The Add-on Effects of Danhong Injection Among Patients With Ischemic Stroke Receiving Western Medicines: a Systematic Review and Meta-analysis

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Abstract

Background: Danhong injection is widely used for treating ischemic stroke in China. However, its effects on ischemic stroke patients when adding to western medicines (i.e., the add-on effect) were not well established.

Methods: We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) and three Chinese databases from inception to 20 July 2020 to identify randomized clinical trials (RCTs) that assessed the effects of Danhong injection as an add-on therapy in patients with ischemic stroke. Pairs of trained reviewers independently screened for eligible studies, assessed risk of bias, and extracted data. The outcomes were National Institutes of Health Stroke Scale Score (NIHSS), Barthel index, activities of daily living (ADL), total cholesterol and homocysteine (Hcy).

Results: 67 RCTs of 6594 patients with varying risk of bias were included. Compared with western medicine alone, the addition of Danhong injection to western medicine significantly lowered NIHSS score (45 RCTs with 4565 patients; MD -4.21, 95% CI -4.96–3.46), total cholesterol (10 trials with 1019 patients; MD -1.14 mmol/L, 95% CI -1.57–0.72) and Hcy (4 trials with 392 patients; MD -3.54 μ mol/L, 95% CI -4.38–2.07). The addition of Danhong also increased Barthel index (14 trials with 1270 patients; MD 8.71, 95% CI 3.68–13.74) and ADL (12 trials with 1114 patients; MD 14.48, 95% CI 9.04–19.92) scores. Subgroup analyses showed differential effects in average cerebral blood flow rate by mean age of patients (<60 years: MD 0.74 cm/s, 95% CI 0.29–1.19; $\geq$ 60 years: MD 4.09 cm/s, 95% CI 2.02–6.16; interaction $P=0.002$) and NIHSS score by type of baseline western medicines (interaction $P<0.00001$).

Conclusions: The addition of Danhong injection to western medicine may improve neurological function, self-care ability and blood lipids of ischemic stroke patients. Furthermore, patients with different age and receiving different baseline western medicines may have different benefits in hemodynamic status and neurological function, respectively.

Background

Ischemic stroke, defined as all thromboembolic and atherosclerotic events resulting in compromised blood flow to cerebral tissue and subsequent infarction[1], is a leading cause of death and long-term disability worldwide. Current recommendations for patients with ischemic stroke include antiplatelet, anticoagulants, volume expansion, vasodilators, neuroprotective agents, intravenous thrombolysis and mechanical thrombectomy[2]. In spite of these, patients with ischemic stroke continue to suffer from high risk of disability and recurrence, and add-on treatments are often necessary [3].

Danhong injection is a Chinese patent medicine extracted from *Salviae Miltiorrhizae* (Danshen in Chinese) and *Flos Carthami* (Honghua in Chinese), which improve microcirculation, prevent platelet aggregation, decrease plasma viscosity and boost the activity of fibrinogen dissolved. Danhong injection has been widely used for cardiovascular and cerebrovascular diseases [4, 5]. Evidence from randomized clinical trials (RCTs) with small sample sizes showed that the combination of Danhong injection and western medicine was effective in improving total efficiency and hemodynamic outcomes among ischemic stroke patients[6–8]. Three systematic reviews also found that, compared with other Chinese herbal injections (e.g., Shuxuening injection), Danhong injection appeared to be beneficial in total clinical effectiveness rate and neurologic impairment [9–11]. However, these reviews included a relatively small number of RCTs, and were limited with improper comparisons, inappropriate outcome selection and analysis, as a result of which the resulting findings and recommendations were not definitive.

Most importantly, Danhong injection is routinely used as an add-on therapy to patients with ischemic stroke receiving western medicine; its add-on effects on ischemic stroke patients still need further systematic assessment to inform current practice. Therefore, we conducted this systematic review and meta-analyses which included a significantly larger number of newly published RCTs.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[12] to conduct and report this systematic review and meta-analysis. This protocol was registered with the International Prospective Register of Systematic Reviews (CRD42022298628).

