Medicine®

Salvianolate injection in the treatment of acute cerebral infarction

A systematic review and a meta-analysis

Yang NanZhu, MD[a,b], Ju AiChun, PhD[c], Li Xin, MD, PhD[d,*], Yun XiangHua, MD[a]

Abstract

To evaluate the effectiveness and safety of Salvianolate injection (SI) in the treatment of acute cerebral infarction (ACI).

We electronically searched databases including PubMed, The Cochrane Library, EMBASE, Chinese Biomedical Literature Database, Chinese National Knowledge Infrastructure, and WanFang Data to collect randomized controlled trials (RCTs) focused on SI treating ACI up to August 2017. Two reviewers independently screened literatures, extracted data, and assessed the risk of bias of included studies. Then, meta-analysis was performed using RevMan 5.3 software.

A total of 39 RCTs involving 4516 patients were included. The results of meta-analysis showed that compared with the Western medicine (WM) therapies group [experimental group (EG)], the total effective rate of SI + WM [control group (CG)] was higher (relative risk = 1.29, 95% CI: 1.24–1.35, $P < .00001$) in 21 RCTs; SI could improve movement function evaluation scores, including National Institute of Health Stroke Scale, Barthel Index, activities of daily living ($P < .00001$). There was no significant difference in modified Rankin Scale scores between the 2 groups ($P = .008$) EG was better than CG in improving Montreal Cognitive Assessment scores ($P = .001$) and Mini-Mental State Examination scores ($P < .00001$). SI could improved not only the hemorheology indexes, including plasma viscosity, whole blood high-shear viscosity, whole blood low-shear viscosity, fibrinogen ($P < .00001$), but also high-sensitivity C-reactive protein and C-reactive protein. EG could achieve a better effect on improving the neural deficit scores ($P < .00001$). There was no significant difference about adverse drug reactions/adverse drug events between the EG and CG ($P = .73$).

Salvianolate can promote recovery of the motor and cognitive function of patients with ACI. However, due to the limited quality and quantity of included studies, more high-quality studies are needed to verify the above conclusion.

Abbreviations: ACI = acute cerebral infarction, ADEs = adverse drug events, ADL = activities of daily living, ADR = adverse drug reaction, BI = Barthel Index, CG = control group, CRP = C-reactive protein, EG = experimental group, FIB = fibrinogen, hs-CRP = high-sensitivity C-reactive protein, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, mRS = Distribution of the modified Rankin Scale, NDS = neural function defect scale, NHISS = National Institute of Health Stroke Scale, PV = plasma viscosity, RCT = randomized controlled trial, RR = relative risk, SI = Salvianolate injection, TCM = traditional Chinese medicine, WBHSV = whole blood high-shear viscosity, WBLSV = whole blood low-shear viscosity, WM = Western Medicine.

Keywords: acute cerebral infarction, cognition disorders, movement disorders, Salvianolate, systematic review

1. Introduction

Stroke, with its high morbidity and mortality, remains an important public health problem. It has been proven that Traditional Chinese Medicine (TCM) is an effective complementary intervention for stroke, especially in the treatment of acute cerebral infarction (ACI). In TCM theories, ACI refers to "apoplexy," majorly due to blood stasis syndrome. Therefore, the therapeutic principle is promoting blood circulation to remove blood stasis of TCM.[1,2] Recently, Salvianolate injection (SI) combined with Western medicine (WM) is widely used in the treatment of ACI. SI is made of the extraction of Danshen (Radix Salviae miltiorrhizae). Salvianolic acid B in Salvia miltiorrhizae biological activity, one of the highest extract has been confirmed in the experiments in vivo and in vitro has neuroprotective and anti-inflammatory effects.[3] Many systematic reviews regarding SI in the treatment of cerebral infarction, both showing the superiority of SI to control group (CG) in improving the activities daily living function, but none of the articles mentioned any improvement in cognitive ability.[1,2,4] In this systematic review, we chose the published, qualified, and well homogeneity clinical studies regarding the combined use of SI for treating ACI to make meta-analysis. In our study, we evaluated the change of activities daily living function and cognitive function, the change of hemorheology indexes, and efficacy and safety of SI.

2. Methods

2.1. Inclusion criteria

2.1.1. Study type. Clinical randomized controlled trials (RCTs) using SI as the adjuvant treatment of ACI, regardless of blinding.

2.1.2. Participants. The diagnostic criterion in terms of the changes of the fourth Chinese National cerebrovascular disease conference in 1995 formulated the cerebrovascular disease

diagnosis Standard, or the World Health Organization criteria.[5] Diagnoses were validated using computed tomography or magnetic resonance imaging scanning. The course of disease was in 72 hours or shorter, and all participants were experiencing the first onset of ACI. Trials that included patients of any age or sex with ischemic stroke were eligible.

2.1.3. Interventions. The main interventions include SI combined with WM versus WM treatments alone. WM treatments included thrombolytic therapy, platelet aggregation, cerebral protection agents, and so on. The drugs could be statins, dextran-40, mannitol, aspirin, citicoline, sodium ozagrel, and so on. No limitation on the doses, treatment courses, and drug manufacturers.

2.1.4. Outcomes. We used different outcomes to evaluate the activities daily living function and cognitive function of the patients with ACI. The primary outcomes were of this meta-analysis were Activities of daily living function evaluation computed by National Institute of Health Stroke Scale (NHISS), Barthel Index (BI), activities of daily living (ADL), and distribution of the modified Rankin Scale (mRS), Cognitive function evaluation computed by Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE).

The secondary outcomes of this meta-analysis were hemorheology indexes, including plasma viscosity (PV), content of fibrinogen (FIB), and C-reactive protein (CRP)/high-sensitivity C-reactive protein (hs-CRP), and adverse drug reactions (ADRs)/adverse drug events (ADEs).

2.1.5. Efficacy criteria. Neural function defect scale (NDS) changes after treatment or nerve function defect improved efficiently. Total clinical effective rate (%) = (number of recovered patients + number of patients with significant progress + number of patients with progress)/total number × 100%.[6] Recovered was determined when the neurological deficit score decreased from 91% to 100%. Significant progress was determined when the neurological deficit score decreased by between 46% and 90%. Progress was determined when the neurological deficit score decreased by between 18% and 45%. No change or worsen was determined when the functional deficit score decreased by <17%.

2.2. Exclusion criteria

(1) Data were incorrect, incomplete, or not available. (2) Patients with severe cardiopathy, such as atrial fibrillation and severe heart failure. (3) Patients with serious complications, such as cognitive disorder, hemorrhagic tendency, or severe liver and kidney diseases. (4) Patients undergoing surgery and acupuncture. (5) There was no other Chinese medicine, acupuncture, surgery performed, or other physical therapy in any experimental group (EG) or trials group. (6) *Salvia miltiorrhiza* drugs allergies.

