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Review Article

A systematic review and meta-analysis of randomized controlled clinical trials of Ginkgo leaf extract and dipyridamole injection combined with aspirin for the treatment of cerebral infarction

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Abstract: Since 2009, a novel method, combining Ginkgo leaf extract and dipyridamole injections (Ginkgo-dipyridamole injection) with aspirin, has been widely used in China for the clinical treatment of cerebral infarction. Up to date, there is lack of evidence-based medicine. Therefore, this study attempted to provide more reliable and powerful evidence for clinical practice by a meta-analysis of randomized clinical controlled trials. Literatures concerning Ginkgo-dipyridamole combined with aspirin in the treatment of cerebral infarction published in PubMed, Web of Science, Chinese Academic Journal Full-text Database (CNKI), China biomedical literature database (CBM), and the Wan Fang database was retrieved and randomized controlled trials were selected according to the inclusion criteria. Meta-analysis was carried out using RevMan 5.3 software and the pooled risk ratio (RR) and standardized mean difference (SMD) of the main outcomes with the 95% confidence interval (95% CI) were estimated. Rating of evidence was also assessed. Fifteen articles involving 1760 cases were included in this study. The results showed that compared with the control group using aspirin treatment, the pooled RR (95% CI) of the effectiveness rate and the cure rate in the group using Ginkgo-dipyridamole combined with aspirin in the treatment of cerebral infarction were 1.16 [1.12, 1.20] and 1.51 [1.31, 1.75], respectively. The pooled SMD (95% CI) of NILSS, blood viscosity, plasma viscosity, high shear viscosity of blood, and fibrinogen were -1.65 [-1.99, -1.31], -3.31 [-5.03, -1.6], -3.20 [-3.88, -2.51], -7.54 [-8.11, -6.97], and -3.37 [-4.86, -1.88], respectively. All of the differences were statistically significant ($P < 0.05$). Based on GRADE rating results, the level of evidence of the outcomes ranged from low to moderate. Compared with aspirin therapy, Ginkgo-dipyridamole injection combined with aspirin achieved a better curative effect for successful treatment of cerebral infarction. However, in view of the limitations of this study, it is suggested that large-scale, high-quality studies should be performed to further verify the above conclusion by critical outcome indicators.

Keywords: Ginkgo leaf extract and dipyridamole injection, aspirin, cerebral infarction, randomized controlled clinical trial, meta-analysis

Introduction

Cerebral infarction is a common and frequently occurring disease associated with high mortality and disability rates. It is a type of ischemic stroke caused by a blockage in the blood vessels supplying blood to the brain. Increased platelet aggregation is an important risk factor for cerebral infarction [1, 2]. Owing to its antiplatelet properties, aspirin has been recognized as an effective drug for the treatment of ischemic cerebrovascular disease. In recent years, a combination of dipyridamole and aspirin has been used for the treatment and prevention of cerebrovascular diseases [3, 4]. Since 2009, a novel method combining Ginkgo leaf extract and dipyridamole injection (Ginkgo-dipyridamole injection) with aspirin has been widely used in China for the treatment of cerebral infarction [5-7]. The Ginkgo-dipyridamole

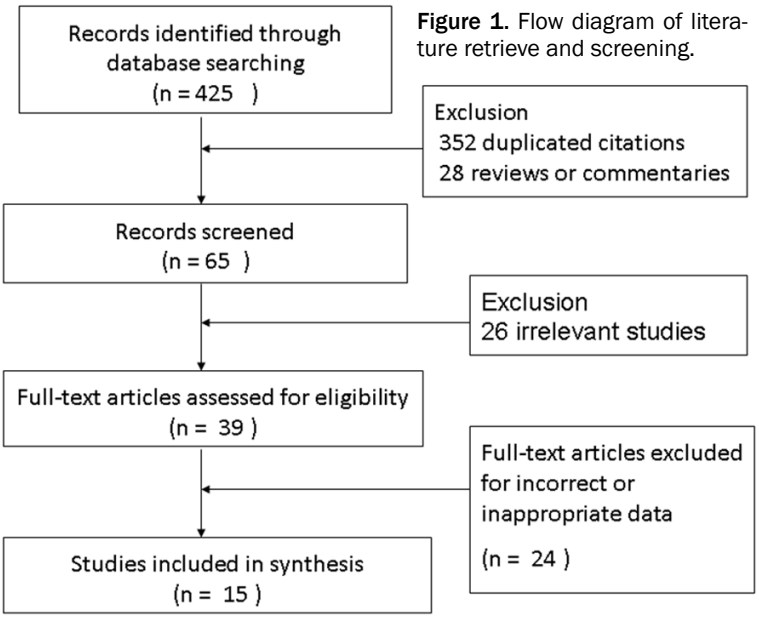

Figure 1. Flow diagram of literature retrieve and screening.

injection is mainly composed of Ginkgo-flavone glycoside, ginkgolide, bilobalide, and dipyridamole [8]. Some studies have suggested that compared to aspirin therapy, combination therapy with Ginkgo-dipyridamole is more effective in the treatment of patients with cerebral infarction. However, to date, there is a lack of evidence-based medicine. Therefore, this study attempted to provide more reliable and powerful evidence for clinical practice by a meta-analysis of clinical randomized controlled trials (RCTs).

