Systematic Review and Meta-Analysis

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Dengzhanxixin injection for cerebral infarction

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: No systematic review has been published in English of Dengzhanxixin (DZXX) injection for cerebral infarction. The aim of this systematic review was to assess the effects and safety of DZXX injection for cerebral infarction.

Methods: Eight databases were searched from their inception. Randomized controlled trials (RCTs) related to DZXX for cerebral infarction in English or Chinese without restrictions on the publication status were included. Neurological deficit, quality of life, and response rates were analyzed. Adverse events were also investigated.

Results: Twenty-three randomized controlled trials (RCTs) with 2291 participants were included. Meta-analysis showed that DZXX injection plus routine western therapy was better than routine western therapy alone for reducing neurologic deficit (MD –2.86, 95% CI –3.87 to –1.86), for improving quality of life (MD 9.48, 95% CI 8.34–10.63), and for improving response rates (RR 1.20, 95% CI 1.15–1.25). No serious adverse drug events (ADE) were reported.

Conclusions: DZXX injection may have a potential therapeutic effect for cerebral infarction in reducing neurologic deficit, improving life quality and response rates. However, we could not draw any definitive conclusions due to the insufficient evidences. More high-quality trials are needed to provide more strong evidence and to assess the safety of DZXX injection.

Abbreviations: ADE = adverse drug events, ADR = adverse drug reactions, AHA = American Heart Association, ALT = alanine transaminase, AMSTAR = Assessment of Multiple Systematic Reviews, ASA = American Stroke Association, BI = Barthel Index, Caf = caffeic acid ester fraction, CFDA = China Food and Drug Administration, CI = confidence intervals, CT = computed tomography, DZH = Dengzhanhua, DZXX = Dengzhanxixin, MD = mean difference, MRI = magnetic resonance imaging, NDS = Nerve Deficiency Scale, NIHSS = National Institutes of Health Stroke Scale, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, RR = risk ratio, rtPA = recombinant tissue-type plasminogen activator, Scu = scutellarin.

Keywords: cerebral infarction, dengzhanxixin injection, meta-analysis, systematic review

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1. Introduction

Cerebral infarction is a common cerebrovascular disease. More than 690,000 adults suffer from this disease each year in the United States.[1,2] Cerebral infarction can lead to neurological impairment, motor weakness, speech difficulty, visual loss, dizziness, severe headache, and even death.[3,4] American Heart Association (AHA) and American Stroke Association (ASA) suggest that cerebral infarction can be treated by intravenous recombinant tissue-type plasminogen activator (rtPA), anti-coagulants, fibrinolytic agents, antiplatelet agents, and other western therapies.[3] However, any medical therapy may carry more than minimal risk and the treatment of intravenous rtPA is associated with increased rates of intracranial hemorrhage, which may be fatal.[3]

Dengzhanxixin (DZXX) injection is a preparation extracted from a Chinese herb called erigeron breviscapus, a plant mainly grows in southwest China.[5–9] Erigeron breviscapus has been used for thousands of years in mainland China to treat ischemic cardio-cerebral vascular diseases.[6–15] DZXX injection has been officially listed in the Chinese pharmacopoeia.[16] It has been approved by China Food and Drug Administration (CFDA) since August 30, 2010. Its approval number is Z53021620/ Z53021569. DZXX injection can be administered intravenously 20 mL to 40 mL once or twice per day, or 4 mL 2 to 3 times a day for intramuscular injection, or 6 mL to 10 mL for acupoint injection. The mechanism of this injection listed in medicine direction is that it can activate blood circulation to dissipate blood stasis and relieve pain. Therefore, DZXX injection can be applied to treat ischemic stroke, coronary heart disease, stenocardia, and other cardio-cerebral vascular diseases. The side effects of DZXX injection may include palpitation, fever chills, cutaneous pruritus, flushing, dizziness, nausea, dyspepsia, bleeding, headache, and decrease in blood pressure. The active components of DZXX injection are caffeic acid ester fraction (Caf) and scutellarin (Scu).[13,16–19] Recent pharmacological and animal experiments prove that Scu can reduce apoptosis and oxidative stress.[20] Besides, Caf and Scu have potential therapeutic neuroprotection for cerebral infarction through astrocytes ,[21] including regulating nitric oxide production,[22] inhibiting hypoxia induced cytotoxicity,[21,23] and rescuing neuronal damage.[12,24,25]

To the best of our knowledge, no systematic review in English has been published of DZXX injection for cerebral infarction. In the recent 5 years, 1 systematic review of DZXX injection for cerebral infarction had been published in Chinese.[26] This review concluded that DZXX injection had a good therapeutic effect for cerebral infarction. However, the evidence still remained unreliable due to the poor methodological quality of this review evaluated by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [27] and Assessment of Multiple Systematic Reviews (AMSTAR).[28] In light of this incomplete evidence and the possibility of adverse effects, a rigorous and high-quality systematic review is still needed to provide strong evidence for DZXX injection on cerebral infarction. The aim of our review is to access the effectiveness and safety of DZXX injection for cerebral infarction.

2. Methods and analysis

As this was a systematic review and meta-analysis of previous studies, therefore, ethical approval and patient consent were not required.

2.1. Search strategy

Because of the language limitation, we searched for relevant trials just in Chinese and English. The key words included "Dengzhan," "Dengzhan injection," "Dengzhanxixin," "Dengzhan-xixin injection," "DZXX," "DZXX injection," "Deng-zhan-xi-xin," "Deng-zhan-xi-xin injection," "cerebral infarction," "stroke," "ischemic stroke," "cerebral apoplexy," and "cerebral ischemic stroke." The following databases were searched from their inception with no limitation of the publication status: Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database), Wan-Fang Database, Cochrane Central Register of Controlled Trials, PubMed, EMBASE, and ClinicalTrials.gov.

2.2. Criteria for study inclusion in this review

2.2.1. Type of studies. Only randomized controlled trials (RCTs) investigating DZXX injection for cerebral infarction in English or Chinese were eligible. There were no restrictions on publication status.

2.2.2. Type of participants. Patients with a clinical diagnosis of cerebral infarction and further confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). The subtypes of cerebral infarction would be included as follows: atherosclerotic thrombotic cerebral infarction, cerebral embolism, and lacunar infarction. But there was no limitation on the area and the scope of infarction. The age of patients should be less than 85 years old, whereas the gender has no limitation. Besides, patients with subarachnoid hemorrhage, cerebral hemorrhage, or other hemorrhagic cerebrovascular diseases would be excluded. Moreover, patients suffered from transient ischemic attack, cerebral vascular dementias, hypertensive encephalopathy, stroke-causing tumors, or accompanied by severe heart, liver, and kidney disease would be excluded.

2.2.3. Type of intervention. RCTs of DZXX injection compared with placebo control, no treatment or drug therapy would be included. RCTs involving DZXX injection combined with another therapy versus this therapy alone would also be included. Trials comparing different types of DZXX injections were excluded. Besides, trials involving DZXX injection plus Chinese medicine compared with Chinese medicine would be excluded.