2.3. Searching strategies

A general search of published literature was conducted in the electronic databases from inception to July 31, 2017. Studies were first identified for inclusion by examining the title and abstract of each record. We then sought the full text version of suitable articles before applying the inclusion criteria. Two independent investigators (YN, YX) performed a systematic literature search in including PubMed, the Cochrane Center Controlled Trials Register, EMBASE, Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, and

Wanfang Database without any restrictions to languages and calendar date. In the Chinese databases, the terms "Dan shen duo fen suan yan Zhu she ye" and "Zhu she yong Dan Shen Duo Fen suan yan," and "Dan shen duo fen suan yan Zhu she ji" were used as subject terms for the initial search, and then "Ji Xing Que Xue Xing Cu Zhong" or "Que Xue Xing Zhong Feng" or "Que Xue Xing Nao Xue Guan Bing" or "Nao Geng Si" or "Nao Geng Se" was used to search again among above results. In English databases, the Mesh terms of "Salvianolate injection," and "Dan Shen Duo Fen suan yan injection" were used as subject words for the initial search, and "acute ischemic stroke," and "acute cerebral infarction" were used for further retrieval. Effort was made to include all available studies, including contact with authors. We also searched references lists of retrieved articles, conference abstracts, and trials registries for additional studies.

The search strategy in PubMed is given below.

(1). "Brain Infarction" [Mesh]
(2). "Acute Cerebral Infarction" [Title/Abstract] OR "Acute Stoke" [Title/Abstract] OR "Acute Brain Embolism" [Title/Abstract] OR "'Acute Ischemic Stroke" [Title/Abstract]
(3). (1) OR (2)
(4). "Salvianolate" [Title/Abstract] OR "Salvia miltiorrhiza" [Title/Abstract] OR "Dan Shen Duo Fen Suan Yan" [Title/Abstract]
(5). (3) AND (4) AND (5)

2.4. Data synthesis and quality assessment

Ethical approval was unnecessary for this meta-analysis, because our meta-analysis was the procedure that just gathered the experimental data in each RCT without any leak of patient information. All the meta-analyses data used Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) to synthesize and analyze.[7] For outcomes, this meta-analysis chose relative risk (RR) to evaluate dichotomous outcomes, whereas using standardized mean difference ± mean difference to assess continuous variables. Each outcome numerical value was presented with 95% confidence intervals as well. Heterogeneity between RCTs was analyzed by chi-square test and estimated by I^2. Meta-analyses were calculated by random-effects model. In addition, We used the Cochrane Risk of bias summary tool to conduct a quality evaluation on the included RCTs, whose items contains sequence generation (selection bias), allocation concealment (selection bias), blinding of patients 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.[8] The RCTs were rated into "high," "unclear," or "low." "High" referred to incorrect random methods, no allocation concealment, or no blinding. "Unclear" referred to no description in the text with which to assess bias. "Low" referred to correct random methods, appropriate blinding without being violated through implementation, and detailed description in the RCT.

3. Results

3.1. Searching result

A total of 176 articles were retrieved from the databases listed above. After reading the full text, by removing case studies and articles that did not meet the inclusion criteria, 39 RCTs were included (Table 1). All RCTs were conducted in China

Table 1

Study characteristics.

Study ID	Sex (M/F)	N (EG/CG)	Age (EG/CG)	Intervention EG	CG	Durationg (days)	Outcomes	Allocation sequence
Ji et al[9]	83/52	74/71	60.76±7.93/61.04±8.0	SI (300 mg/d)+WM (1)	WM	14 d	①②	II
Zhang et al[10]	67/53	60/60	65.3±9.34/64.92±9.68	SI (200 mg/d)+WM (3)	WM	14 d	⑦⑨⑩⑪	II
Mi[11]	172/128	150/150	63.5±11.6/64.1±10.8	SI (200 mg/d)+WM (3)	WM	14 d	⑧⑪	II
Ma and Pan[12]	92/51	78/65	38~73	SI (200 mg/d)+WM (3)	WM	Unclear	⑦⑧	I
Chen[13]	86/64	75/75	60.8±10.1/61.6±9.7	SI (200 mg/d)+WM (2)	WM	14 d	⑧⑩	II
Li and Zhou[14]	56/50	56/50	69.22±7.25/70.15±8.16	SI (200 mg/d)+WM (3)	WM	14 d	⑦⑪	II
Sun[15]	39/35	38/36	62±13	SI (130 mg/d)+WM (2)	WM	14 d	①②⑪	II
Zhang et al[16]	42/28	35/35	37~79,57.7±2.12	SI (200 mg/d)+WM (2)	WM	14 d	①②④⑤⑥⑫	II
He et al[17]	44/32	35/32	59.61±4.18	SI (200 mg/d)+WM (1)	WM	14 d	①②⑧⑩	II
Liu and Jiang[18]	41/29	35/35	61.3±3.8/60.7±3.9	SI (200 mg/d)+WM (3)	WM	14 d	①⑧⑫	I
Pei and Zhou[19]	55/29	42/42	65.9±9.2/65.1±9.7	SI (200 mg/d)+WM (3)	WM	14 d	⑦⑨	II
Peng and Cjen[20]	114/86	102/98	54~76/55~78	SI (200 mg/d)+WM (3)	WM	7 d	①③⑧	I
Wang[21]	45/35	39/41	70±5.0	SI (200 mg/d)+WM (3)	WM	14 d	①③⑫	III
Wang and Zhao[22]	58/42	50/50	61.5±3.7/62.7±3	SI (200 mg/d)+WM (1)	WM	14 d	①③	II
Wang[23]	49/31	40/40	65.2±3.4/64.8±3.2	SI (130 mg/d)+WM (2)	WM	14 d	①②	II
Zhao[24]	69/51	65/65	58.22±18	SI (200 mg/d)+WM (3)	WM	14 d	⑧⑫	IV
Fang[25]	66/84	75/75	57.83±7.79/56.91±7.62	SI (130 mg/d)+WM (2)	WM	14 d	⑨⑪⑫	I
Pei and Zhou[26]	34/26	30/30	59.4±7.43/58.83±7.32	SI (200 mg/d)+WM (3)	WM	14 d	①	II
Zhang and Chen[27]	56/40	32/32 32/32	65.42±11.25	SI (200 mg/d)+WM (1) SI (100 mg/d)+WM (1)	WM	14 d	③⑦⑧⑫	Unclear
Hao[28]	52/42	47/47	44.72±10.66/58.92±13.9	SI (200 mg/d)+WM (3)	WM	14 d	②⑩⑪	Unclear
Hou and Wang[29]	114/86	100/100	66.28±10.25/68.23±11.72	SI (100 mg/d)+WM (2)	WM	14 d	①③⑧	Unclear
Tao et al[30]	56/42	49/49	66.5±6.3	SI (200 mg/d)+WM (3)	WM	14 d	①②⑨⑪	Unclear
Xu and Wang[31]	Unclear	53/53	Unclear	SI (130 mg/d)+WM (2)	WM	14 d	①②④	Unclear
Zhang[32]	43/37	40/40	61.55±6.89/62.11±7.12	SI (200 mg/d)+WM (1)	WM	14 d	①③⑩⑪	Unclear
Huang[33]	47/41	44/44	56.9±4.3/57.4±4.2	SI (100 mg/d)+WM (1)	WM	14 d	①②④⑤⑥	Unclear
Kang et al[34]	40/36	43/43	57.1±5.1/58.7±4.5	SI (? mg/d)+WM (1)	WM	7 d	①②④⑤⑥⑫	Unclear
Shan[35]	81/67	74/74	61.38±7.28/60.76±7.13	SI (200 mg/d)+WM (3)	WM	7 d×3	①③	Unclear
Wang et al[36]	48/33	41/40	60.34±2.15/60.15	SI (200 mg/d)+WM (3)	WM	14 d	①⑧⑨⑩⑫	Unclear
Zhu[37]	59/41	50/50	64.5±2.0/65±2.5	SI (200 mg/d)+WM (1)	WM	14 d	①⑧⑪⑫	Unclear
Wang et al[38]	47/39	43/43	62.5±7.3	SI (200 mg/d)+WM (3)	WM	14 d×2	⑤⑥	Unclear
Zhou[39]	19/19	19/19	64.5±9.3/65.7±8.2	SI (200 mg/d)+WM (3)	WM	14 d	⑧⑪	Unclear
Hao and An[40]	31/29	30/30	60.3±15.3/61.92±17.92	SI (200 mg/d)+WM (3)	WM	14 d	⑦	Unclear
Gao[41]	97/33	65/65	61.03±4.06/60.41±4.28	SI (200 mg/d)+WM (3)	WM	14 d	⑧⑨	Unclear
Shi et al[42]	unclear	44/44	58.9±3.4/63.1±3.2	SI (200 mg/d)+WM (3)	WM	14 d	⑧⑨⑫	Unclear
An[43]	45/35	40/40	65.31±9.35/65. 32±9.34	SI (100 mg/d)+WM (3)	WM	14 d	⑪	Unclear
Zhou[44]	106/76	91/91	61.24±3.15	SI (200 mg/d)+WM (3)	WM	14 d	⑧⑪	Unclear
Chang[45]	148/66	107/107	44±12/46±14	SI (200 mg/d)+WM (3)	WM	35 d×2	⑧	Unclear
Zhao[46]	95/65	80/80	58±7.7	SI (250 mg/d)+WM (3)	WM	15 d	⑦⑧	Unclear
Du[47]	88/52	70/70	47-78	SI (200 mg/d)+WM (1)	WM	15 d	⑦	Unclear