Materials and methods

Literature retrieval

Computerized information retrieval was carried out on a number of databases to obtain relevant data. The databases chosen for this study were PubMed, Web of Science, the China Academic Journal Full-text Database (CNKI), the Chinese biomedical literature database (CBM), and the Wanfang database. The articles published between 1980 and 2016 were retrieved. The search terms used to identify relevant studies were “aspirin”, “ginkgo”, “dipyridamole”, “cerebral infarction”, “stroke”, “Ginkgo leaf extract and dipyridamole injection”, and “cerebrovascular disease”. The protocols of this study were based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [9, 10].

Inclusion criteria

The inclusion criteria were set as follows: i) the research content is Ginkgo-dipyridamole injection combined with aspirin in the treatment of cerebral infarction; ii) the study type is a randomized controlled clinical trial, and the control group uses aspirin alone; iii) the diagnostic criteria are clear [11]; iv) the study refers to a proposed standard method using the National Institute of Health stroke scale (NIHSS) for assessing the efficacy [12] as follows: healing-neurological impairment score decreased by more than 89%, significant improvement-neurologic impairment score decreased by more than 46%, effective-neurologic impairment score decreased by more than 18%, no change-neurologic impairment score reduced by 18% or less, and deterioration-score greater than the admission score or death; and v) the article provides or can be converted to data to obtain the relative risk (RR), the standard mean difference (SMD), and a 95% confidence interval (interval confidence, CI).

Exclusion criteria

The exclusion criteria were as follows: i) incomplete data, incorrect or incomplete information; ii) case reports and research carried out on animals; iii) the design of the test is not rigorous research; iv) duplicates; and v) studies concerning patients with cerebral infarction coupled with cerebral hemorrhage.

Literature selection and data extraction

According to the inclusion and exclusion criteria, two researchers independently performed literature selection and data extraction. The disagreements were resolved by consensus with a third reviewer. The main contents of data extraction included first author, publication year, study design, sample size, intervention measures, and main outcomes (effectiveness rate, cure rate, NIHSS, the Barthel score, blood viscosity, plasma viscosity, high shear viscosity

Table 1. The general characteristics of the included literature

First author	Reference	Publication year	Experimental group (N)	Control group (N)	Intervention		The time of Therapy	JADAD scores
					Experimental group (ml)*	Control group (mg)#		
JW Wang	[15]	2016	100	100	25	100	14 d	2
ZY Chai	[16]	2015	49	48	20	100	14 d	2
L Yang	[17]	2014	37	37	20	100	14 d	2
Q Wang	[18]	2014	60	60	25	120	14 d	2
SM Huang	[19]	2014	50	50	20	100	Unclear	3
SY Bao	[20]	2014	43	43	20	100	14 d	2
X Jiang	[21]	2014	50	50	20	100	14 d	2
JJ Xue	[22]	2013	31	31	20	100	Unclear	2
XJ Tang	[23]	2013	39	39	20	100	14 d	2
YH Wang	[24]	2012	60	59	20	100	14 d	2
HM Tang	[25]	2009	45	45	20	100	14 d	2
JL Zhu	[26]	2009	50	50	20	100	14 d	2
N Wang	[27]	2009	59	55	20	100	Unclear	2
XD Zheng	[28]	2007	30	30	20	100	14 d	2
QJ Zhai	[29]	2005	180	180	20	75 mg	28 d	2

*Daily usage of Ginkgo leaf extract and dipyridamole injection in experimental group, usage: Ginkgo leaf extract and dipyridamole Injection plus 0.9% Sodium chloride injection or 5%-10% glucose injection, intravenous infusion, 1-2 times each day, daily oral aspirin. #Daily aspirin dose in control group, usage: daily oral aspirin, once a day.

of blood, fibrinogen, adverse reaction, and quality score).

Literature quality evaluation

The literature quality was assessed by two researchers according to the JADAD scale [13, 14]. Randomization, allocation concealment, blinding, withdrawals, and dropouts were used to assign quality scores to the included literature.