2.2.4. Type of outcomes. The primary outcome was the neurologic deficit measured by National Institutes of Health Stroke Scale (NIHSS) and Nerve Deficiency Scale (NDS). The secondary outcomes were: ① quality of life measured by Barthel Index (BI); ② response rates (proportion of patients improved): cure (neurologic deficit scores reduced rate from 91% to 100%), significantly effective (neurologic deficit scores reduced rate more from 46% to 90%), effective (neurologic deficit scores reduced rate from 18% to 46%), and ineffective (neurologic deficit scores scores reduced rate less than 18%); ③ safety: adverse drug events and reactions caused by DZXX injection during scheduled treatment and follow-up.

2.3. Study selection

Two reviewers (JW and JZ) independently scanned the titles and abstracts of all records identified in the electronic databases. The studies that met inclusion criteria listed above were included. Any disagreements were resolved by consensus discussion between reviewers, or with a third party (YX and XL) if necessary.

2.4. Data extraction and management

A standard data extraction form was used for data collection, which including the following items: general information such as study ID, sample size, age of the participants, treatment details of the experimental and the control, outcomes; trial characteristics such as the method of randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other.

2.5. Quality assessment

Two reviewers (JW and SZ) independently evaluated the methodological quality by Cochrane Handbook for Systematic Review of Interventions, Version 5.1.0.[29] The items included 7 parts, such as random 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 reporting (reporting bias), and other bias. Each assessment was categorized into 3 levels: low risk, unclear risk, and high risk. Then, trials would be evaluated as having high risk of bias (at least 1 item was in the high risk of bias), or unclear risk of bias (at least 1 item was in the unclear risk of bias), or low risk of bias (all the items were in the low risk of bias).

2.6. Data synthesis and analysis

The RevMan V.5.3 software from the Cochrane Collaboration was applied for the data synthesis.[29] The Higgins I^2 test was used for heterogeneity prior to the meta-analysis to find out if the included studies were inconsistencies. If the I^2 statistics were less than 50%, the heterogeneity could be accepted. Then, the combination of a risk ratio (RR) of each study and 95% confidence intervals (CI) with the fixed effect model was applied for the dichotomous data. Also, the combination of a mean difference (MD) of each study and 95% CI with the fixed effect model was applied for the continuous data. However, there was significant heterogeneity among the studies if the I^2 statistics exceeded 50% and the random effect model would be used to pool data. For data that could not be able to do quantitative analysis, we would perform as qualitative analysis.

Subgroup analysis would be performed according to the different intervention types in experimental and control groups, outcome measures, and different measure stages during the treatment course. A sensitivity analysis was applied to assess the potential bias of individual trials on the outcome of the meta-analysis. If there were more than 10 studies included in 1 meta-analysis, the funnel plots would be used to assess the publication bias.

3. Results

3.1. Study search results

Through electronic searching, 8488 records were identified. After removing duplicates, 1463 records were identified for screening. Approximately 130 studies potentially met the inclusion criteria, and these studies were identified for full-text screening. Finally, 23 randomized controlled trials (RCTs) were included.[30–52] The details of study selection are shown in Fig. 1.

3.2. Characteristics of the included studies

A total of 2291 participants in 23 trials were included and the sample sizes were ranging from 39 to 316. The age of patients ranged from 35 to 91 years. The disease course ranged from 1 hour to 15 days. DZXX injection was administered intravenously in all included studies. The doses of DZXX injection were ranging from 20 mL to 40 mL. Only 2 trials did not mention the solvent[38,42]; the other 21 trials used 0.9% normal saline (NS) (150–500 mL) or 5% glucose (GS) (250–500 mL) as the solvent for DZXX injection. Patients in 22 trials received DZXX injection once a day and twice a day in 1 trial .[52] The treatment duration ranged from 14 to 120 days.

There were no trials comparing DZXX injection with placebo or no treatment. One trial compared DZXX injection with Gegensu injection.[34] There were 21 trials compared DZXX injection plus routine western therapy with routine western therapy alone; 1 trial compared DZXX injection plus routine western therapy and rehabilitation with routine western therapy plus rehabilitation.[49] The routine western therapy included platelet aggregation inhibitor, anticoagulants, neuroprotective drugs, neurotrophy agents, dehydrating agents, diuretic, hypotensive drugs, hypoglycemic drugs, and lipid-lowering drugs.

The neurological deficit was measured by National Institutes of Health Stroke Scale (NIHSS) in 6 trials [32,38,39,43,48,51] and measured by the Nerve Deficiency Scale (NDS) in 6 trials.[30,33,36,44,47,49] The quality of life was measured by the Barthel Index (BI) in 4 trials,[35,38,49,51] and 18 trials evaluated response rates after treatment.[30,31,33,34,36,37,40–47,49–52] In addition, 3 trials reported the adverse events during treatment.[31,36,43]

The details of study characteristics are summarized in Table 1.

3.3. Quality assessment of the included trials

All the included trials mentioned randomization, but only 7 trials described the method of randomization,[32,33,39,41,43,46,51] including random number table [32,39,41,43,46,51] and simple randomization.[33] Only 2 trials mentioned allocation concealment of envelopes and cards.[31,32] There was no information relating to the blind method. Only 2 trials reported relevant information regarding follow-up.[38,52] There were no trials reporting any dropout rate, or performing intention-to-treat analysis. Therefore, all the trials were evaluated as having the high risk of bias (Fig. 2).

3.4. Outcomes of interventions

3.4.1. Primary outcomes

3.4.1.1. Neurologic deficit—National Institutes of Health Stroke Scale (NIHSS). Six trials measured neurologic deficit by the National Institutes of Health Stroke Scale (NIHSS).[32,38,39,43,48,51] All these 6 trials compared DZXX injection plus routine western therapy with routine western therapy alone. However, there was significant heterogeneity among these 6 trials ($I^2=75\%$). Then, the random effect model was used to pool data. It showed that DZXX injection plus routine western therapy was better than routine western therapy alone for reducing neurologic deficit (MD –2.71, 95% CI –3.89 to –1.53, $P<.00001$) (Fig. 3).

In addition, through sensitivity analysis, we found out that the patients in 1 trial [38] were all much more serious than patients in the other 5 trials.[32,39,43,48,51] In this trial,[38] the scores of NIHSS in both experimental and control groups were much higher than the scores in the other trials before and after treatment, which may lead to heterogeneity. Hence, another meta-analysis was performed among the other 5 trials,[32,39,43,48,51] which indicated that DZXX injection plus routine western therapy was better than routine western therapy alone for reducing neurologic