Eligibility criteria

We included randomized controlled trials (RCTs) that compared efficacy and safety of Danhong injection combined with western medicine therapy versus western medicine alone in patients with ischemic stroke. There was no limitation on the dosages and courses of treatment. Eligible studies explicitly reported outcomes data on National Institute of Health Stroke Scale (NIHSS), Fugl-Meyer Assessment, Barthel index, activities of daily living (ADL), intima-media thickness (IMT), cerebral blood flow, average cerebral blood flow rate, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), homocysteine (Hcy), D-dimer and adverse drug reactions (ADRs)/adverse drug events (ADEs). We excluded RCTs that involved other Chinese herbal medicine.

Literature search

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure Database (CNKI), Wanfang database and Chinese Scientific Journal Database to identify relevant studies from inception to 20 July, 2020. The subject terms (e.g., MeSH terms) and free-text words were used to search for potentially eligible studies, and language restriction was imposed in English and Chinese. The specific retrieval strategy was provided in Appendix 1.

Study process

Two reviewers (Yu Ma and Ke Deng) independently screened titles/abstracts and full texts for eligibility, assessed risk of bias, and collected data from each eligible study using a prespecified form. Reviewers dealt with discrepancies through discussion or, if required, adjudication by a third researcher (Ling Li).

Risk of bias assessment

We used the modified Cochrane Risk of Bias Assessment Tool to assess risk of bias of included RCTs[13]. The items contained random 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. The judgment for each item included low/high/unclear risk of bias.

Data extraction

We collected the following information from included RCTs: general study characteristics (first author, year of publication, total number of patients randomized); patients' characteristics (age, sex); intervention and control characteristics (medications used across groups (baseline treatment), details of Danhong injection treatment and control group (dose, type of western medicines used), and course of treatment); and outcomes data (mean and standard deviation of continuous variables, and number of patients occurring adverse drug reactions/adverse drug events in each group).

Statistical Analysis

The mean difference (MD) was calculated for continuous variables; effects of each outcome were estimated with 95% confidence intervals (95% CIs). We used the Cochran's Chi-squared test and the I^2 statistic to examine statistical heterogeneity among RCTs. Meta-analysis was calculated by random-effects model.

We explored sources of heterogeneity with three prespecified subgroup hypotheses: length of treatment (≤ 2 vs > 2 weeks; larger effect in trials with longer treatment), mean age of patients (< 60 vs ≥ 60 years old; larger effect in trials with younger patients) and types of baseline western medicine treatment (conventional therapy vs intravenous thrombolysis vs anti-platelet aggregation vs dilation of blood vessels vs statins vs neuroprotective agents vs other therapies).

In addition, we used the funnel plot and Egger's test for examining publication bias [14]. We also used the Duval and Tweedie trim-and-fill method for exploring the influence of a single trial on publication bias [15].

Results

As shown in Figure 1, our search retrieved 3080 citations during the initial detection by the search strategy. After screening titles and abstracts, 671 reports were included for full further text screening. Sixty-seven RCTs were eligible for meta-analysis ultimately.

These 67 RCTs[6–8, 16–79] were comprised of 3293 patients in the combination treatment group and 3301 patients in the control group. The mean age of included patients ranged from 42.2 to 71.5 years, and the sample size ranged from 40 to 300 patients. All

RCTs were conducted among Chinese populations in China. Patients in the combination treatment group received Danhong injection 10-40 ml once or twice daily (Table 1).