Statistical analysis

Meta-analysis was conducted using RevMan 5.3 software. The statistical heterogeneity across studies was determined using I^2 statistical analysis. According to the heterogeneity of data, a fixed effects model or random effects model was selected, and the effect values with 95% CI for the main outcomes were calculated. The publication bias in the meta-analysis was observed using a funnel plot. RR was adopted to express the effect size of dichotomous data, such as the effectiveness and cure rates. SMD was used to assess the difference in continuous data, including NILSS, blood viscosity, plasma viscosity, the high shear viscosity of blood, and fibrinogen. The evaluation of publication bias was carried out using funnel plots as well as Begg's and Egger's tests. The effect of evidence evaluation was assessed using the Easy Grade Pro software.

Results

Description of studies

We identified 425 articles from the aforementioned literature databases. Of these, 380 were removed after screening, with further 26 articles being excluded following more screening in accordance with the inclusion and exclusion criteria. Another 24 papers were excluded after their full text versions were read, leaving 15 articles for this study [15-29], comprising 1760 cases of cerebral infarction. The literature screening process is shown in **Figure 1**. The general characteristics of the articles included in this meta-analysis are shown in **Table 1**. The results of literature quality analysis showed that the JADAD scores ranged from 2 to 3, suggesting that there were considerable limitations in the experimental design or execution of the included studies (**Table 1**).

Meta-analysis of the curative effect of the combination

Comparative efficacy was presented for all the 15 included studies [15-29]. Of the individual

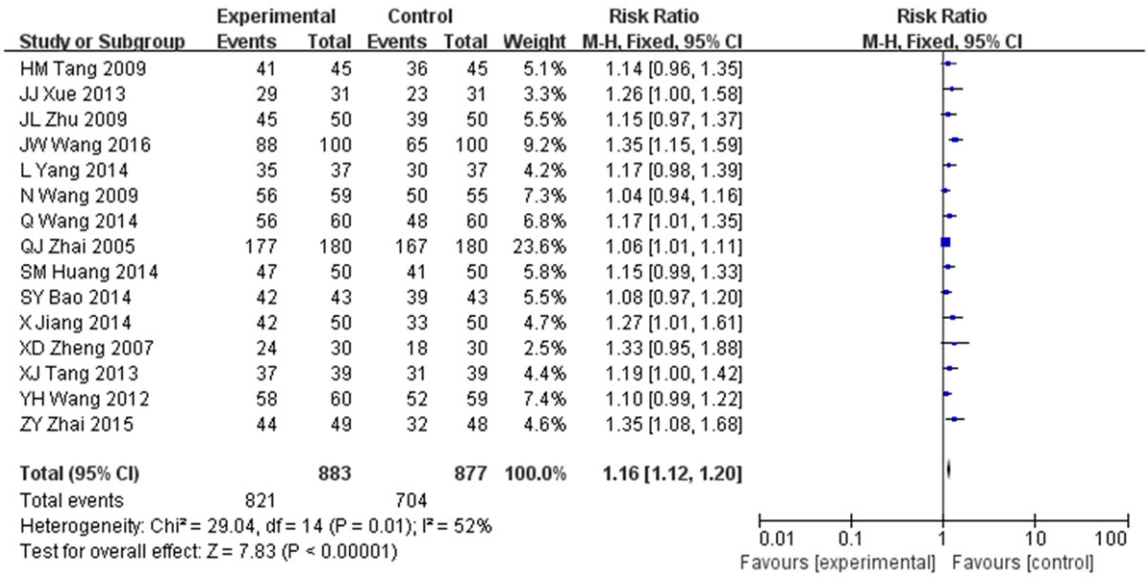

Figure 2. Meta-analysis of the pooled risk ratio of the effectiveness rate.