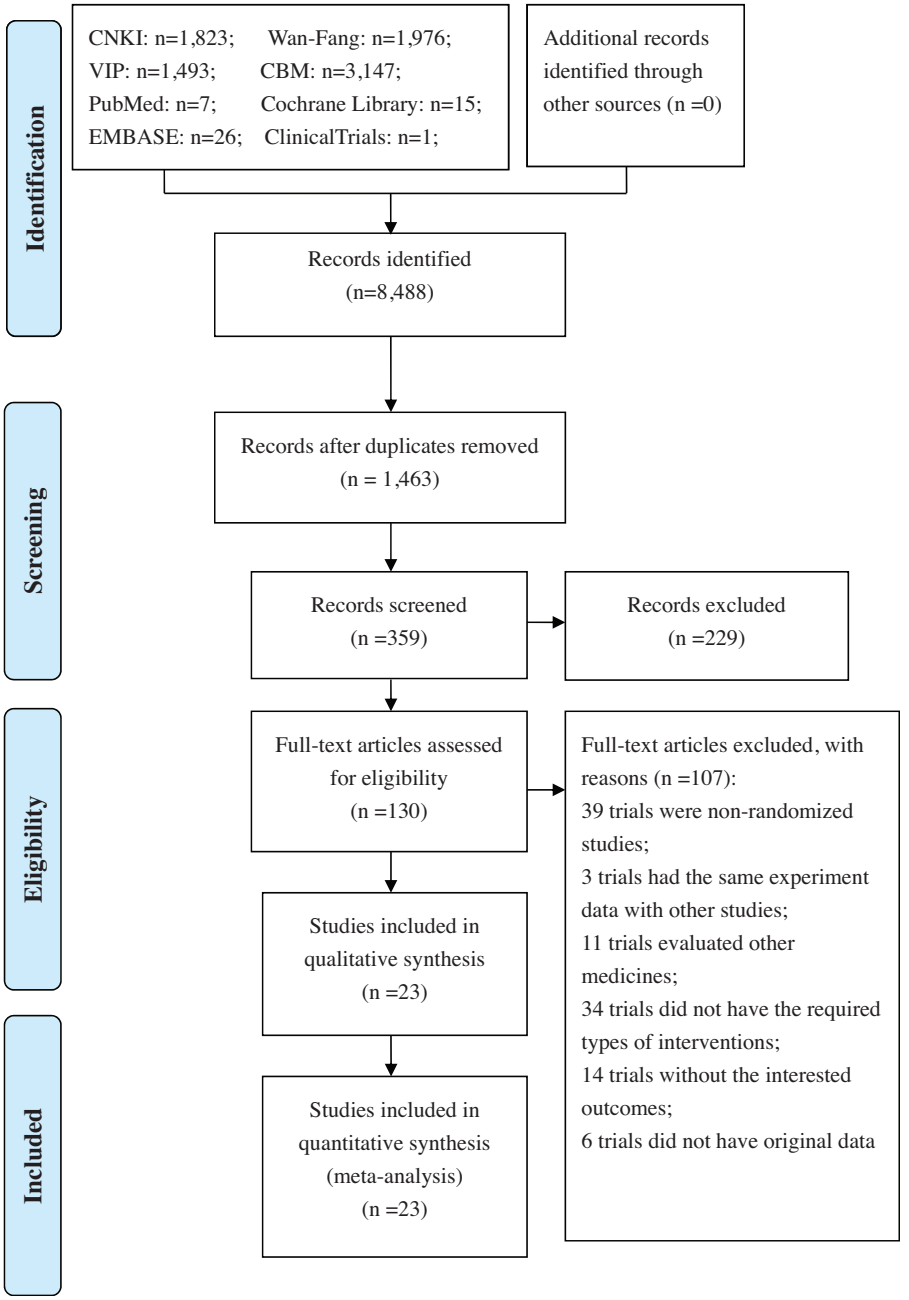

Figure 1. Flow diagram for the process of selecting eligible RCTs. RCTs = randomized controlled trials.

deficit (MD –2.11, 95% CI –2.73 to –1.48, $P < .00001$, $I^2 = 0\%$) (Fig. 4).

3.4.1.2. Neurologic deficit—Nerve Deficiency Scale (NDS). Six trials measured neurologic deficit by the Nerve Deficiency Scale.[30,33,36,44,47,49]

Five trials showed that DZXX injection plus routine western therapy was better than routine western therapy alone for reducing neurologic deficit (MD –2.86, 95% CI –3.87 to –1.86, $P < .00001$, $I^2 = 31\%$)[30,33,36,44,47] (Fig. 5).

One trial indicated the effect of DZXX injection plus routine western therapy and rehabilitation was much better than routine western therapy plus rehabilitation for reducing neurologic deficit (MD –5.00, 95% CI –7.20 to –2.80, $P < .00001$).[49]

3.4.2. Secondary outcomes.

3.4.2.1. Quality of life—Barthel Index (BI). There were 4 trials investigating the quality of life by the Barthel Index (BI).[35,38,49,51]

Three trials showed that DZXX injection plus routine western therapy was better than routine western therapy alone for improving life quality (MD 9.48, 95% CI 8.34–10.63, $P < .00001$, $I^2 = 2\%$) [35,38,51] (Fig. 6).

One trial showed that the effect of DZXX injection plus routine western therapy and rehabilitation was better than routine western therapy plus rehabilitation for improving quality of life (MD 11.00, 95% CI 4.46–17.54, $P = .0010$).[49]

3.4.2.2. Response rates. Eighteen trialsincluding 1960 participants evaluated response rates (divided into 5 grades from

Table 1

Characteristics of included studies.

Study ID	Sample size (T / C)	Age, years	Disease course	Intervention	Control	Treatment course (d)	Outcome measures
An and Hao, 2013[30]	120 (60/60)	T:38–74/C:41–75	1–7d	DZXX +RWT,30 mL,250 mL0.9%NS, ivgtt, Qd	RWT	14	NDS,RR
Chen, 2014 [31]	316 (158/158)	38–81	6.25±1.29d	DZXX +RWT,40 mL,150 mL0.9%NS, ivgtt,Qd	RWT	28	RR;ADR
Hou, 2014[32]	40 (20/20)	T:42–88/C:49–81	NR	DZXX +RWT,30 mL,250 mLNS,ivgtt, Qd	RWT	7	NIHSS
Huang et al, 2005[33]	60 (30/30)	T:50–82/C:53–91	T:1h-1w/C:1.5h-1w	DZXX +RWT,40 mL,250 mLNS/5%GS, ivgtt, Qd	RWT	14	NDS,RR
Huang and Yuan, 2004[34]	119 (60/59)	T:45–76/C:44–75	T:1–27h/C:1–26h	DZXX, 40 mg,50 g/L GS 500 mL,ivgtt, Qd	GI	14	RR
Jin and Luo, 2013[35]	60 (30/30)	T:62.8±7.3/C:63.9 ±8.4	NR	DZXX +RWT,20–40 mL,500 mL0.9% NS,ivgtt,Qd	RWT	120	BI
Li and Yan, 2005[36]	80 (40/40)	T:45–71/C:47–69	T:33.24±5.68h/ C:31.35±6.45h	DZXX +RWT,40 mL,250 mLNS, ivgtt, Qd	RWT	14	NDS,RR,ADE/ADR
Li, 2009[37]	160 (80/80)	T:45–74/C:46–73	T:2–22h/C:2–23h	DZXX +RWT,40 mL,250 mL5%GS, ivgtt, Qd	RWT	14	RR
Lin, 2014[38]	136 (68/68)	T:62.53±9.35/ C:63.22±8.41	NR	RWT+DZXX,40 mL,ivgtt, Qd	RWT	14	NIHSS, BI
Lin, 2012[39]	39 (18/21)	T:46–79/C:45–80	NR	DZXX +RWT,30 mL,250 mLNS,ivgtt, Qd	RWT	14	NIHSS
Qian, 2003[40]	76 (38/38)	T:57.1±15.8/ C:56.9±16.1	T:1.4±0.7d/C:1.3 ±0.9d	DZXX +RWT,40 mL,250 mLNS/5%GS, ivgtt,Qd	RWT	35	RR
Wang, 2015[41]	80 (40/40)	T:47–68/C:48–70	T:1–13d/C:1–15d	DZXX +RWT,40 mL,250 mL0.9%NS, ivgtt, Qd	RWT	14	RR
Wu et al, 2006[42]	80 (40/40)	T:45–78/C:42–79	NR	DZXX +RWT,30 mL,ivgtt, Qd	RWT	20	RR
Xu et al, 2013[43]	70 (38/32)	T:63.6±5.2/C:64.5 ±3.0	NR	DZXX +RWT, 40 mL,250–500 mL0.9%NS,ivgtt, Qd	RWT	14	NIHSS,RR, ADE
Yang et al, 2011[44]	145 (74/71)	T:64.58±9.77/ C:66.35±12.49	NR	DZXX +RWT,30 mL,250 mLNS, ivgtt, Qd	RWT	14	NDS,RR
Yang and Wang, 2015[45]	96 (48/48)	T:59.7±10.85/ C:60.4±11.62	NR	DZXX +RWT, 40 mL,250 mLNS,ivgtt, Qd	RWT	14	RR
You et al, 2014[46]	86 (43/43)	60–82	0–72h	DZXX +RWT,40 mL,250 mLNS,ivgtt, Qd	RWT	14	RR
Zhao, 2009[47]	105 (53/52)	NR	NR	DZXX +RWT,30 mL,250 mLNS, ivgtt, Qd	RWT	14	NDS,RR
Zhen et al, 2012[48]	56 (28/28)	T:43–75/C:45–75	0–72h	DZXX +RWT,40 mL,250 mL0.9%NS, ivgtt,Qd	RWT	14	NIHSS
Zhen et al, 2010[49]	66 (35/31)	T:40–70/C:42–69	T:3h-7d/C:5h-5d	DZXX +RWT+RE,40 mL,250 mL0.9% NS,ivgtt,Qd	RWT+RE	28	NDS,RR,BI
Zhou et al, 2011[50]	81 (42/39)	T:62.7±12.8/ C:61.8±11.5	NR	DZXX +RWT,30 mL,250 mL0.9%NS, ivgtt,Qd	RWT	15	RR
Miao and Chen, 2016[51]	84 (42/42)	35–80	1–10d	DZXX +RWT,40 mL,250 mL0.9%NS, ivgtt,Qd	RWT	14	NIHSS,RR, BI
Zhang, 2015[52]	136 (68/68)	T:43–78/C:46–75	T:3.19±2.74d/ C:3.27±2.59d	DZXX +RWT,30 mL,250 mL0.9%NS, ivgtt,Bid	RWT	14	RR