Table 1
Baseline characteristics of included randomized controlled trials

Author (year)	Phase of disease	Sample size, EG/CG	Mean age (year)		Interventions		Dosages of Danhong Injection	Course	Outcomes
			EG	CG	EG	CG			
Cao 2020	Acute phase	49/49	63.11	62.47	rt-PA, DHI	rt-PA	Once daily, 20ml	14d	(1) (12) (14)
Cheng 2019	NR	20/20	58.40	56.10	Edaravone, DHI	Edaravone	Once daily, 30ml	14d	(14)
Zhang 2019	NR	55/55	53.80	53.20	Clopidogrel, DHI	Clopidogrel	Once daily, 30mg	28d	(14)
Deng 2019	NR	50/50	63.77	63.28	Edaravone, DHI	Edaravone	Once or twice daily, 20-40ml	14d	(1)
Li 2017	Acute phase	40/40	66.50	66.50	Edaravone, DHI	Edaravone	Once daily, 30ml	14d	(1) (4) (14)
Li 2017	Acute phase	30/30	61.48	62.03	Ozagrel Sodium, DHI	Ozagrel Sodium	Once daily, 40ml	14d	(1) (8) (9) (10) (11)
Wang 2016	Acute phase	35/37	NR	NR	Aspirin, DHI	Aspirin	Once daily, 40ml	14d	(3) (14)
Zhang 2015	Acute phase	50/50	58.60	60.30	Vinpocetine, DHI	Vinpocetine	Once daily, 30ml	14d	(1)
Yin 2014	Acute phase	60/60	52.80	53.10	Hyperbaric Oxygen, DHI	Hyperbaric Oxygen	Twice daily, 20ml	56d	(1)
Shen 2012	Acute phase	36/36	NR	NR	Edaravone, DHI	Edaravone	Once daily, 30ml	14d	(1) (4) (14)
Zhuang 2020	NR	56/56	61.11	61.15	CT, DHI	CT	Once daily, 30ml	14d	(1) (14)
Liu 2018	NR	83/83	NR	NR	Edaravone, DHI	Edaravone	Once daily, 20-40ml	14d	(1) (14)
Shi 2018	Acute phase	40/40	64.00	65.00	Alprostadil, DHI	Alprostadil	Once daily, 40ml	14d	(1) (4)
Yang 2018	Acute phase	47/47	NR	NR	Edaravone, DHI	Edaravone	Once daily, 40ml	14d	(1) (3) (8) (9)
Ma 2017	NR	40/42	60.01	65.26	CT, DHI	CT	Once daily, 20ml	14d	(1) (2) (13)

CG= control group; EG=experiment group (Danhong Injection group); NR=not reported; CT=conventional treatment.

Outcomes: (1)=NIHSS, (2)=Fugl-Meyer Assessment, (3)=Barthel index, (4)=ADL, (5)=IMT, (6)=cerebral blood flow, (7)=average cerebral blood flow rate, (8)=total cholesterol, (9)=triglycerides, (10)=HDL, (11)=LDL, (12)=Hcy, (13)=D-dimer, (14)=ADRs.

Author (year)	Phase of disease	Sample size, EG/CG	Mean age (year)		Interventions		Dosages of Danhong Injection	Course	Outcomes
			EG	CG	EG	CG			
Liu 2010	Acute phase	44/43	63.70	64.40	Fasudil Hydrochloride, DHI	Fasudil Hydrochloride	Once daily, 30ml	14d	(4) (14)
Chen 2017	NR	32/32	53.12	52.93	CT, DHI	CT	Once daily, 30ml	7d	(8)
Zhang 2018	Acute phase	54/54	61.80	60.20	Alprostadil, DHI	Alprostadil	Once daily, 30ml	14d	(1) (14)
Zhang 2017	Acute phase	45/45	68.90	69.30	Edaravone, DHI	Edaravone	Twice daily, 20ml	14d	(14)
Pen 2017	NR	39/39	NR	NR	Atorvastatin Calcium, DHI	Atorvastatin Calcium	Once daily, 10ml	14d	(5)
Fan 2018	Acute phase	35/35	49.32	50.45	CT, DHI	CT	Once daily, 40ml	14d	(1) (4)
Li 2017	Acute phase	48/48	55.76	56.37	Clopidogrel, DHI	Clopidogrel	Once daily, 30ml	14d	(1) (4) (14)
Jiang 2020	Acute phase	60/60	60.47	59.82	rt-PA, Sodium Heparin, DHI	rt-PA, Sodium Heparin	Once daily, 20ml	14d	(1) (5) (14)
Liu 2019	Acute phase	56/56	56.91	55.73	Edaravone, DHI	Edaravone	Once daily, 20mg	14d	(2) (3) (6) (7)
Liu 2017	NR	30/30	60.24	58.49	CT, DHI	CT	Once daily, 30ml	14d	(13)
Ge 2018	NR	37/37	62.13	61.52	Atorvastatin Calcium, DHI	Atorvastatin Calcium	Once daily, 20ml	14d	(1) (14)
Yun 2017	Acute phase	31/31	69.50	68.20	Aspirin, DHI	Aspirin	Once daily, 30ml	14d	(7)
Liu 2019	Acute phase	33/32	41.84	42.53	Butylphthalide soft capsules, DHI	Butylphthalide soft capsules	Once daily, 40ml	14d	(1)
Dai 2018	Acute phase	47/47	56.42	56.43	Aspirin, Nimodipine, DHI	Aspirin, Nimodipine	Twice daily, 40ml	15d	(1) (4) (8) (9)
Yang 2018	Acute phase	39/39	64.08	63.22	Atorvastatin Calcium, DHI	Atorvastatin Calcium	Once daily, 20ml	14d	(1) (3)
Li 2015	Acute phase	105/105	71.30	71.60	Edaravone, DHI	Edaravone	Once daily, 30ml	14d	(1) (8) (9)