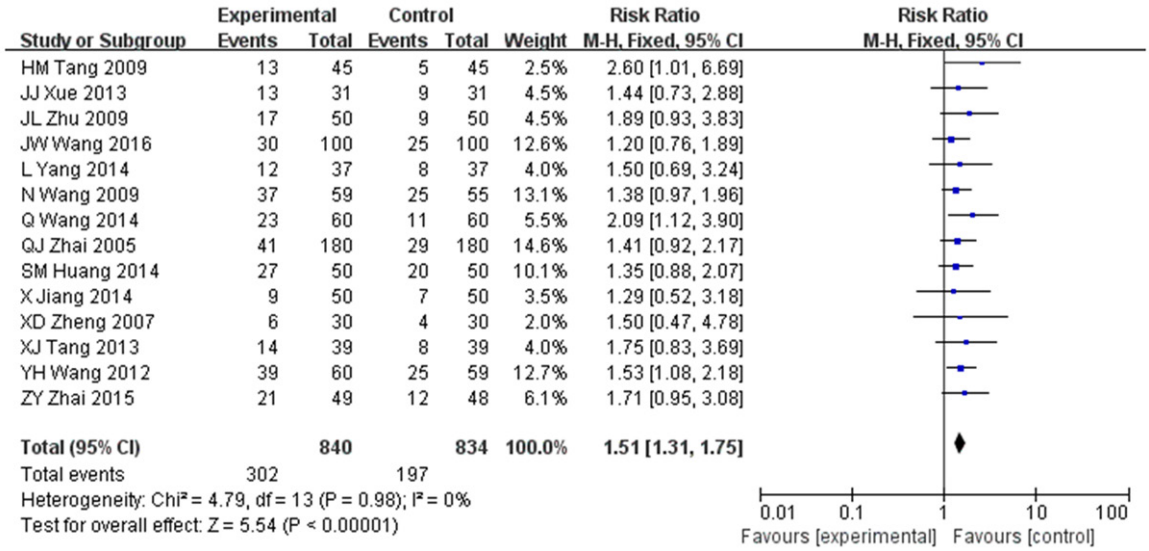

Figure 3. Meta-analysis of the pooled risk ratio of the clinical cure rate.

1760 cases, 883 were placed in the experimental group, with 877 falling under the control group.

The meta-analysis results showed that the pooled RR (95% CI) of the effectiveness and cure rates in the group using ginkgo-dipyridamole combined with aspirin in the treatment of cerebral infarction were 1.16 [1.12, 1.20], $P < 0.05$ (**Figure 2**) and 1.51 [1.31, 1.75], $P < 0.05$ (**Figure 3**), respectively, when compared to those in the control group (using aspirin treatment exclusively).

NIHSS and the Barthel score

In this meta-analysis, five studies reported NIHSS data. The pooled SMD (95% CI) of NILSS was -1.65 [-1.99, -1.31], $P < 0.05$ (**Figure 4**). Two studies reported Barthel scores [19, 27] and both the studies showed higher scores for the experimental group ($P < 0.05$). Owing to the

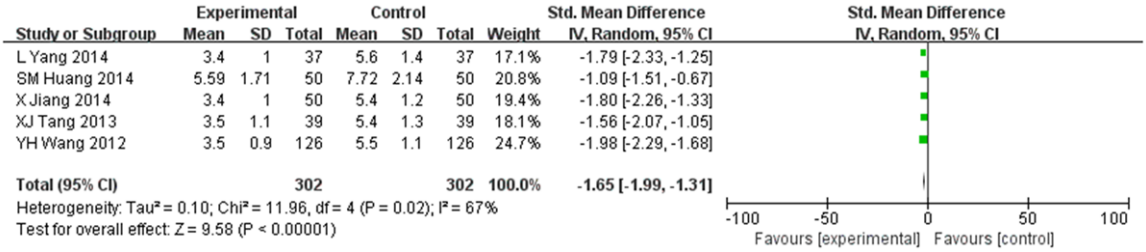

Figure 4. Meta-analysis of the pooled standardized mean difference of National Institute of Health stroke scale scores.

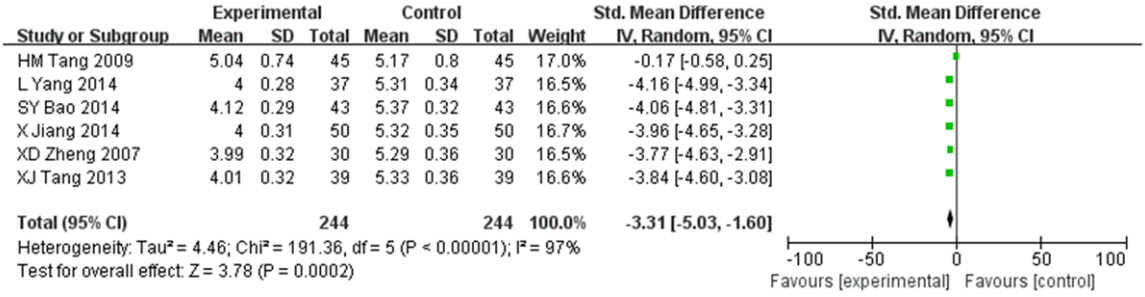

Figure 5. Meta-analysis of the pooled standardized mean difference of blood viscosity.

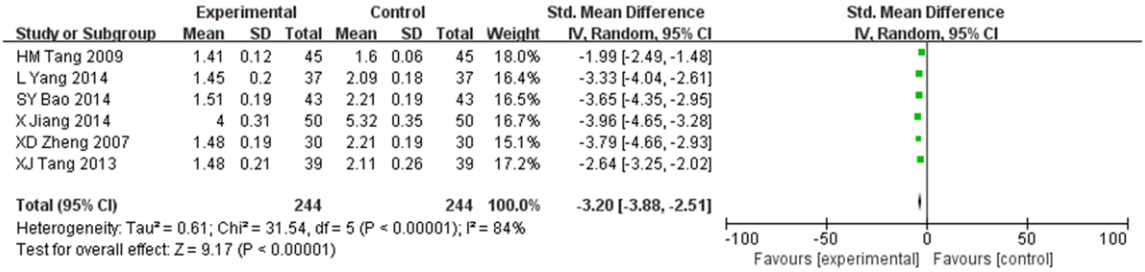

Figure 6. Meta-analysis of the pooled standardized mean difference of plasma viscosity.

relatively small number of papers, we did not conduct the meta-analysis of Barthel score.