ADE=adverse drug events, ADR=adverse drug reactions, BI=Barthel index, C=control group, DZXX=Dengzhanxixin injection, GI=Gegensu injection, NDS=Nerve Deficiency Scale, NIHSS=National Institutes of Health Stroke Scale, NR=not reported, RE=rehabilitation, RR=response rates, RWT=routine western therapy, T=treatment group.

deterioration or unchanged to cure), and we converted these outcomes to dichotomous data.[30,31,33,34,36,37,40–47,49–52]

Sixteen trials showed a statistically significant benefit compared DZXX injection plus routine western therapy with routine western therapy alone for improving response rates (RR 1.20, 95% CI 1.15–1.25, $P<.00001$, $I^2=0\%$)[30,31,33,36,37,40–47,50–52] (Fig. 7).

One trial showed that DZXX injection was better than Gegensu injection for improving response rates (RR 1.49, 95% CI 1.24–1.79, $P<.0001$).[34]

However, DZXX injection plus routine western therapy and rehabilitation showed no difference for improving response rates compared with routine western therapy plus rehabilitation (RR 1.06, 95% CI 0.87–1.28, $P=.58$).[49]

3.4.2.3. Safety. One trial reported that 3 participants in the DZXX injection group and 4 participants in the control group had adverse drug reactions (ADR) of skin purpura,[36] which disappeared after all the treatment withdrawal. In addition, all the participants had adverse drug events (ADE) of fibrinogen decrease in both experimental and control groups. But no more details had been mentioned about these ADE in this trial.

One trial reported that in both experimental and control groups, 4 participants had alanine transaminase (ALT) increase

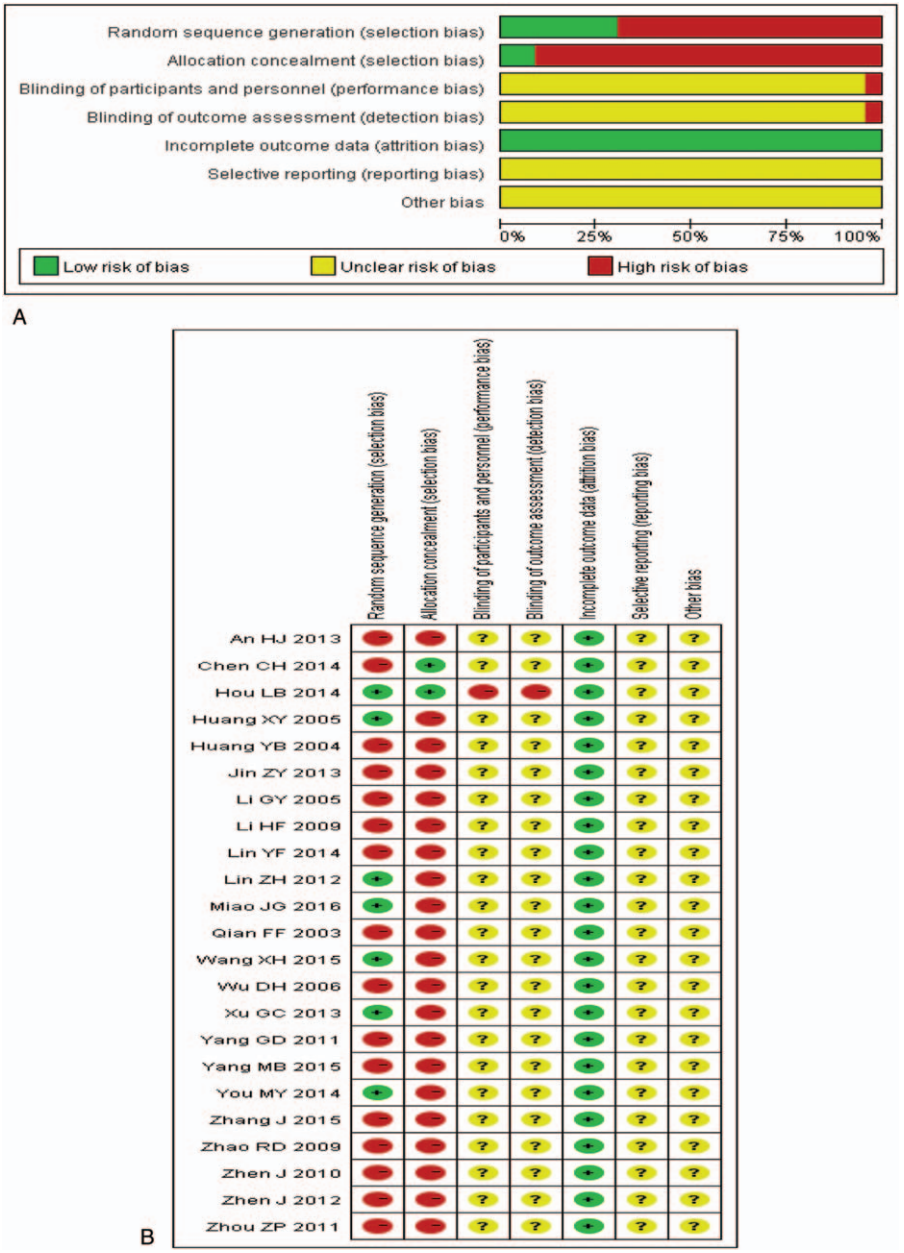

Figure 2. (A) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (B) Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

during the treatment duration.[43] However, as this trial did not mention any other details, we regarded this as ADE.