CG= control group; EG=experiment group (Danhong Injection group); NR=not reported; CT=conventional treatment.

Outcomes: (1)=NIHSS, (2)=Fugl-Meyer Assessment, (3)=Barthel index, (4)=ADL, (5)=IMT, (6)=cerebral blood flow, (7)=average cerebral blood flow rate, (8)=total cholesterol, (9)=triglycerides, (10)=HDL, (11)=LDL, (12)=Hcy, (13)=D-dimer, (14)=ADRs.

Author (year)	Phase of disease	Sample size, EG/CG	Mean age (year)		Interventions		Dosages of Danhong Injection	Course	Outcomes
			EG	CG	EG	CG			
Li 2020	Acute phase	52/52	68.34	68.58	3-n-butylphthalide, DHI	3-n-butylphthalide	Once daily, 30ml	14d	(1) (7)
Liu 2017	Acute phase	54/55	56.83	56.94	CT, DHI	CT	Once daily, 20ml	14d	(1)
Luo 2018	Acute phase	56/56	65.40	65.10	CT, DHI	CT	Twice daily, 30ml	28d	(2) (14)
Kang 2020	Acute phase	65/60	55.42	54.95	Tirofiban Hydrochloride, Clopidogrel, Aspirin, DHI	Tirofiban Hydrochloride, Clopidogrel, Aspirin	Once daily, 20ml	14d	(1) (4) (14)
Yang 2018	Acute phase	58/58	57.86	57.09	Clopidogrel, DHI	Clopidogrel	Once daily, 30ml	14d	(1) (14)
Liu 2020	Acute phase	71/71	63.24	61.97	Edaravone, DHI	Edaravone	Once daily, 20ml	14d	(1) (3) (7)
Wang 2016	Acute phase	56/56	NR	NR	CT, DHI	CT	Once daily, 450mg	168d	(1)
Yuan 2019	Acute phase	38/38	65.50	65.39	Edaravone, DHI	Edaravone	Once daily, 40ml	14d	(1) (2) (3) (12)
Su 2012	Acute phase	38/37	61.58	63.01	CT, DHI	CT	Once daily, 40ml	14d	(8) (9) (11) (14)
Luo 2012	Acute phase	90/90	NR	NR	Ozagrel Sodium, DHI	Ozagrel Sodium	Once daily, 40ml	14d	(1)
Zou 2013	Acute phase	40/40	58.70	57.90	Vinpocetine, DHI	Vinpocetine	Once daily, 30ml	14d	(1)
Liang 2014	Acute phase	45/45	53.50	52.60	CT, DHI	CT	Once daily, 30ml	14d	(4)
Ma 2015	Acute phase	45/45	65.37	65.64	CT, DHI	CT	Once daily, 20ml	28d	(2) (3)
Fan 2015	NR	45/45	62.30	61.50	CT, DHI	CT	Once daily, 20ml	28d	(8) (9) (10) (11)
Zeng 2016	Acute phase	55/55	63.00	63.30	Edaravone, DHI	Edaravone	Once daily, 20ml	15d	(3)
Feng 2016	Acute phase	20/20	59.82	60.50	rt-PA, DHI	rt-PA	Once daily, 20ml	14d	(3) (13)
CG= control group; EG=experiment group (Danhong Injection group); NR=not reported; CT=conventional treatment.									
Outcomes: (1)=NIHSS, (2)=Fugl-Meyer Assessment, (3)=Barthel index, (4)=ADL, (5)=IMT, (6)=cerebral blood flow, (7)=average cerebral blood flow rate, (8)=total cholesterol, (9)=triglycerides, (10)=HDL, (11)=LDL, (12)=Hcy, (13)=D-dimer, (14)=ADRs.									