Meta-analysis of hemorheology measurements

According to the results of the meta-analysis, the pooled SMDs (95% CI) of blood viscosity, plasma viscosity, high shear viscosity of blood, and fibrinogen were -3.31 [-5.03, -1.60] (**Figure 5**), -3.20 [-3.88, -2.51] (**Figure 6**), -7.54 [-8.11, -6.97] (**Figure 7**), and -3.37 [-4.86, -1.88] (**Figure 8**), respectively. All differences were statistically significant ($P < 0.05$).

Publication bias and evidence rating

Both Begg's and Egger's tests showed that there was a publication bias ($P < 0.05$). The funnel plot is shown in **Figure 9**. GRADE ratings showed that the levels of evidence in the effectiveness rate, cure rate, and NIHSS were moderate, while those in blood viscosity, plasma viscosity, high shear viscosity of blood, and fibrinogen were low (**Table 2**). Based on the GRADE rating, the level of evidence was characterized as low to moderate.

Side effects

Of the 15 studies considered, 12 reported no side effects [15-29]. Three papers reported adverse reactions, mainly nausea, headache, and ecchymosis [18, 21, 22]. These symptoms relieved following treatment. No serious adverse reactions or deaths were reported in the included studies.

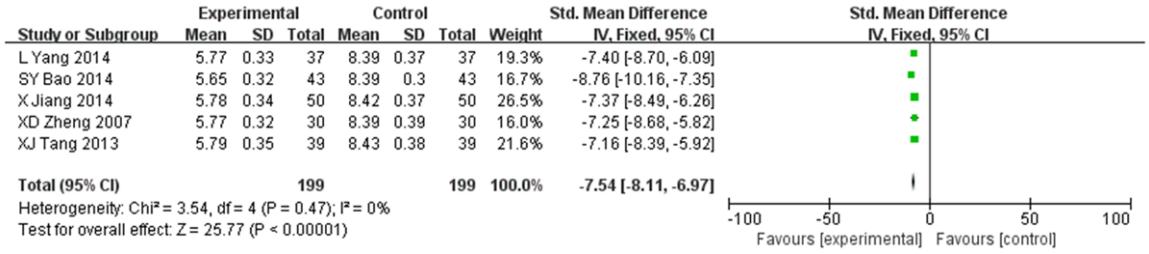

Figure 7. Meta-analysis of the pooled standardized mean difference of high shear viscosity of blood.

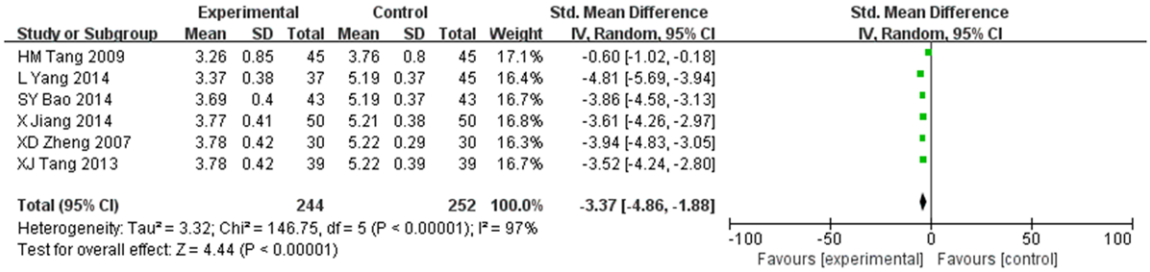

Figure 8. Meta-analysis of the pooled standardized mean difference of fibrinogen.

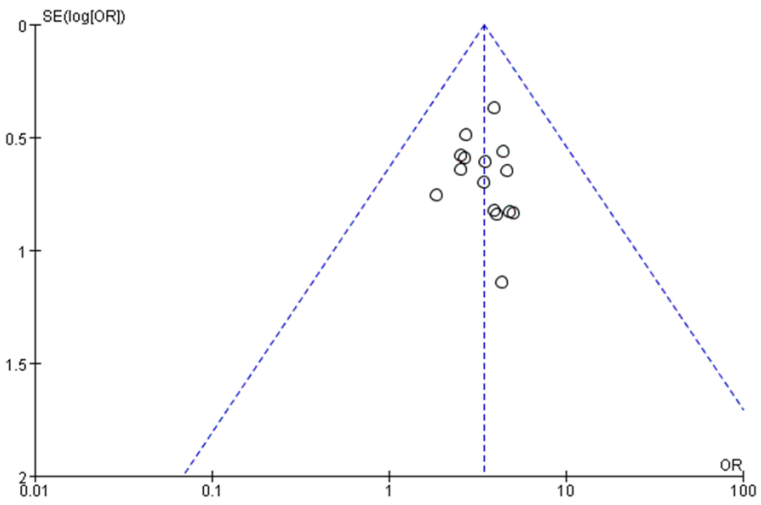

Figure 9. Funnel plot of the literatures included in this Meta-analysis.