One trial reported that 5 patients in the experimental group appeared ADR of face flushing; 8 patients appeared ADR of nausea and dyspepsia.[31] All these symptoms disappeared after slowing the infusion speed. In the control group, 6 participants also had ADR of dyspepsia, rash and dizziness; 3 patients had ADR of dizziness and nausea. All these symptoms disappeared after the treatment duration without any other treatment.

The other 20 trials did not mention any ADE/ADR. None of serious ADE/ADR was reported in the 23 trials.

3.5. Publication bias

There were 18 trials evaluating response rates in 1 meta-analysis, which were applied to a funnel plot. The funnel plot was not symmetric, which indicated reporting bias existed. In these 18 trials, most of them had small samples and none of them reported sample size estimation methods. In addition, all the trials were published in Chinese. The detail of funnel plot of different comparisons evaluating response rates is showed in Fig. 8.

4. Discussion

The role of Traditional Chinese Medicine (TCM) in health care and disease control is being increasingly recognized, including Traditional Chinese Medicine injections (TCM injections).[53] Most of TCM injections are the preparations extracted from different Chinese herbs, except that a few are extracted from animals. They have been wildly used in mainland China to manage different diseases and have become one of the character-

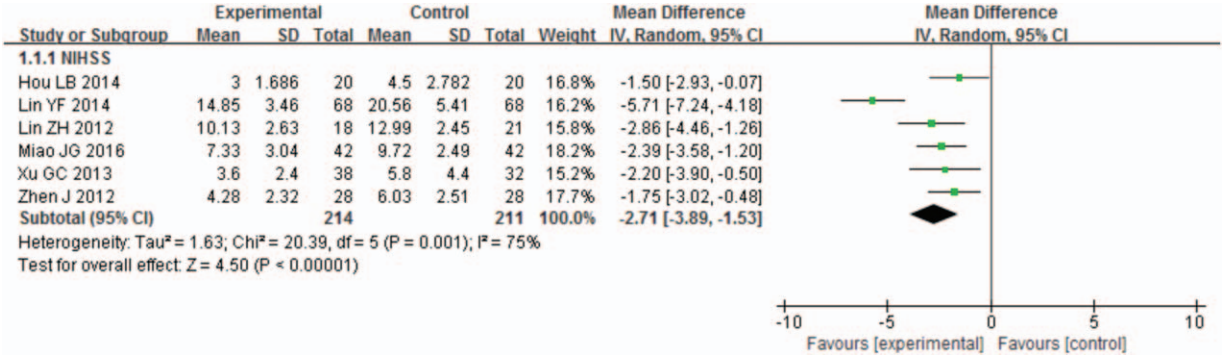

Figure 3. Forest plot of the effect of DZXX injection plus routine western therapy versus routine western therapy on NIHSS using the random model. DZXX = Dengzhanxixin, NIHSS = National Institutes of Health Stroke Scale.

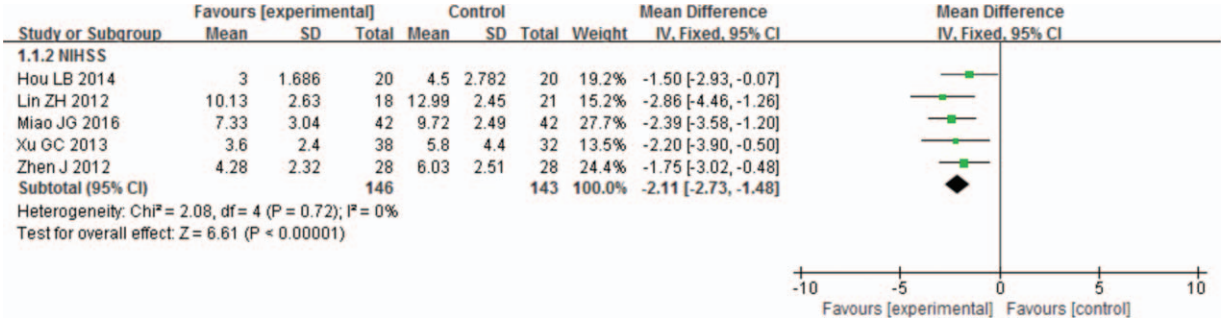

Figure 4. Forest plot of the effect of DZXX injection plus routine western therapy versus routine western therapy on NIHSS using the fixed model. DZXX = Dengzhanxixin, NIHSS = National Institutes of Health Stroke Scale.

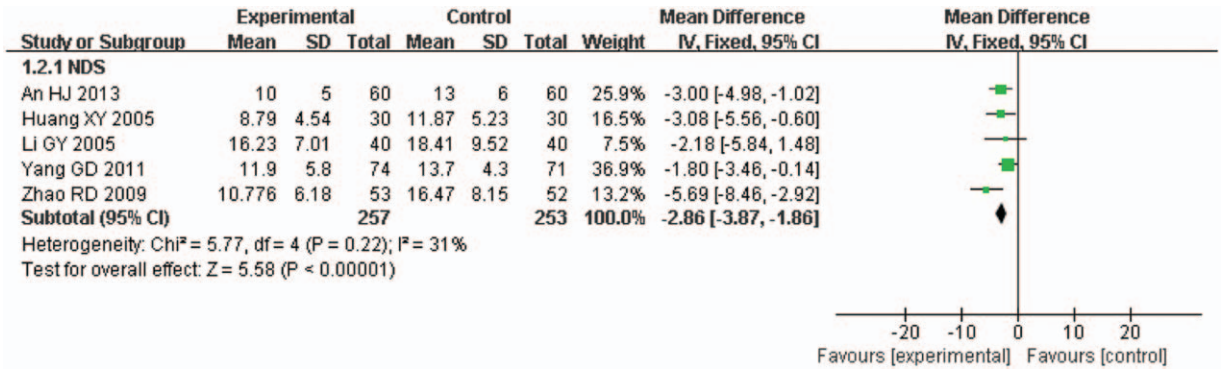

Figure 5. Forest plot of the effect of DZXX injection plus routine western therapy versus routine western therapy on NDS using the fixed model. DZXX = Dengzhanxixin, NDS = Nerve Deficiency Scale.

istics of modern Chinese clinical practice. DZXX injection is one of TCM injections used widely to treat cardio-cerebral vascular diseases in both western and TCM hospitals in mainland China. However, due to the adverse drug reactions (ADR) caused by different TCM injections,[54,55] the safety management of TCM injections is becoming increasingly important.[51] In recent years, China Food and Drug Administration advocated active drug surveillance on TCM injections, which has made remarkable achievements.[53] DZXX injection has been approved for using in clinic for nearly 6 years. Although the previous study in Chinese had assessed DZXX injection for cerebral infarction, their evidence was too weak to draw any definitive conclusion.[26]