CG = control group, EG = experiment group, F = Females, M = Males, WM = western medicine therapies.

Allocation sequence: I = Therapies, II = random figure table, III = random queue insertion; IV = random draw envelope principle.

Salvianolate injection in intervention: (1) = Shang Hai Green Valley Pharmaceutical Company, (2) = Tian Jin Tasly Pride Pharmaceutical Company, (3) = unkonwn.

Outcomes: ① = National Institute of Health Stroke Scale, ② = BI, ③ = ADL, ④ = mRS, ⑤ = MoCA, ⑥ = MMSE, ⑦ = NDS, ⑧ = Total clinical effective rate, ⑨ = Plasma viscosity, ⑩ = FIB, ⑪ = CRP/hs-CRP, ⑫ = ADRs/ADEs.

and published in full (Fig. 1; flow chart of literature search). The 39 RCTs included 4516 cases, among which 2273 cases were in the EGs, whereas 2243 in the CGs. In the all of the RCTs, the maximum sample size was 300 cases, whereas the minimum sample size was 38 cases. All patients in the RCTs were diagnosed as having ACI by the diagnostic standard. As for intervention, the EG was SI and WM and the CG was WM. WM included aspirin, defibrase, and so on. The daily dose of SI ranged from 100 to 300 mg. The duration of treatments ranged from 7 to 70 days.

3.2. Quality of the included studies

We used the Cochrane Risk of bias summary Tool to conduct a quality evaluation on the included RCTs (Fig. 2; risk of bias summary). The results showed that 18 RCTs[9–26] described the method to generate the allocation sequence, among which 12 RCTs [9–11,13–17,19,22,23,26] used the random figure table, 1 RCT[21] used the random queue insertion, and 1 RCT[24] used the random draw envelope principle. Four RTCs[12,18,20,25] were divided into groups by different therapies. And the remaining RCTs were randomly divided into 2 groups. All of RCTs did not provide information on blinding. Actually the overall quality of the included RCTs was generally not high.

3.3. Outcomes

Some of the RCTs were divided into subgroups caused by the differences in the course. The results of each subgroup were analyzed as follows.
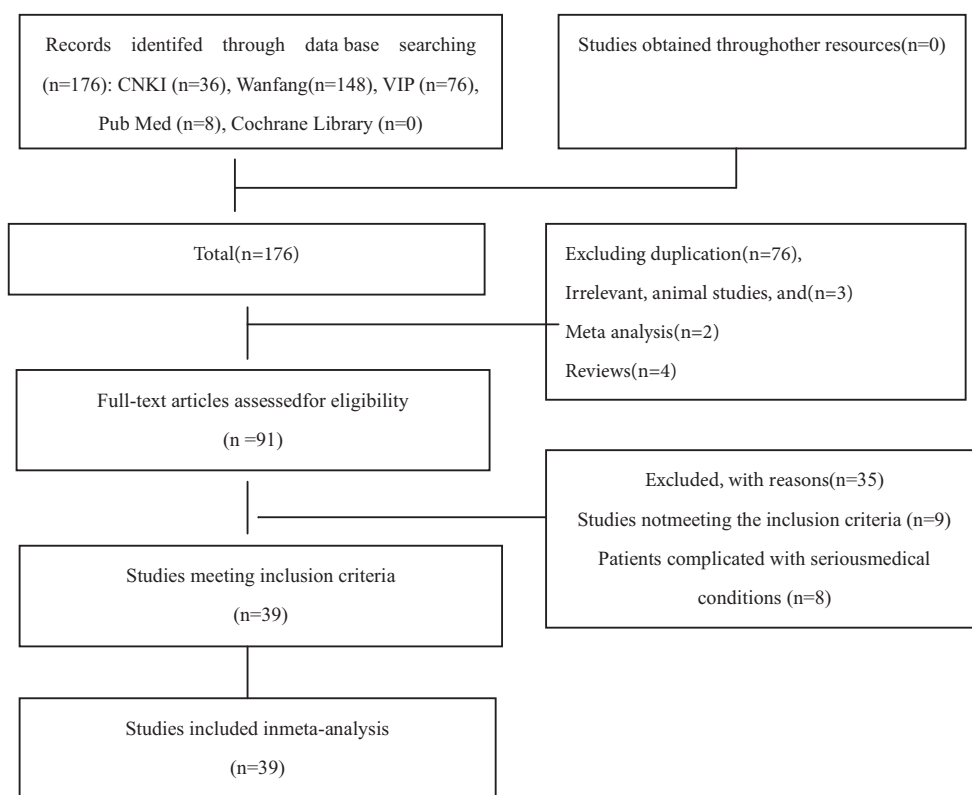
Figure 1. Flow chart of study search and selection. CNKI = Chinese National Knowledge Infrastructure.