Discussion

Cerebral infarction is the most common acute cerebral vascular disease. After infarction, the nerve cells die rapidly owing to ischemia and hypoxia, resulting in high risks of death or disability. This makes the treatment of cerebral infarction a major challenge in clinical practice. Aspirin is used to treat and prevent cerebral infarction owing to its ability to inhibit platelet thromboxane A2 [30].

In recent years, certain injections of traditional Chinese herb extracts [31-36], such as Huangqi, Danshen, Shenmai, and Qinkailian have been approved for clinical treatment by China's State Food and Drug Administration (SFDA). Since 2009, Ginkgo-dipyridamole injections have been widely used in the clinical treatment of cardiovascular and cerebrovascular diseases. Ginkgo-dipyridamole injection is a compound preparation containing 10 mL dose each of 9-11 mg of Ginkgo flavones and 3.6-4.4 mg of dipyridamole [37]. Pharmacological research suggested that Ginkgo flavone causes the expansion of coronary artery and cerebral blood vessels, thereby improving the symptoms of cerebral ischemia and memory function [38]. In recent years, there has been an increase in the prescription of Ginkgo-dipyridamole injections across China [39].

To evaluate the curative effect of Ginkgo-dipyridamole injection combined with aspirin on cerebral infarction, we conducted a meta-analysis

Table 2. GRADE evidence rating for the outcomes in this study

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Outcomes				
Effectiveness rate	Study population		RR 1.16 (1.13 to 1.18)	1760 (15 studies)	⊕⊕⊕⊖ moderate	
	803 per 1000	931 per 1000 (907 to 948)				
	Medium risk population					
	800 per 1000	928 per 1000 (904 to 944)				
Cure rate	Study population		RR 1.51 (1.31 to 1.75)	1674 (14 studies)	⊕⊕⊕⊖ moderate	
	236 per 1000	356 per 1000 (309 to 413)				
	Medium risk population					
	211 per 1000	319 per 1000 (276 to 369)				
NIHSS		The mean NIHSS in the intervention groups was 1.7 standard deviations lower (1.88 to 1.51 lower)		604 (5 studies)	⊕⊕⊖⊖ low	SMD -1.65 (-1.99 to -1.31)
Blood viscosity		The mean blood viscosity in the intervention groups was 3.31 standard deviations lower (5.03 to 1.60 lower)		488 (6 studies)	⊕⊕⊖⊖ low	SMD -3.31 (-5.03 to -1.60)
Plasma viscosity		The mean plasma viscosity in the intervention groups was 3.20 standard deviations lower (3.88 to 2.51 lower)		488 (6 studies)	⊕⊕⊖⊖ low	SMD -3.20 (-3.88 to -2.51)
High shear viscosity of blood		The mean high shear viscosity of blood in the intervention groups was 7.54 standard deviations lower (8.11 to 6.97 lower)		398 (5 studies)	⊕⊕⊕⊖ moderate	SMD -7.54 (-8.11 to -6.97)
Fibrinogen		The mean fibrinogen in the intervention groups was 3.37 standard deviations lower (4.86 to 1.88 lower)		496 (6 studies)	⊕⊕⊕⊖ moderate	SMD -3.37 (-4.86 to -1.88)

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. NIHSS: National Institute of Health stroke scale.

in this study. Sixteen articles reporting RCTs were included in this study. These articles included 1760 cases of cerebral infarction, suggesting that this study has a large sample size. The meta-analysis results showed that both effectiveness and cure rates improved in patients treated with Ginkgo-dipyridamole injections, compared with those in the control group using aspirin treatment exclusively. According to the meta-analysis, the pooled SMD (95% CI) of NILSS was -1.65 [-1.99, -1.31], suggesting that it was conducive to the recovery of neural function. Two studies reported Barthel scores, and both the results showed that the Barthel scores were higher in the experimental group. Because the number of research papers was too small, we did not conduct meta-analysis of the Barthel score. These results indicate that this combination therapy can achieve a better curative effect.

The pooled SMDs (95% CI) of blood viscosity, plasma viscosity, high shear viscosity of blood, and fibrinogen were -3.31 [-5.03, -1.6], -3.20 [-3.88, -2.51], -7.54 [-8.11, -6.97], and -3.37 [-4.86, -1.88], respectively, which suggests that the treatment can help in reducing blood viscosity and fibrinogen.