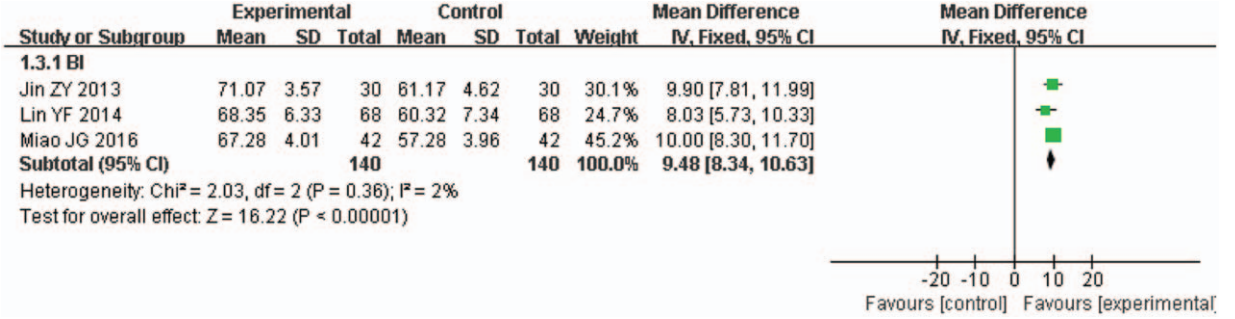

Figure 6. Forest plot of the effect of DZXX injection plus routine western therapy versus routine western therapy on BI using the fixed model. BI = Barthel index, DZXX = Dengzhanxixin.

According to the meta-analysis of this review, we will provide the latest investigation of the effectiveness and safety of DZXX injection for cerebral infarction.

4.1. Summary of therapy effectiveness

With evaluating the reduction of neurologic deficit using National Institutes of Health Stroke Scale (NIHSS) or Nerve Deficiency Scale (NDS), some potential positive therapeutic effects of DZXX injection could be found. But all the 12 trials did this measurement no more than 30 days. Pre-study suggested that the neurologic deficit would recover quickly in the first 90 days after the onset of stroke and the best time to measure the neurologic deficit was 3 months after stroke onset.[57] However, none of the included trials measured neurologic deficit 3 months after the symptom onset. Therefore, the evidence on the effectiveness of DZXX injection in reducing neurologic deficit was indefinite. Future studies should attach more importance to the long-term effect of DZXX injection for cerebral infraction.

Meta-analysis of the quality of life indicated that DZXX injection had an effect for cerebral infraction in improving life quality. But as only 4 trials did this measurement in this review, the evidence of this benefit may be insufficient. Therefore, further studies should attach importance to patients' quality of life.

After evaluating the improvement of response rates using the percentage of neurological deficit scores reduced rate, DZXX injection may have some therapeutic value for improving response rates, which was consistent with the conclusions of another trial.[26] Another preparation called Dengzhanhua injection (DZH) is also extracted from erigeron breviscapus. A cochrane systematic review of DZH showed that it was effective for acute cerebral infarction in improving response rates.[58] However, due to the high risks of bias of the included trials, the evidence may be insufficient. In addition, although the response

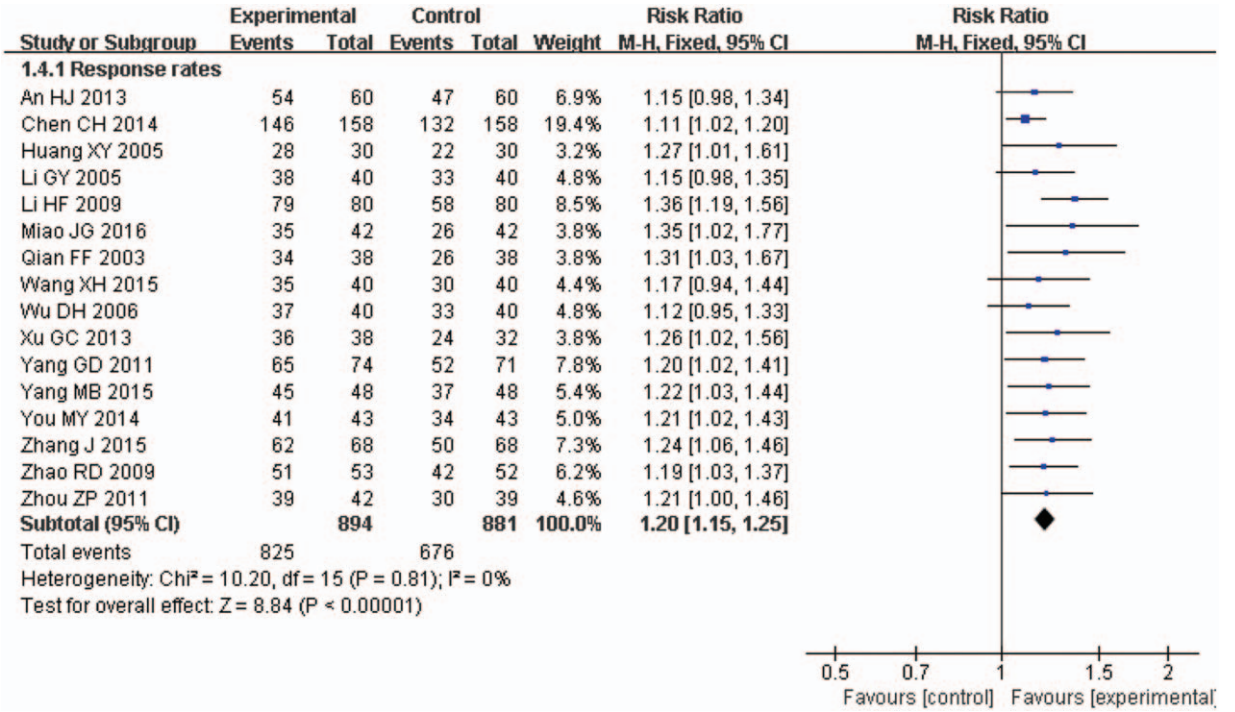

Figure 7. Forest plot of the effect of DZXX injection plus routine western therapy versus routine western therapy on response rates using the fixed model. DZXX = Dengzhanxixin.

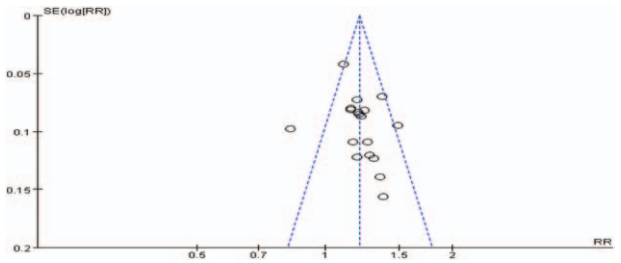

Figure 8. Funnel plot of different comparisons evaluated response rates.

rates were measured according to the percentage of neurological deficit scores reduced rate, not all the trials provided the exact scores and reduced rate. Therefore, we were not sure whether their measuring procedures were objective or not. Moreover, researchers and participants might have been aware of the therapeutic interventions as most trials did not describe the allocation concealment and blind method. Those would also bring some other potential bias.

