurrence rate, but all included RCTs did not mention continuing observations and follow-up, which makes the evaluation of efficacy and safety inadequate. It should be emphasized that prognosis of stroke recurrence is different in ischemic stroke subtypes. For example, cognitive impairment was a frequent finding in patients with multiple lacunar infarction recurrences,[46] and in cardioembolic stroke, early recurrent embolization is the most important predictor for in-hospital mortality.[47] Moreover, further study of additional adverse reactions reports is required to establish its safety profile.

Conclusions

Overall, our meta-analysis showed that XST combined with WM could achieve a better effect in TER, NI, whole blood high shear viscosity, whole blood low shear viscosity, plasma viscosity, and plasma fibrinogen than CSM combined with WM when they were used to treat

ACI. However, because the quality of the included studies is general, multi-center RCTs with larger sample sizes are needed to verify the conclusions of this study.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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