The results of JADAD score call into question the overall quality of the literature that was consulted for this study, because common pre-existing problems, such as unclear allocation concealment, inadequate blinding, and unexplained withdrawals or dropouts were present. GRADE ratings showed that the level of evidence in the effectiveness rate, the cure rate, and NIHSS was moderate, while that in blood viscosity, plasma viscosity, high shear viscosity of blood, and fibrinogen was low. Based on these GRADE ratings, the level of evidence was characterized as low to moderate. However, the publication bias in this meta-analysis and the low GRADE ratings may downgrade the quality of evidence of this meta-analysis.

Very few low-risk adverse reactions to the treatment were reported suggesting that Ginkgo-dipyridamole injection is relatively safe.

The findings of this study suggest that compared with aspirin therapy, Ginkgo-dipyridamole injection combined with aspirin may help to achieve a better curative effect in the treatment of cerebral infarction. However, in view of the limitations of the study, it is suggested that large-scale, high-quality studies should be performed to further verify this.

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Disclosure of conflict of interest

None.

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References

[1] Abumiya T, Houkin K. Association of recurrent cerebral infarction with adenosine diphosphate- and collagen-induced platelet aggregation in patients treated with ticlopidine and/or aspirin. J Stroke Cerebrovasc Dis 2011; 20: 319-323.

[2] Kario K, Yano Y, Matsuo T. Morning blood pressure surge, morning platelet aggregation, and silent cerebral infarction in older Japanese hypertensive patients. J Hypertens 2011; 29: 2433-2439.

[3] Flynn RW, MacDonald TM, Murray GD. Persistence, adherence and outcomes with antiplatelet regimens following cerebral infarction in the Tayside stroke cohort. Cerebrovasc Dis 2012; 33: 190-197.

[4] Offerhaus L. The combination of acetylsalicylic acid and dipyridamole is more effective in secondary prevention following transient ischaemic attack or cerebral infarction: the debate is closed. Ned Tijdschr Geneeskd 2006; 150: 2673-2674.

[5] Xia X. The research progress of clinical application of ginkgo dipyidamolum. Journal of Practical Medical Techniques 2008; 15: 1344-1346.

[6] Zhao GJ, An M. Progress of clinical application of ginkgo dipyidamolum. Baotou Medical College Acta 2013; 29: 144-146.

[7] Brown DG, Wilkerson EC, Love WE. A review of traditional and novel oral anticoagulant and antiplatelet therapy for dermatologists and dermatologic surgeons. J Am Acad Dermatol 2015; 72: 524-534.