However, in this review, we were not able to obtain evidence of whether DZXX injection could reduce the death and disability rates or not. Cerebral infarction was one of the leading causes of death over the world.[2–4] American Heart Association (AHA) and American Stroke Association (ASA) suggested that the death and disability should be an important outcome measure for cerebral infarction.[56] However, none of the trials applied this outcome measure. In addition, most studies were prone to reporting positive results without mentioning any negative results such as death and disability. Therefore, future researches should pay more attention to evaluate the effect of DZXX injection for cerebral infarction in reducing death and disability rates. Also, TCM researchers should report all results without avoiding negative results.

Based on the meta-analysis, we suggested that DZXX injection might have potential therapeutic effects for reducing neurologic deficit, improving the quality of life and response rates. But large-scale and high-quality clinical trials were still needed to provide more strong evidence.

4.2. Summary of therapy safety

In this systematic review, several adverse drug events (ADE) were reported, including decrease of fibrinogen and increase of alanine transaminase (ALT). There also appeared several adverse drug reactions (ADR), including face flushing, nausea, dyspepsia, rash, dizziness, and skin purpura. They were all slight symptoms and disappeared after treatment withdrawal, or after slowing the infusion speed, or without any other treatment. All the ADR had already been listed on the medication direction of DZXX injection. No serious ADE/ADR was mentioned. However, due to the high risks of bias of these trials, we could not draw any definitive conclusion about the exact safety. What's more, as only 2 trials mentioned the relevant information of follow-up, the long-term safety of DZXX injection remained uncertain.

4.3. Summary of methodological quality

Seven trials described the method of random sequence generation, but no trials provided the details of the randomization procedures. Also, only 2 trials performed allocation concealment. These may lead to selection bias. There was no information relating to the method of blinding, which may lead to performance and detection bias. Moreover, the information of sample size calculation, dropouts account, and intention-to-treat analysis were also unclear. Inadequate reporting of these items may lead to other bias. In addition, all the trials were published in China, which may lead to publication bias. Therefore, these risks of bias may impact the evidence to some extent.

4.4. Limitations

First, because of the language barrier, we only searched databases in Chinese and English; Korean and Japanese databases were not covered. Thus, some relevant clinical trials may be missed, which may influence the final conclusion. In addition, we did not contact with pharmaceutical factories to search relevant gray literatures to broaden our searching. Thus, some relevant studies may be lost. Second, although we had tried our best to contact with the first or corresponding authors to obtain more detailed information, a lot of missing information still remained unclear. This may impact our judgment of the methodological quality and brought some potential bias. Third, all the included trials were conducted in China, and most of them had selection, performance, detection, and other bias. These high risks of bias may influence our conclusions. Finally, as only 2 trials mentioned follow-up, the long-term effectiveness, and safety of DZXX injection still remained unobtainable.

5. Conclusion

According to the meta-analysis of this systematic review, DZXX injection as a complementary therapy may have some potential therapeutic effect for reducing the neurologic deficit, improving patients' quality of life and response rates. In addition, DZXX injection may be safe for cerebral infarction. But due to the high risk of bias of included trials, we cannot draw any definite conclusions. Higher methodological quality trials are still needed in further clinical research. If the positive effects and safety of DZXX injection can be firmly convinced, it will provide valuable implications for clinical practice.

References

[1] Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2014;129:e28–92.
[2] Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 2014;45:2160–236.
[3] Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870–947.
[4] Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754–832.
[5] Li X, Peng LY, Zhang DS, et al. The relationships between chemical and genetic differentiation and environmental factors across the distribution of Erigeron breviscapus (Asteraceae). PLoS One 2013;8:e74490.
[6] Yin S, Wang ZF, Duan JG, et al. Extraction (DSX) from Erigeron breviscapus modulates outward potassium currents in rat retinal ganglion cells. Int J Ophthalmol 2015;8:1101–6.
[7] Li X, Song K, Yang J, et al. Isolation and characterization of 11 new microsatellite loci in Erigeron breviscapus (Asteraceae), an important Chinese traditional herb. Int J Mol Sci 2011;12:7265–70.
[8] Lu XJ, Zhang FW, Cheng L, et al. Effect on multifocal electroretinogram in persistently elevated intraocular pressure by erigeron breviscapus extract. Int J Ophthalmol 2011;4:349–52.