3.3.1. Activities of daily living function evaluation scores.
There were 21 studies,[9,15–18,21–23,26–37] which mentioned the comparison of activities daily living function evaluation scores between SI + WM and WM. Different Outcomes were used, including NHISS, BI, ADL, and mRS. There were 19 trials,[9,15–18,20–23,26,29–37] which mentioned the change of NHISS scores. And the meta-analysis showed that the effect of EG was better than CG in improving NHISS scores ($P < .00001$). Totally 10 trials[9,15–17,23,28,30,31,33,34,] mentioned the change of BI scores. Meta-analysis results indicated a statistically significant difference between EG and CG ($P < .00001$). There were 7 trials,[20–22,27,29,32,35] which mentioned the change of ADL scores. And the meta-analysis showed that the effect of EG was better than CG in improving ADL scores ($P < .00001$). From the results of different dose subgroups analysis, the activities daily living function evaluation scores of 2 subgroups was statistically significant difference in MoCA scores between the groups in the 100 mg subgroups. Four trials[16,31,33,34] mentioned the change of mRS scores (Table 2). There was no significant difference in mRS scores between the 2 groups ($P = .008$).

3.3.2. Cognitive function evaluation scores. There were 5 studies,[16,33–35,38] which mentioned the comparison of cognitive function evaluation scores between SI + WM and WM. Different Outcomes were used, including MoCA and MMSE scores. There were 4 trials,[16,33,34,38] which mentioned the change of MoCA scores. The meta-analysis showed that the effect of EG was better than CG in improving MoCA scores ($P = .001$). From the results of 100 mg subgroups analysis, showed statistically significant difference between 2 groups ($P = .0011$). There was no significant difference in MoCA scores between the 1 groups in the 200 mg subgroups ($P = .069$).

There were 5 trials,[16,33–35,38] which mentioned the change of MMSE scores. And the meta-analysis showed that the effect of EG was better than CG in improving MMSE scores ($P < .00001$). (Table 3) There was no significant difference in MMSE scores between the 100 mg subgroups ($P = .001$) and 200 mg subgroups ($P < .00001$).

3.3.3. Hemorheology indexes. In all, 14 RCTs[10,11,13,17–20,25,28,30,32,36,41,42] mentioned hemorheology indexes, including PV, whole blood high-shear viscosity (WBHSV), whole blood low-shear viscosity (WBLSV), and content of FIB. More details are presented in Table 4.

(1) PV: There were 7 studies,[10,19,25,30,36,41,42] which referred to PV. The result of meta-analysis signified that the effect of EG was better than CG in decreasing PV ($P < .00001$).
(2) WBHSV: There were 7 studies,[10,11,13,18,19,25,30] which mentioned the WBHSV. Meta-analysis result indicated that there was a statistically significant difference between the EG and CG groups ($P < .00001$).
(3) WBLSV: There were 7 studies,[10,11,13,18,20,25,30] which mentioned the WBLSV. Meta-analysis result indicated that there was a statistically significant difference between the EG and CG groups ($P < .00001$).
(4) FIB: There were 6 studies,[10,13,17,28,32,36] which mentioned the content of FIB. Meta-analysis result indicated that there was a statistically significant difference between the EG and CG groups ($P < 0.00001$).

3.3.4. hs-CRP and CRP. There were 3 studies,[15,25,30] which mentioned the change of hs-CRP, and 9 studies[10,11,14,28,32,

Figure 2. Risk of bias summary.

3.4. Total clinical effective rate

A total of 21 studies[11–13,15,17,20,23–25,27,29,36,37,39–46] reported the total effective rate. Meta-analysis results indicated a statistically significant difference between EG and CG. The statistical difference between the 2 groups was significant ($P < .00001$) (shown in Fig. 3). Figure 4 displayed a funnel plot on publication bias for clinical total effective rate, which was depicted by RR values and the standard error of RR values. The funnel plot presented a general symmetry, and the studies included concentrated upon the upper part of it.

3.5. Neural function defect scale

Totally 8 studies[10,12,14,19,27,40,46,47] reported the NDS. Meta-analysis result manifested that there was a statistically significant difference between the 2 groups, and the combination of SI and WM could achieve a better effect on improving the NDS ($P < .00001$) (shown in Fig. 5).

3.6. Safety

A total of 10 studies[16,18,21,24,25,27,34,36,37,46] mentioned obvious ADRs/ADEs, during the implementation of trials, ADRs including headache, dizziness, gastrointestinal reaction, and so on. The incidence of adverse effects was 7.81% (40/512). And the incidence of adverse effects was 9.57% (43/449) No severe adverse events were reported. Only 1 study indicated that there were no ADRs/ADEs in both groups. There was no significant difference about ADRs/ADEs between the EG and CG ($P = .73$) (shown in Fig. 6).

4. Discussion

According to the results of this meta-analysis, we found that compared with WM therapies, SI combined with WM demonstrated a potential beneficial effect for ACI patients. A total of 39 randomized trials including 4516 participants were included. In addition, the methodological quality of all trials was limited. SI can make a more noticeable impact for ACI patients, which was embodied in the following aspects: first of all, a combination use of SI and WM has a notable performance on improving clinical total effective rate, perfecting neurologic deficiency, improving activities daily living function, and cognition disorders. There was no significant difference in mRS scores between the EG and the CG. Secondly, the combined use of Salvianolate and WM therapy can improve the hemorheology indexes, including PV, WBHSV, WBLSV, and FIB levels. And there were statistically significant differences between the 2 groups in improving the hs-CRP and CRP levels. In terms of ADRs/ADEs, there was no definite conclusion about safety between 2 groups. In a summary, the results of subgroup analysis showed that high dose neither significantly improve the efficacy nor reduce the risk about safety. That means the course of SI should be in strict accordance with the drug instructions.

At present, there is a lack of systemic reviews about comparing SI + WM and WM in evaluate the effectiveness and safety of SI on motor and cognitive function of patients with ACI. There were 2 related systematic reviews in database, which published in 2013[4] and 2017.[48] In Lu et al's study,[4] the evaluation indexes including the change of activities daily living function evaluation and ADRs/ADEs, but no more exact figures were mentioned. Five RCTs were included in the study, but 2 RCTs of them[11,49] had the same authors and similar study phase. The data in 2 RCTs

37,39,43,44] mentioned the change of CRP. Meta-analysis result showed that both of them have statistically significant difference between the EG and CG groups ($P < .00001$) (Table 5).

Table 2

Meta-analysis for comparison of movement function evaluation scores between Salvianolate injection + Western medicine and Western medicine.

Outcomes	Study or subgroup, mg	N (EG/CG)	Statistical heterogeneity	Results
NHISS	100–130	275/273	$(P=.46)$; $I^2=0\%$	MD = −3.10, 95% CI [−4.03,−2.17] $(P<.00001)$
	200	678/672	$(P<.00001)$; $I^2=94\%$	MD = −3.49, 95% CI [−3.72,−3.26] $(P<.00001)$
	300	148/142	$(P=.73)$; $I^2=0\%$	MD = −1.44, 95% CI [−2.17,−0.70] $(P=.0001)$
	Total	1144/1130	$(P<.00001)$; $I^2=92\%$	MD = −3.22, 95% CI [−3.42,−3.0] $(P<.00001)$
BI	130	91/89	$(P=.18)$; $I^2=46\%$	MD = 10.99, 95% CI [8.42,13.56] $(P<.00001)$
	200	348/345	$(P=.002)$; $I^2=68\%$	MD = 10.86, 95% CI [9.12,12.61] $(P<.00001)$
	300	148/142	$(P=.57)$; $I^2=0\%$	MD = 3.96, 95% CI [0.71,7.22] $(P<.00001)$
	Total	630/619	$(P<.0001)$; $I^2=70\%$	MD = 9.82, 95% CI [8.51,11.14] $(P<.00001)$
ADL	100	132/132	$(P=.64)$; $I^2=0\%$	MD = 3.13, 95% CI [1.18,5.09] $(P=.002)$
	200	337/335	$(P<.00001)$; $I^2=92\%$	MD = 7.97, 95% CI [6.75,9.19] $(P<.00001)$
	Total	469/467	$(P<.00001)$; $I^2=92\%$	MD = 6.62, 95% CI [5.59,7.66] $(P<.00001)$
mRS	100–130	97/97	$(P=.06)$; $I^2=73\%$	MD = 0.17, 95% CI [−0.40,0.05] $(P=.31)$
	200	35/35	$(P=.06)$; $Z=1.89$	MD = −0.51, 95% CI [−1.04,0.02] $(P=.06)$
	Total	175/175	$(P=.14)$; $I^2=45\%$	MD = −0.26, 95% CI [−0.45, 0.07] $(P=.008)$