Author (year)	Phase of disease	Sample size, EG/CG	Mean age (year)		Interventions		Dosages of Danhong Injection	Course	Outcomes
			EG	CG	EG	CG			
Ou 2017	Acute phase	60/60	58.10	57.20	CT, DHI	CT	Once daily, 20ml	14d	(1) (4) (12)
Wu 2016	Acute phase	49/49	67.40	68.10	Alprostadi, Edaravone, Aspirin, DHI	Alprostadi, Edaravone, Aspirin	Once daily, 40ml	14d	(1) (3) (12) (14)
Chen 2017	Acute phase	40/40	67.34	66.46	CT, DHI	CT	Once daily, 20ml	14d	(2) (14)
Qiu 2017	Acute phase	58/58	70.69	69.88	CT, DHI	CT	Once daily, 30ml	14d	(1) (4) (8) (9)
Liu 2017	Acute phase	48/48	52.33	52.05	CT, DHI	CT	Once daily, 20ml	14d	(1)
Wei 2017	Acute phase	47/47	62.60	60.73	CT, DHI	CT	Once daily, 20ml	14d	(1) (14)
Jing 2020	Acute phase	44/44	62.70	63.20	CT, DHI	CT	Once daily, 20ml	14d	(1) (3) (6) (7)
Li 2018	Acute phase	50/50	51.90	52.30	Atorvastatin Calcium, DHI	Atorvastatin Calcium	Once daily, 20ml	14d	(14)
Jin 2019	Acute phase	50/50	52.00	54.00	rt-PA, DHI	rt-PA	Once daily, 20ml	14d	(1)
Chai 2019	Acute phase	42/42	64.08	63.17	Ozagrel Sodium, Aspirin, DHI	Ozagrel Sodium, Aspirin	Once daily, 40ml	14d	(1) (4)
Chen 2019	Acute phase	74/74	54.69	52.61	CT, DHI	CT	Once daily, 20ml	14d	(1)
Li 2019	Acute phase	42/42	63.49	63.58	Urinary Kallidinogenase, DHI	Urinary Kallidinogenase	Once daily, 20ml	14d	(1) (14)
Zhu 2020	Acute phase	30/30	56.34	57.62	CT, DHI	CT	Once daily, 20ml	14d	(1) (3)

CG= control group; EG=experiment group (Danhong Injection group); NR=not reported; CT=conventional treatment.

Outcomes: (1)=NIHSS, (2)=Fugl-Meyer Assessment, (3)=Barthel index, (4)=ADL, (5)=IMT, (6)=cerebral blood flow, (7)=average cerebral blood flow rate, (8)=total cholesterol, (9)=triglycerides, (10)=HDL, (11)=LDL, (12)=Hcy, (13)=D-dimer, (14)=ADRs.

Author (year)	Phase of disease	Sample size, EG/CG	Mean age (year)		Interventions		Dosages of Danhong Injection	Course	Outcomes
			EG	CG	EG	CG			
Cao 2019	Acute phase	150/150	59.70	59.00	CT, DHI	CT	Once daily, 30ml	14d	(13) (14)
Song 2014	Acute phase	65/65	65.23	65.89	CT, DHI	CT	Once daily, 30ml	14d	(1) (3) (8) (9) (11) (13) (14)
Lv 2018	Acute phase	40/40	63.01	62.34	rt-PA	rt-PA	Once daily, 20ml	14d	(3) (14)
Huo 2020	Acute phase	45/45	NR	NR	Deproteinised Calf Blood Injection, DHI	Deproteinised Calf Blood Injection	Once daily, 30mg	14d	(1)
Cao 2016	Acute phase	34/33	54.50	58.90	CT, DHI	CT	Once daily, 30ml	14d	(1) (14)
Ren 2011	Acute phase	34/34	62.20	63.10	CT, DHI	CT	Once daily, 40ml	14d	(1)
Xue 2010	NR	37/49	65.70	67.50	CT, DHI	CT	Once daily, 30ml	14d	(5) (8) (10) (11) (14)
CG= control group; EG=experiment group (Danhong Injection group); NR=not reported; CT=conventional treatment.									
Outcomes: (1)=NIHSS, (2)=Fugl-Meyer Assessment, (3)=Barthel index, (4)=ADL, (5)=IMT, (6)=cerebral blood flow, (7)=average cerebral blood flow rate, (8)=total cholesterol, (9)=triglycerides, (10)=HDL, (11)=LDL, (12)=Hcy, (13)=D-dimer, (14)=ADRs.									