[9] Liu H, Yang X, Ren T, et al. Effects of Erigeron breviscapus ethanol extract on neuronal oxidative injury induced by superoxide radical. Fitoterapia 2005;76:666–70.
[10] Chen X, Jin J, Chen Y, et al. Effect of scutellarin on the metabolism and pharmacokinetics of clopidogrel in rats. Biopharm Drug Dispos 2015;36:64–8.
[11] Chu QC, Wu T, Fu L, et al. Simultaneous determination of active ingredients in Erigeron breviscapus (Vant.) Hand-Mazz. by capillary electrophoresis with electrochemical detection. J Pharm Biomed Anal 2005;37:535–41.
[12] Wang SX, Guo H, Hu LM, et al. Caffeic acid ester fraction from Erigeron breviscapus inhibits microglial activation and provides neuroprotection. Chin J Integr Med 2012;18:437–44.
[13] Gao M, Huang W, RoyChowdhury M, et al. Microwave-assisted extraction of scutellarin from Erigeron breviscapus Hand-Mazz and its determination by high-performance liquid chromatography. Analytica Chimica Acta 2007;591:161–6.
[14] Luo LH, Kim HJ, Nguyen DH, et al. Depigmentation of melanocytes by (2Z,8Z)-matricaria acid methyl ester isolated from Erigeron breviscapus. Bill Pharm Bull 2009;32:1091–4.
[15] Gao M, Huang W, Liu CZ. Separation of scutellarin from crude extracts of Erigeron breviscapus (vant.) Hand. Mazz. by macroporous resins. J Chromatogr B Analyt Technol Biomed Life Sci 2007;858:22–6.
[16] The Pharmacopoeia Commission of PRC. Pharmacopoeia of the People's Republic of China (version 2005, vol. 1). Beijing Chemical Industry Press: Beijing 2005.
[17] Lin LL, Liu AJ, Liu JG, et al. Protective effects of scutellarin and breviscapine on brain and heart ischemia in rats. J Cardiovasc Pharmacol 2007;50:327–32.
[18] Gao M, Gu M, Liu CZ. Two-step purification of scutellarin from Erigeron breviscapus (vant.) Hand. Mazz. by high-speed counter-current chromatography. J Chromatogr B Analyt Technol Biomed Life Sci 2006;838:139–43.
[19] Zhang HF, Hu XM, Wang LX, et al. Protective effects of scutellarin against cerebral ischemia in rats: evidence for inhibition of the apoptosis-inducing factor pathway. Planta Med 2009;75:121–6.
[20] Wang Z, Yu JG, Wu BJ, et al. Scutellarin protects cardiomyocyte ischemia-reperfusion injury by reducing apoptosis and oxidative stress. Life Sci 2016;157:200–7.
[21] Chai L, Guo H, Li H, et al. Scutellarin and caffeic acid ester fraction, active components of Dengzhanxixin injection, upregulate neurotrophins synthesis and release in hypoxia/reoxygenation rat astrocytes. J Ethnopharmacol 2013;150:100–7.
[22] Liu H, Yang X, Tang R, et al. Effect of scutellarin on nitricoxide production in early stages of neuron damage induced by hydrogen peroxide. Pharmacol Res 2005;51:205–10.
[23] Hong H, Liu GQ. Protection against hydrogen peroxide-induced cytotoxicity in PC12 cells by scutellarin. Life Sci 2004;74:2959–73.
[24] Hu XM, Zhou MM, Zeng FD. Neuroprotective effects of scutellarin on rat neuronal damage induced by cerebral ischemia/reperfusion. Acta Pharmacol Sin 2005;26:1454–9.
[25] Guo H, Hu LM, Wang SX, et al. Neuroprotective effects of scutellarin against hypoxic-ischemic-induced cerebral injury via augmentation of antioxidant defense capacity. Chin J Physiol 2011;54:399–405.
[26] Xiong XJ, Zhong S, Wang JT, et al. Meta-analysis of lamp asarum in treatment of cerebral infarction (Chinese). J Liaoning Univ TCM 2014;16:141–3.
[27] Moher D, Liberati A, Tetzlaff J, et al. The PRISMA Group (2009) preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;7:e1000097.
[28] Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 2007;7:10.
[29] Higgins JPT, Green S. The Cochrane CollaborationCochrane Handbook for Systematic Reviews of Interventions Version 5.1 ([updated March 2011). 2011;Available from www.cochrane–handbook.org.
[30] An HJ, Hao SJ. Clinical observation of Dengzhanxixin injection for acute cerebral infarction (Chinese). Shanxi Med J 2013;42:1410–1.
[31] Chen CH. Clinical effect observation of sodium ozagrel combined with DengzhanXixin in the treatment of progressive cerebral infarction (Chinese). China Mod Med 2014;21:73–5.
[32] Hou LB. Fleabane Injection on blood stasis in patients with acute cerebral infarction VEGF, MMP-9 and EPOs standards (Chinese). Guangzhou Univ Chin Med 2014.
[33] Huang XY, Ding YJ, Fang HW. Study of fleabane injection on acute brain infarction (Chinese). Mod J Integr Trad Chin Western Med 2005;14:1964–5.
[34] Huang YB, Yuan JX. Observation on the efficacy of Dengzhanxixin injection on 60 acute cerebral infarction patients (Chinese). Guangdong Med J 2004;25:888.
[35] Jin ZY, Luo YY. Erigeron injection in treatment of ischemic stroke and its influence on serum hs-CRP and UA levels (Chinese). Chin Arch Trad Chin Med 2013;31:1390–2.
[36] Li GY, Yan XY. Observation of clinical efficacy of Dengzhanxixin combined with low molecular heparin for acute cerebral infarction (Chinese). Chin J Misdiagnostics 2005;5:3316–7.
[37] Li HF. Observation on the clinical efficacy of Dengzhanxixin injection on 80 acute cerebral infarction patients (Chinese). J Emerg Tradit Chin Med 2009;18:1991–2.
[38] Lin YF. Observation on the clinical efficacy of vinpocetine combined with fleabane on non-acute cerebral infarction (Chinese). Chin J Pract Nervous Dis 2014;17:35–7.
[39] Lin ZH. Changes of plasma PaO2 and PaCO2 in patients treated by Dengzhanxixin injection with acute cerebral infarction (Chinese). Guangdong Med J 2012;33:2339–40.
[40] Qian FF. Observation on the efficacy of Dengzhanxiin injection assisted cerebrolysin for 38 acute cerebral infarction patients (Chinese). Chin J Integr Tradit Western Med Intensive Crit Care 2003;10:298.
[41] Wang XH. Observation on the clinical efficacy of Dengzhanxixin injection in improving brain blood circulation for cerebral infraction patients (Chinese). J Chin Med 2015;47:23–4.
[42] Wu DH, Liu DJ, Zeng H. Effect of Dengzhanxixin injection for cerebral infarction patients and the influence on hemorheology (Chinese). Guangdong Med J 2006;27:1088–9.
[43] Xu GC, Chen HZ, Zhang J, et al. Observation on efficacy of Dengzhanxiixn combined with Butylphthalide Soft Capsules for 38progressive cerebral infarction patients (Chinese). J Guiyang Coll Tradit Chin Med 2013;35:156–8.
[44] Yang GD, Du LL, Wang SL, et al. Clinical observasion of Dengzhanxixin combined with edaravone on 145 acute cerebral infarction patients (Chinese). Guangdong Med J 2011;32:2854–6.
[45] Yang MB, Wang EC. To observe the effect of breviscapine combined with sodium ozagrel in treatment of progressive cerebral infarction. Mod Diagn Treat 2015;26:3160–1.
[46] You MY, Cai YH, Wang SJ, et al. The effect of erigeron breviscapus injection on endothelin and nitric oxide levels of senior patients with cerebral infarction (Chinese). J Guiyang Med Coll 2014;39:333–5.
[47] Zhao RD. Observation on efficacy of sodium ozagrel combined with Dengzhanxixin for 53 progressive cerebral infarction patients (Chinese). China Practical Med 2009;4:147–8.
[48] Zhen J, Lai JY, Dong J, et al. Clinical observation on BDNF expression with Dengzhanxiixn injection in acute cerebral infarction patients (Chinese). J Chin Med Mater 2012;35:670–2.
[49] Zhen J, Li ZD, Yang YJ, et al. The treatment of Dengzhanxixin combined with rehabilitation training for 35 acute cerebral infarction patients (Chinese). Chin J Practical Med 2010;37:46–7.
[50] Zhou ZP, Yang GS, Wang AY. Effect of Erigeron Injection on MMP-9 in patient with acute cerebral infarction (Chinese). Mod Prev Med 2011;38:2660–1.
[51] Miao JG, Chen SM. Clinical study on Dengzhanxixin injection combined with citicoline sodium capsules in treatment of cerebral infarction (Chinese). Drugs Clin 2016;31:41–4.
[52] Zhang J. Effect of Dengzhanxixin Injection on the stability of carotid plaques and MMP-9 in patient with acute cerebral infarction (Chinese). Mod J Integr Tradit Chin Western Med 2015;24:3513–5.
[53] Zhang L, Yan JB, Liu XM, et al. Pharmacovigilance practice and risk control of traditional Chinese medicine drugs in China: current status and future perspective. J Ethnopharmacol 2012;140:519–25.
[54] Hu J, Shang HC, Li J, et al. Adverse drug reactions linked to Ciwujia injection: a systematic review of 521 cases. J Evid Based Med 2010;3:37–43.
[55] SFDA. Notice on Suspension of the manufacturing approval applications and clinical use of Yuxingcao injection and 7 other related injections. SFDA-SAFETY No. 218. 2006.
[56] Katzan IL, Spertus J, Bettger JP, et al. Risk adjustment of ischemic stroke outcomes for comparing hospital performance: a statement for health-care professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:918–44.
[57] Kotila M, Waltimo O, Niemi ML, et al. The profile of recovery from stroke and factors influencing outcome. Stroke 1984;15:1039–44.
[58] Cao WZ, Liu WM, Wu TX, et al. Dengzhanhua preparations for acute cerebral infarction. Cochrane Database Syst Rev 2008;4:CD005568. doi: 10.1002/14651858.CD005568.pub2.