ADL = activities of daily living, BI = Barthel index, CG = control group, EG = experimental group, mRS = distribution of the modified Rankin Scale, NHISS = National Institute of Health Stroke Scale.

Table 3

Meta-analysis for comparison of cognitive function evaluation scores between Salvianolate injection + Western medicine and Western medicine.

Outcomes	Study or subgroup, mg	N (EG/CG)	Statistical heterogeneity	Results
MoCA	100	44/44	$(P=.001)$; $Z=3.20$	MD = 2.34, 95% CI [0.91,3.77] $(P=.0011)$
	200	78/78	$(P=.003)$; $I^2=89\%$	MD = 0.17, 95% CI [−0.70,1.04] $(P=.69)$
	Total	165/165	$(P=.0002)$; $I^2=84\%$	MD = 1.10, 95% CI [0.44,1.76] $(P=.001)$
MMSE	100	44/44	$(P=.001)$; $Z=3.29$	MD = 2.10, 95% CI [0.85,3.35] $(P=.001)$
	200	152/152	$(P=.93)$; $I^2=0\%$	MD = 2.31, 95% CI [1.57,3.05] $(P<.00001)$
	Total	239/239	$(P=.98)$; $I^2=0\%$	MD = 2.18, 95% CI [1.62,2.75] $(P<.00001)$

CG = control group, EG = experimental group, MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment.

maybe have some overlap. Therefore, these 2 systematic reviews can be considered from the same test. That means the experimental design is not rigorous. In Zeng et al's[48] study the experimental design is not rigorous, too. The objective of the study is to evaluate the effectiveness and safety of SI on motor and cognitive function of patients with ACI. But in fact the change of cognitive function was not included in evaluation indexes.

This study shows that SI has the function of improving activities of daily living function and cognitive function, and

promoting the recovery of nerve function, In our inclusion criteria, the EG only used SI combined with WM, the CG used WM single, just for avoiding other TCM preparations possible interference on the results. And the RCTs' quality assessment was conducted by the Cochrane Risk of Bias Assessment Tool. Our study not only updated the latest RCTs but also analyzed the differences of high dose and low dose.

No severe adverse events were reported. There was no significant difference about ADRs/ADEs between the EG and

Table 4

Meta-analysis for comparison of hemorheologyindexes between Salvianolate injection + Western medicine and Western medicine.

Outcomes	Study	N (EG/CG)	Statistical heterogeneity	Results
PV, mPa·s		376/375	$(P=.00001)$; $I^2=99\%$	MD = −0.61, 95% CI [−0.63,−0.58] $(P<.00001)$
WBHSV, mPa·s		486/486	$(P<.00001)$; $I^2=99\%$	MD = −1.73, 95% CI [−1.74,−1.71] $(P<.00001)$
WBLSV, mPa·s		486/486	$(P<.00001)$; $I^2=87\%$	MD = −1.07, 95% CI [−1.21,−0.93] $(P<.00001)$
FIB, g/L		298/294	$(P<.00001)$; $I^2=99\%$	MD = −0.81, 95% CI [−0.90,−0.72] $(P<.00001)$

CG = control group, EG = experimental group, FIB = fibrinogen, PV = plasma viscosity, WBHSV = whole blood high-shear viscosity, WBLSV = whole blood low-shear viscosity (mPa·s).

Table 5

Meta-analysis for comparison of C-reactive protein and high-sensitivity C-reactive protein between Salvianolate injection + Western medicine and Western medicine.

Outcomes	Study	N (EG/CG)	Statistical heterogeneity	Results
hsCRP, mg/dL		260/258	$(P<.00001)$; $I^2=90\%$	MD = −2.05, 95% CI [−2.31,−1.79] $(P<.00001)$
CRP, mg/dL		553/547	$(P<.00001)$; $I^2=96\%$	MD = −2.40, 95% CI [−2.55, −2.26] $(P<.00001)$

CG = control group, CRP = C-reactive protein, EG = experimental group, hsCRP = high-sensitivity C-reactive protein.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2012 ChangSJ	103	107	69	107	7.6%	1.49 [1.29, 1.73]	
2012 HaoSJ	27	30	23	30	2.5%	1.17 [0.93, 1.48]	
2012 MiYX	120	150	93	150	10.3%	1.29 [1.11, 1.50]	
2013 ZhangQ	54	64	22	32	3.2%	1.23 [0.95, 1.59]	
2014 MaFC	69	78	47	65	5.7%	1.22 [1.03, 1.45]	
2014 ZhouXJ	18	19	16	19	1.8%	1.13 [0.90, 1.40]	
2015 AnWF	37	40	30	40	3.3%	1.23 [1.01, 1.51]	
2015 ChenY	64	75	49	75	5.4%	1.31 [1.08, 1.58]	
2015 GaoM	59	65	43	65	4.8%	1.37 [1.13, 1.66]	
2015 HouXW	91	100	75	100	8.3%	1.21 [1.07, 1.38]	
2015 SunLX	27	38	15	36	1.7%	1.71 [1.10, 2.64]	
2015 ZhaoY	69	80	50	80	5.5%	1.38 [1.14, 1.67]	
2015 ZhouBZ	70	91	52	91	5.7%	1.35 [1.09, 1.66]	
2016 HeYL	29	35	19	32	2.2%	1.40 [1.01, 1.93]	
2016 PengF	74	102	61	98	6.9%	1.17 [0.96, 1.42]	
2016 WangQ	36	41	30	40	3.4%	1.17 [0.95, 1.45]	
2016 WangWF	35	40	24	40	2.7%	1.46 [1.10, 1.93]	
2016 ZhaoZJ	63	65	57	65	6.3%	1.11 [1.00, 1.22]	
2016 ZhuQY	48	50	38	50	4.2%	1.26 [1.07, 1.49]	
2017FangG	65	75	49	75	5.4%	1.33 [1.10, 1.60]	
2017ShiX	41	44	28	44	3.1%	1.46 [1.16, 1.86]	
Total (95% CI)		**1389**		**1334**	**100.0%**	**1.29 [1.24, 1.35]**	
Total events	1199		890				