All RCTs reported methods of random sequences generation. None of the trials mentioned allocation concealment. Only three trials [31, 39, 52] (4%) blinded patients and caregivers. No trials mentioned loss to follow-up. No details were identified in the domains of other bias (Supplementary table 1).

Treatment effects

In total, 45 RCTs[8, 16, 19–21, 23–30, 33, 36–38, 40, 42–46, 48–51, 53, 54, 60, 61, 63–66, 68–72, 74, 76–78] involving 4565 patients reported NIHSS score. For Danhong injection combined with western medicine group, the NIHSS score significantly changed -10.50 (95% CI: -11.50–9.51), and the control group changed -6.22 (95% CI: -7.05–5.39). Meta-analysis showed that Dahong injection combined with western medicine had a better effect in improving neurological impairment than western medicine alone (NIHSS score MD -4.21, 95% CI -4.96–3.46)(Figure 2).

Six RCTs[6, 30, 47, 51, 56, 62] involving 552 patients showed that Danhong injection combined with western medicine could significantly improve the Fugl-Meyer Assessment than western medicine alone (MD 14.28, 95% CI 9.47–19.09) (Figure 3). Compared with western medicine alone, Danhong injection plus western medicine suggested a significant improvement on Barthel index (14 trials with 1270 patients; MD 8.71, 95% CI 3.68–13.74) and ADL score (12 trials with 1114 patients; MD 14.48, 95% CI 9.04–19.92) (Figure S1 and S2 in appendix 3).

Meta-analysis showed that compared with western medicine alone, combination therapy of Danhong injection and western medicine could significantly lower the IMT (3 trials with 284 patients; MD -0.23 mm, 95% CI -0.26–0.20), increase the cerebral blood flow (2 trials with 200 patients; MD 1.16 mL/s, 95% CI 0.64–1.68) and average cerebral blood flow rate (5 trials with 508 patients; MD 3.05 cm/s, 95% CI 1.61–4.50) (Figures S3–S5 in appendix 3).

The combination therapy of Danhong injection and western medicine could significantly lower total cholesterol (10 trials with 1019 patients; MD -1.14 mmol/L, 95% CI -1.57–0.72) (Figure 4), triglycerides (8 trials with 869 patients; MD -1.00 mmol/L, 95% CI -1.69 –0.31) and LDL (5 trials with 441 patients; MD -0.91 mmol/L, 95% CI -1.33–0.49), and increase the level of HDL (3 trials with 236 patients; MD 0.31 mmol/L, 95% CI 0.22–0.40) (Figures S6–S8 in appendix 3).

Four RCTs [16, 51, 60, 61] with a total of 392 individuals reported the data of serum Hcy level. The results revealed a significant lowering effect on Hcy in the Danhong injection combination therapy (MD -3.54 μ mol/L, 95% CI -4.38–2.07) (Figure 5).

Meta-analysis of five trials with a total of 612 patients showed no statistically significant difference in D-dimer (MD -0.12 mg/L, 95% CI -0.61–0.37, $P=0.64$) between treatment groups (Figure S9 in appendix 3).

Subgroup Analysis

Subgroup analysis by mean age showed differential effects in average cerebral blood flow rate (<60 years old: MD 0.74 cm/s, 95% CI 0.29–1.19; ≥ 60 years old: MD 4.09 cm/s, 95% CI 2.02–6.16; interaction $P=0.002$). The analysis by length of treatment showed differential effects in ADL (≤ 2 weeks: MD 15.08, 95% CI 9.11–21.05; >2 weeks: MD 8.18, 95% CI 6.21–10.15; interaction $P=0.03$). Subgroup analysis by type of baseline western medicines showed differential effects (conventional therapy: MD -3.79, 95% CI -4.83 –2.76; intravenous thrombolysis: MD -2.19, 95% CI -3.52–0.86; anti-platelet aggregation: MD -3.79, 95% CI -5.06–2.51; dilation of blood vessels: MD -4.23, 95% CI -5.85–2.62; statins: MD -2.87, 95% CI -4.07–1.67; neuroprotective agents: MD -5.88, 95% CI -8.90–2.87; other therapies: MD -10.20, 95% CI -12.54–7.86; interaction $P<0.00001$).