[8] Bin C. The research progresss of the pharmacology and the clinical application of ginkgo leaf extract and dipyridamole injection. China Pharmaceuticals 2010; 19: 88-90.
[9] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.
[10] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009; 6: e1000100.
[11] The Fourth National Cerebrovascular Diseases Conference of Chinese Medical Association. Diagnosis of various types of cerebrovascular diseases. Chinese Journal of Neurology 1996; 29: 379-380.
[12] The Fourth National Cerebrovascular Diseases Conference of Chinese Medical Association. Scoring of the degree of clinical neurological deficits in stroke patients (1995). Chinese Journal of Neurology 1996; 29: 381-383.
[13] Alam M, Rauf M, Ali S, Nodzenski M, Minkis K. A systematic review of reporting in randomized controlled trials in dermatologic surgery: Jadad scores, power analysis, and sample size determination. Dermatol Surg 2014; 40: 1299-1305.
[14] Clark HD, Wells GA, Huet C, McAlister FA, Salmi LR, Fergusson D, Laupacis A. Assessing the quality of randomized trials: reliability of the Jadad scale. Control Clin Trials 1999; 20: 448-452.
[15] Wang JW. Clinical observation of aspirin combined with ginkgo leaf extract and dipyridamole in treatment of acute cerebral infarction. China Medical Guide 2016; 14: 62-63.
[16] Chai ZY. Effect of aspirin combined with ginkgo leaf extract and dipyridamole in treatment of acute cerebral infarction. Henan Medical Research 2015; 7: 118-119.
[17] Yang L. Clinical curative effect of ginkgo leaf extract and dipyridamole combined with aspirin in the treatment of acute cerebral infarction. For All Health (Late Edition) 2014; 8: 491.
[18] Wang Q, Zhang YF. Aspirin combined with ginkgo was presented edaravone treatment of multiple cerebral infarction. Medical Aesthetics and Cosmetology 2014: 158-159.
[19] Huang SM, Wang LL, Ceng Y. Clinical observation of ginkgo dipyidamolum adjuvant therapy of acute cerebral infarction. Electronic Journal of Integrated Traditional Chinese and Western Cardiovascular Disease 2014; 11: 16-17.
[20] Bao SY. Clinical observation of ginkgo leaf extract and dipyridamole injection combined with aspirin in the treatment of acute cerebral infarction. Journal of Clinical Rational Drug Use 2014;7: 146-148.
[21] Jiang X. The study of dipyridamole combined with aspirin in treatment of acute cerebral infarction. China Foreign Medical Treatment 2014; 29: 144-146.
[22] Xue JJ. Curative effect observation of aspirin combined with ginkgo leaf extract and dipyridamole in treatment of acute cerebral infarction. The Medical Forum 2013; 35: 4701-4702.
[23] Tang XJ. Curative effect of aspirin combined with ginkgo leaf extract and dipyridamole on patients with acute cerebral infarction. Hebei Medical Journal 2013; 35: 1188-1189.
[24] Wang YH. Clinical curative effect of ginkgo leaf extract and dipyridamole combined with aspirin in the treatment of acute cerebral infarction. China Health Care & Nutrition (Late Edition) 2012; 22: 2126-2126.
[25] Tang HM, Tang HN, Chen X. Curative effect of aspirin combined with ginkgo leaf extract and dipyridamole in treatment of acute cerebral infarction. Chinese Journal of Misdiagnostics 2009; 9: 8844-8845.
[26] Zhu JL. Clinical observation of ginkgo leaf extract and dipyridamole combined with aspirin for the treatment of 100 cases of patients with cerebral infarction. Chinese Journal of Medical Guide 2009; 11: 447.
[27] Wang N, Yang CH, Ai ZY. Ginkgo leaf extract and dipyridamole plus aspirin in treatment of acute cerebral infarction and its effect on plasma lysophosphatidic acid and phosphatidic acid level. Journal of Practical Medicine 2009; 25: 4032-4034.
[28] Zheng XD. Curative effect of ginkgo leaf extract and dipyridamole combined with aspirin in the treatment of acute cerebral infarction. Modern Clinical Medicine 2007; 33: 171-173.
[29] Zhai QJ, Han EJ, Guo P. Effect on a small dose of aspirin plus ginkgo leaf extract and dipyridamole injection on platelet function in patients with acute cerebral infarction. Modern Journal of Integrated Traditional Chinese and Western Medicine 2005; 14: 2235-2237.
[30] Gardner CD, Zehnder JL, Rigby AJ, Nicholus JR, Farquhar JW. Effect of ginkgo biloba (EGb 761) and aspirin on platelet aggregation and platelet function analysis among older adults at risk of cardiovascular disease: a randomized clinical trial. Blood Coagul Fibrinolysis 2007; 18: 787-793.
[31] Zhang C, Zhu C, Ling Y, Zhou X, Dong C, Luo J, Liu Y. The clinical value of huangqi injection in the treatment of leucopenia: a meta-analysis of clinical controlled trials. PLoS One 2013; 8: e83123.

[32] Zhu C, Gao Y, Jiang T, Hao C, Gao Z, Sun Y. Meta-analysis of huangqi injection for the adjunctive therapy of aplastic anemia. Int J Clin Exp Med 2015; 8: 10256-10264.
[33] Shi L, Xie Y, Liao X, Chai Y, Luo Y. Shenmai injection as an adjuvant treatment for chronic cor pulmonale heart failure: a systematic review and meta-analysis of randomized controlled trials. BMC Complement Altern Med 2015; 15: 418.
[34] Zhu C, Cao H, Zhou X, Dong C, Luo J, Zhang C, Liu J, Ling Y. Meta-analysis of the clinical value of danshen injection and huangqi injection in liver cirrhosis. Evid Based Complement Alternat Med 2013; 20: 842824.
[35] Wu J, Zhang X, Zhang B. Qingkailing injection for the treatment of acute stroke: a systematic review and meta-analysis. Journal of Traditional Chinese Medicine 2014; 34: 131-139.
[36] Liu Y, Huang Y, Zhao C, Qin X, Zhu Q, Chen S, Qu J. Salvia miltiorrhiza injection on pulmonary heart disease: a systematic review and meta-analysis. The American Journal of Chinese Medicine 2014; 42: 1315-1331.
[37] Du XF, Zhan WH, Zhang ML. The progress of the clinical application of ginkgo leaf extract and dipyridamole injection. Clinical Focus 2007; 22: 1367-1368.
[38] Belougne E, Aguejouf O, Imbault P, Azougagh Oualane F, Doutremepuich F, Droy-Lefaix MT, Doutremepuich C. Experimental thrombosis model induced by laser beam. Application of aspirin and an extract of ginkgo biloba: EGb 761. Thromb Res 1996; 82: 453-458.
[39] Chang LC, Huang N, Chou YJ, Kao FY, Hsieh PC, Huang YT. Patterns of combined prescriptions of aspirin-ginkgo biloba in Taiwan: a population-based study. J Clin Pharm Ther 2008; 33: 243-249.