Heterogeneity: Chi² = 23.66, df = 20 (P = 0.26); I² = 15%
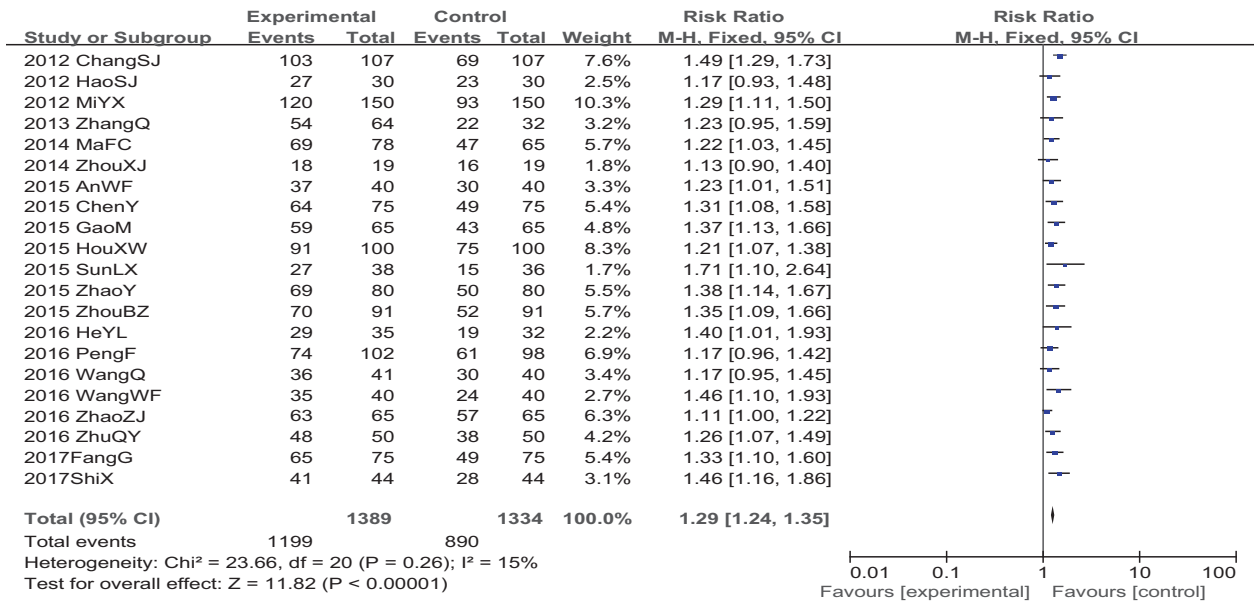Test for overall effect: Z = 11.82 (P < 0.00001)

Figure 3. Meta-analysis for comparison of acute cerebral infarction (ACI) total effective rate between Salvianolate injection (SI) + Western medicine (WM) and WM. CI = confidence interval.
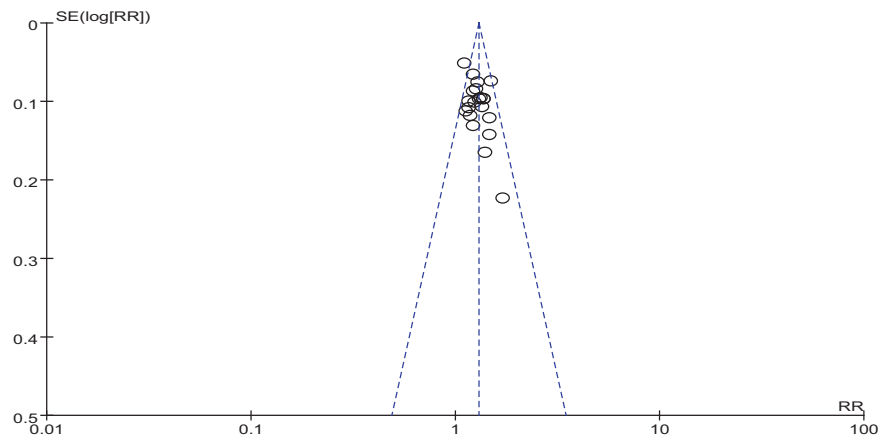

Figure 4. Funnel plot of publication bias. RR = relative risk.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
2010 ZhangZ	10.55	5.25	60	13.27	5.01	60	4.6%	-2.72 [-4.56, -0.88]	
2012 HaoSJ	10.25	4.68	30	12.74	6.53	30	1.9%	-2.49 [-5.36, 0.38]	
2013ZhangQ（100mg）	17.75	2.74	32	18.53	3.63	32	6.3%	-0.78 [-2.36, 0.80]	
2013ZhangQ（200mg）	15.43	3.05	32	18.53	3.63	32	5.8%	-3.10 [-4.74, -1.46]	
2014 DuYH	10.2	6.07	70	14.32	5.68	70	4.1%	-4.12 [-6.07, -2.17]	
2014 MaFC	9.42	3.21	78	14.26	2.86	65	15.8%	-4.84 [-5.84, -3.84]	
2015 LiY	10.02	1.15	56	13.66	1.75	50	48.0%	-3.64 [-4.21, -3.07]	
2015 ZhaoY	10.3	3.1	80	14.4	4.7	80	10.3%	-4.10 [-5.33, -2.87]	
2016 PeiY	10.47	5.31	42	13.62	5.11	42	3.2%	-3.15 [-5.38, -0.92]	
Total (95% CI)			**480**			**461**	**100.0%**	**-3.61 [-4.00, -3.21]**	

Heterogeneity: Chi² = 21.15, df = 8 (P = 0.007); I² = 62%
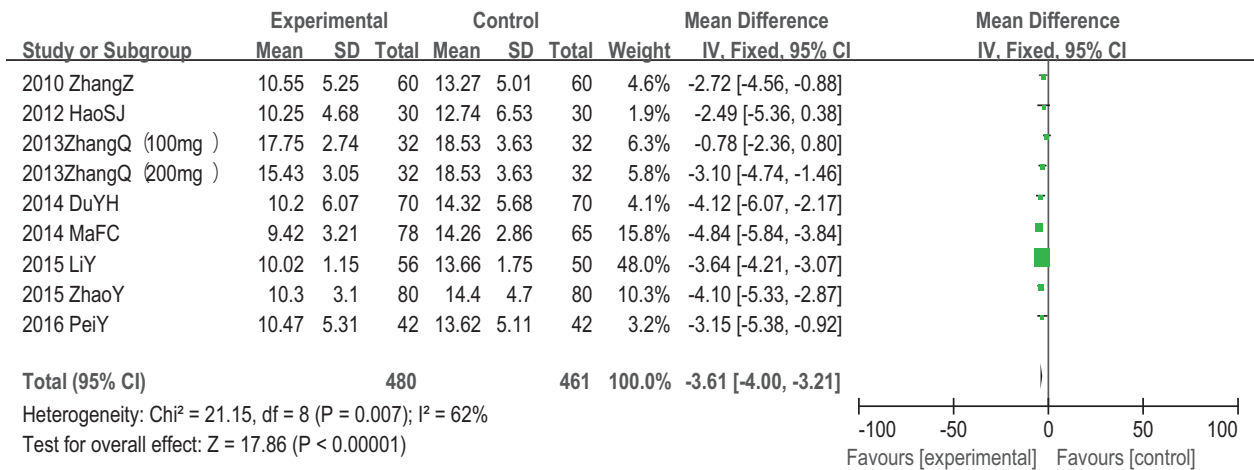Test for overall effect: Z = 17.86 (P < 0.00001)