As for Fugl-Meyer Assessment, Barthel index, total cholesterol, triglycerides, LDL, Hcy and D-dimer, subgroup analyses by length of treatment, mean age of patients, and types of baseline western medicine treatment showed no statistically differential effects.

Safety

Of the 67 included trials, 16 studies [20, 22, 25–27, 31, 33, 34, 37, 40, 49, 62, 65, 67, 71, 75] reported at least one case of ADRs, 12 studies [16–18, 38, 47, 48, 52, 61, 73, 74, 77, 79] reported no ADRs/ADEs during the study, and 39 RCTs did not mention the information of ADRs/ADEs.

The main ADRs occurred during the trials were gastrointestinal reactions (4.48% vs 4.76% in Danhong injection plus western medicine and western medicine alone group, respectively, $P=0.76$), dizzy (3.69% vs 2.74% in each group, $P=0.61$) and skin rash (8.53% vs 7.31% in each group, $P=0.56$). ADRs occurred during the trials in either group were shown in Supplementary table 2.

Assessment of Publication Bias

The funnel plots for NIHSS, Barthel index and ADL were near asymmetric, and no important publication bias was detected by Egger's tests (Egger's test $P=0.055$, $P=0.342$ and $P=0.998$, respectively). Egger's test of total cholesterol suggested potential publication bias (Egger's test $P=0.019$). The sensitivity analysis by the trim-and-fill method showed that the results were robust despite the potential bias (trim-and-fill method adjusted MD -1.14 mmol/L, 95% CI -1.57–0.72) (Figure S10–11 in appendix 3).

Discussion

Findings and interpretations

In this systematic review and meta-analysis of 67 randomized controlled trials, we found that Danhong injection adding to western medicine could significantly improve neurological function (e.g., improving NIHSS, Fugl-Meyer Assessment), self-care ability (e.g., improving Barthel index and ADL scores), hemodynamic outcomes (cerebral blood flow, average cerebral blood flow rate), blood lipids and Hcy in patients with ischemic stroke. Furthermore, patients with different age and receiving different baseline western medicines may have different benefits in hemodynamic status and neurological function, respectively.

NIHSS is a stroke-specific quantitative scale with excellent reliability and validity for ischemic stroke outcome, and measures stroke-related neurological deficits such as the level of consciousness, language function, visual field, eyes movement sensory function, and coordination [80–82]. In our study, we found that NIHSS scores were significantly decreased in patients receiving Danhong injection plus western medicine. This suggested that Danhong injection adding to western medicine would be beneficial in reducing the severity of ischemic stroke and improving neurological status. Overactivation of inflammatory factors and aggregation of platelets cause

thrombosis and can lead to vascular occlusion, resulting in cerebrovascular ischemia, and then contribute to neurological deficit and physical dysfunction[83–85]. Since Danhong injection could inhibit platelet aggregation and boost the activity of fibrinogen dissolved, thus the add-on effects of Danhong injection and western medicine play a key role in improving NIHSS.

Fugl-Meyer Assessment is considered as one of the most comprehensive and evaluative measures for assessment of recovery in the poststroke patients[86]. As approximately 85% of patients with stroke present with arm weakness[87], our study found that the scores in Fugl-Meyer Assessment were significantly increased in patients treated by the integrated treatment with Danhong injection and western medicine, which suggests that Danhong injection adding to western medicine have the potential of enhancing limb function in stroke recovery.

PPAR- α , a transcription factor that regulates diverse aspects of lipid metabolism, plays a key role in the regulation of hepatic lipid metabolism[88, 89]. Our study showed that the combination of Danhong injection and western medicine had a noteworthy effect on reducing blood lipids (e.g., total cholesterol, triglycerides and LDL). Our study also showed that Danhong injection adding to western medicine performed a marked impact on increasing cerebral blood flow and average cerebral blood flow rate, which can be explained that Danhong injection could improve hemodynamic indices such as high shear viscosity, low shear viscosity, hematocrit, platelet aggregation rate[90].

Our study found the most common ADR in these reported RCTs were gastrointestinal reactions including nausea, flatulence and vomiting, which are a consequence of the drug's normal pharmacological effects[91]. About 58.2% of RCTs did not mention the information of ADRs in this study, thus we were unable to make a conclusion on safety so far. More credible evidences are warranted to confirm the safety of add-on effect of this drug in the future.

Comparison with other studies

Three previous systematic reviews and meta-analyses[9–11] have assessed the effect of Danhong injection for treatment of ischemic stroke. In terms of efficacy, all these three studies compared Danhong injection with other Chinese herbal injections such as Shuxuening injection, Yinxingdamo injection and so on. Instead of making a claim of comparative effectiveness between traditional Chinese medicines, we aimed to address whether the addition of traditional Chinese medicine to routinely used medications would improve the effects on ischemic stroke, which was a question that need strong evidence for conclusion. As it turned out, our study has provided reliable assessment of the effects.

Strengths and Limitations

Our study has several strengths. Firstly, we used rigorous methods to search, screen, and collect data from eligible RCTs. Secondly, we included several newly-published RCTs to summarize the efficacy and safety of Danhong injection in patients with ischemic stroke, aiming to provide a more comprehensive, up-to-date and new level of clinical evidence. Thirdly, we included a large number of RCTs, and used both patients reported important outcomes (e.g., NIHSS, Fugl-Meyer Assessment scores) and other objective outcomes (e.g., blood lipids, hemodynamic outcomes) to comprehensively assess the efficacy and safety of Danhong injection in patients with ischemic stroke. Fourthly, we conducted three prespecified subgroup analyses to explore sources of heterogeneity.

However, our study also has some limitations. The included RCTs may be at risk of high risk of bias. As a result, the findings may be susceptible to the bias. Additional well-designed and rigorously trials with long-term outcomes may be needed to further consolidate our findings.

Conclusions

Danhong injection adding to western medicine may improve the effects of neurological function, self-care ability, hemodynamic status, blood lipids and Hcy for patients with ischemic stroke. Furthermore, patients with different age and receiving different baseline western medicines may have different benefits in hemodynamic status and neurological function, respectively.

Abbreviations

ADEs: adverse drug events

ADL: activities of daily living

ADRs: adverse drug reactions

CIs: confidence intervals

CNKI: China National Knowledge Infrastructure Database

Hcy: homocysteine

HDL: high-density lipoprotein

IMT: intima-media thickness

LDL: low-density lipoprotein

MD: mean difference

NIHSS: National Institutes of Health Stroke Scale Score

NR: not reported

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

RCTs: randomized clinical trials.

Declarations

Ethics approval and consent to participate

Not applicable; this systematic review utilizing publicly available information, does not require ethics approval.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are supported by the published articles in database, and all data are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Yu Ma: Literature searches, Data extraction, Data analysis, Writing- Original Draft. **Ke Deng:** Literature searches, Data extraction, Writing- Review & Editing. **Jiali Liu:** Writing- Review & Editing. **Bin Ma:** Writing- Review & Editing. **Fan Mei:** Writing- Review & Editing. **Wen Hui:** Writing- Review & Editing. **Xiaochao Luo:** Writing- Review & Editing. **Minghong Yao:** Writing- Review & Editing. **Yanmei Liu:** Writing- Review & Editing. **Xuan Qin:** Writing- Review & Editing. **Xu Zhou:** Writing- Review & Editing. **Kang Zou:** Writing- Review & Editing. **Ling Li:** Conceptualization, Supervision, Project administration, Data analysis, Writing- Review & Editing. **Xin Sun:** Conceptualization, Supervision, Project administration, Data analysis, Writing- Review & Editing. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of study selection

Figure 2

Meta-analysis of NIHSS between DHI+WM and WM in patients with Ischemic Stroke

Figure 3

Meta-analysis of Fugl-Meyer Assessment between DHI+WM and WM in patients with Ischemic Stroke

Figure 4

Meta-analysis of total cholesterol between DHI+WM and WM in patients with Ischemic Stroke

Figure 5

Meta-analysis of Hcy between DHI+WM and WM in patients with Ischemic Stroke

Supplementary Files

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