Figure 5. Meta-analysis of NDS of Salvianolate injection (SI) for testing acute cerebral infarction (ACI). CI = confidence interval, NDS = neural function-defect scale, SD = standard deviation.
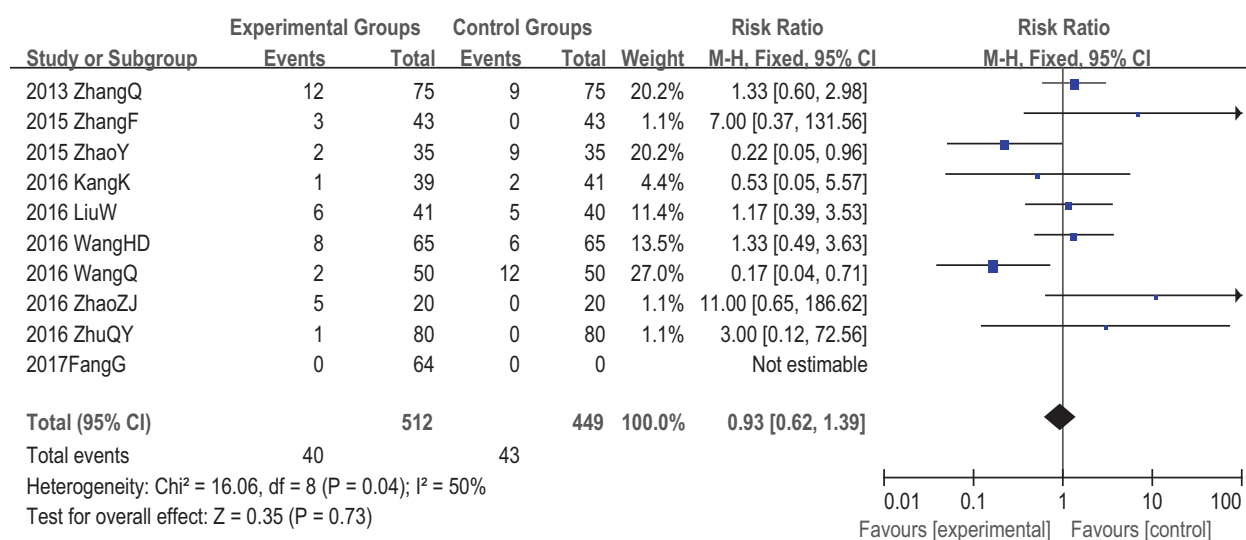
Study or Subgroup	Experimental Groups Events	Total	Control Groups Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2013 ZhangQ	12	75	9	75	20.2%	1.33 [0.60, 2.98]
2015 ZhangF	3	43	0	43	1.1%	7.00 [0.37, 131.56]
2015 ZhaoY	2	35	9	35	20.2%	0.22 [0.05, 0.96]
2016 KangK	1	39	2	41	4.4%	0.53 [0.05, 5.57]
2016 LiuW	6	41	5	40	11.4%	1.17 [0.39, 3.53]
2016 WangHD	8	65	6	65	13.5%	1.33 [0.49, 3.63]
2016 WangQ	2	50	12	50	27.0%	0.17 [0.04, 0.71]
2016 ZhaoZJ	5	20	0	20	1.1%	11.00 [0.65, 186.62]
2016 ZhuQY	1	80	0	80	1.1%	3.00 [0.12, 72.56]
2017FangG	0	64	0	0		Not estimable
Total (95% CI)		512		449	100.0%	0.93 [0.62, 1.39]
Total events	40		43			

Heterogeneity: Chi² = 16.06, df = 8 (P = 0.04); I² = 50%
Test for overall effect: Z = 0.35 (P = 0.73)

Figure 6. Meta-analysis of adverse drug reactions (ADRs)/adverse drug events (ADEs) of Salvianolate injection (SI) for testing acute cerebral infarction (ACI). CI = confidence interval.

CG. Therefore, the clinical usage of SI should be in strict accordance with the instructions, to avoid the occurrence of compatibility and ADRs.

5. Limitations

This study has several limitations. First, the review included a total of 39 RCTs; however, the overall quality of the included RCTs was general, and they lacked of large-scale RCTs. Totally 17 included studies mentioned "random" in RCTs, but none of them makes a detailed description about how to generate random sequence, conceal allocation, or whether carried out blinding, which may bring about certain bias for assessment and influence the grade of evidence. Although Egger test and Begg test showed that there was no publication bias in this study, the included RCTs concentrated upon the upper part of funnel plot. It revealed that our meta-analysis may lack RCTs whose sample size was quality. Second, the systematic review included only published studies in the database, with no the relevant gray literature, which possibly cause a selection bias in the literature. And the included RCTs were performed in Chinese patients; therefore, it is unclear whether the conclusions of our study apply to other populations. Third, the treatment course of included RCTs was short and clinicians did not conduct follow-up visit. Despite the above limitations, our study provided a complete evaluation for the effectiveness and safety of SI on treating cerebral infarction.

6. Conclusion

To sum up, our study evaluated the effectiveness and safety of SI in the treatment of ACI. We found that SI could improve the motor and cognitive function of patients with ACI. In general, we draw a conclusion that SI had a positive effect on treating cerebral infarction, improving motor and cognitive function, but more multicenter and high-quality RCTs should be implemented in the future to support evidence.

Author contributions

Data curation: Yun XiangHua.

Writing – original draft: Yang NanZhu.
Writing – review and editing: Ju AiChun, Li Xin.

References

[1] Liu S, Wu JR, Zhang D, et al. Comparative efficacy of Chinese herbal injections for treating acute cerebral infarction: a network meta-analysis of randomized controlled trials. BMC Complement Altern Med 2018; 18:120.

[2] Wang K, Zhang D, Wu J, et al. A comparative study of Danhong injection and Salvia miltiorrhiza injection in the treatment of cerebral infarction: a systematic review and meta-analysis. Medicine (Baltimore) 2017;96:e7079.

[3] Wang Y, Jiang YF, Huang QF, et al. Neuroprotective effects of salvianolic acid B against oxygen-glucose deprivation/reperfusion damage in primary rat cortical neurons. Chin Med J (Engl) 2010; 123:3612–9.

[4] Lu YQ, Wang Y, He ZF. The systematic evaluation of the treatment of acute cerebral infarction by salvia salvia.[J]. Chin J Gerontol 2013; 33:4559–60.

[5] The fourth national conference on cerebrovascular diseases. Diagnostic points of cerebrovascular diseases. Chin J Neurol 1996;29:379–80.

[6] Li WH. Degree of cerebral apoplexy patients with clinical nerve function defect score standard. Chin J Neurol 1996;29:381–3.

[7] Review Manager (RevMan) (Computer program). Version 5.3. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration; 2014.

[8] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011;343:d5928.

[9] Ji PZ, Luo ZQ, Wang CG. Treatment of acute ischemic stroke by salvia salicylate. Pharm CareRes 2010;10:4.

[10] Zhang Z, Yin ZL, Liu YJ. Observation on the curative effect of salvianolate on patients with acute cerebral infarction. J Hunan N ormal Univ (Med Sci) 2010;3:65–6.

[11] Mi YX. The effect of Salvianolate on the level of serum C-reactive protein and hemorheology in patients with acute cerebral infarction. Medical Recapitulate 2012;18:3903–5.

[12] Ma FC, Pan SM. Effects of Salvia miltiorrhizal injection on acute cerebral infarction and the influence of TNF-α and IL-6. Chin J Pract Nerv Dis 2014;17:86–7.

[13] Chen Y. Curative effect analysis and hemorheology study of injection of Salvia miltiorrhiza for cerebral infarction. J New Chin Med 2015;47: 31–3.

[14] Li Y, Zhou Q. Observation on the effect of Salvia miltiorrhiza in treating senile patients with acute cerebral infarction. Ningxia Med J 2015; 12:1120–1.

[15] Sun LX. The effect of injection of Salvia miltiorrhiza in the treatment of progressive cerebral infarction. China Med 2015;10:816–8.

[16] Zhang F, Qiu J, Zhang LM, et al. Clinical study on the effect of salvia polyphenolic acid on motor and cognitive function in patients with acute cerebral infarction. Chin J Clin Health 2015;18:232–4.

[17] He YL, Gao Y, Guo XX. Clinical study on salvianolate in treatment of acute cerebral infarction. Drugs Clin 2016;31:1354–9.

[18] Liu W, Jiang AZ. Study of salvianolate on treatment for acute cerebral infarction. Chin J Thromb Hemost 2016;22:636.637.640.

[19] Pei Y, Zhou HW. The clinical effect and application value of salvia polyphenolic acid in treatment of acute cerebral infarction. China Prac Med 2016;22:156–7.

[20] Peng F, Cjen SF. Treatment of acute cerebral infarction by salvia polyphenolic acid injection. J Baotou Med Coll 2016;32:39–41.

[21] Wang HD. Analysis curative effect of salvianolate injection in teatment of patients with acute cerebral infarction. China Contin Med Educ 2016;18:182–3.

[22] Wang HQ, Zhao SL. The effects of salvia polyphenolic in improving cerebral hemodynamics and neurologic function and daily life. Chin J Pract Nerv Dis 2016;19:64–6.

[23] Wang WF. The therapeutic effect of salvia miltiorrhiza in the treatment of progressive cerebral infarction. Chin J Pract Nerv Dis 2016;1:7107–8.

[24] Zhao ZJ. Clinical observation on the therapeutic effect of salvia polyphenolic acid salt in the treatment of progressive cerebral infarction. Inner Mongol J Tradit Chin Med 2017;2:86.

[25] Fang G. The clinical effect analysis of the treatment of ischemic cerebral apoplexy by injection of salvia polyphenolic acid. Chin J Integr Med Cardio-/Cerebrovasc Dis 2017;15:725–7.

[26] Pei Y, Zhou HW. Efficacy and safety of salvianolic acids in treatment of cerebral infarction evaluation and analysis of drug–use in hospitals of China. Eval Anal Drug Use Hosp China 2017;17:202–4.

[27] Zhang Q, Chen SY. Clinical study of salt from Salvia miltiorrhiza on patients with acute cerebral ischemia. Pract Pharm Clin Remedias 2013;16:114–6.

[28] Hao YC. Effects of salvia salicylate on hemorheology and neurological function in patients with cerebral infarction. Chin J Pract Nerv Dis 2014;117:67–8.

[29] Hou XW, Wang YH. The curative effect analysis of salvianolate in acute ischemic stroke. China Modern Doctor 2015;53:100–2.

[30] Tao Z, Cao BZ, Wang SC, et al. The effect of Salvia miltiorrhiza on serum hs-CRP and nervous function in elderly patients with acute ischemic stroke. Chin J PractNerv Dis 2015;18:29–31.

[31] Xu W, Wang CX. Clinical study on the treatment of Salvianolic acid for mild to moderate cerebral onfarction. Chin J Clin Rational Drug Use 2015;8:14–5.

[32] Zhang XW. Effects of salvia polyphenate on fibrinogen and c-reactive protein in acute cerebral infarction. Zhejiang J TradChin Med 2015; 50:544.

[33] Huang XL. Effect of Salvia miltiorrhiza on motor and cognitive function in patients with acute cerebral infarction. China Contin Med Educ 2016;7:180–1.

[34] Kang K, Jin SJ, Li. The effect of salvia polyphenolic acid on motor and cognitive function in patients with acute cerebral infarction. HeNan Med Res 2016;25:326–7.

[35] Shan XY. The effect of salvia polyphenolic acid on cognitive dysfunction after acute stroke. Chin J Pract Nerv Dis 2016;19:108–9.

[36] Wang Q, Zhang YP, Zhan Y. Clinical observation on the treatment of acute cerebral infarction with salvia miltiorrhiza injection. Chin J Clin Ration Drug Use 2016;19:29–30.

[37] Zhu QY. Effect analysis of Salvia miltiorrhiza injection in the treatment of acute cerebral infarction. China Mod Med 2016;23:138–40.

[38] Wang Y, Jie LP, Lu YQ, et al. Clinical observation of Salvia miltiorrhizal injection on the cognitive dysfunction after stroke. Chin J Clin Rational Drug Use 2014;7(7A):63–4.

[39] Zhou XJ. Effect observation on salvianolate in the treatment of acute cerebral infarction. Chin J Mod Drug Appl 2014;8:28–9.

[40] Hao SJ, An HJ. Observation on the curative effect of salvianolate on acute cerebral infarction. Chin J Integr Med 2012;10:1076–7.

[41] Gao M. Treatment of acute cerebral infarction in patients by Salvia miltiorrhiza. Diet Care 2015;2:63–4.

[42] Shi X, Han L, Wang QL. Treatment of acute cerebral infarction in patients with acute cerebral infarction by injection of salvia. World Latest Med Inform 2017;17:103–4.

[43] An WF. Treatment of acute cerebral infarction by injection of salvia polyphenolic acid. HeNan Med Res 2016;25:1312–3.

[44] Zhou BZ. Observation of the effect of salvia polyphenolic acid in the treatment of cerebral infarction. HeNan Med Res 2015;24:120–1.

[45] Chang SJ. The treatment of 107 cases of cerebral infarction by salvia polyphenolic acid salt. Clin Med 2012;32:100.

[46] Zhao Y. Treatment of acute cerebral infarction in patients by injection of salvia polyphenate. Health Way 2015;14:159.

[47] Du YH. Treatment of acute cerebral infarction with salvia salicylate in patients with acute cerebral infarction. For All Health 2014;8:143.

[48] Zeng M, Bian JM, Tian GX, et al. The effect of salvianolate on motor and cognitive function of patients with acute cerebral infarction: asystematic review. Chinese J Evid Based Cardiovasc Med 2016;8: 1301–7.

[49] Mi Y, Su HT, Zhang GY, et al. The effect of Salvianolate on the level of serum C-reactive protein in patients with acute ischemic stroke. Chin J Mod Drug Appl 2012;6:9–10.