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Inkgo Biloba-like Injection of Traditional Chinese Medicine for Acute Ischemic Stroke Net Meta-Analysis of Validity and Safety

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Abstract: ***Objective To systematically evaluate the efficacy and safety of Ginkgo biloba-based herbal injections for the treatment of acute ischemic stroke (AIS). Methods SinoMed, VIP, Wan Fang Data, CNKI, Pub Med, EMbase, The Cochrane Library, and Web of Science databases were searched to collect randomized controlled trials (RCTs) with the efficacy and safety of Ginkgo biloba-based herbal injections for the treatment of AIS, and the search timeframe was from the establishment of the database to the end of December 2022. December 2022, the time frame of the search was from the establishment of the database to December. Literature screening, extraction of information, quality and risk of bias evaluation were independently operated by 2 researchers, and after the extracted data were used to create a database using Excel, reticulated Meta-analysis was performed using Stata 16.0 software. Results A total of 148 RCTs were included, and a total of 6 ginkgo biloba herbal injections were included: shuxinin injection combined with conventional western medicine (SXN + CT), ginkgoloderm injection combined with conventional western medicine (GD + CT), ginkgo biloba leaf extract injection combined with conventional western medicine (EGb + CT), ginkgolide injection combined with conventional western medicine (GK + CT), ginkgolides diterpene lactone Glucosamine Injection combined with Western medicine conventional treatment (DGMI + CT), Apricot Ligustrum Sodium Chloride Injection combined with Western medicine conventional treatment (FT + CT) and Western medicine conventional treatment (CT). The results of reticulated Meta-analysis showed that: 1) In terms of enhancing the effective rate, the cumulative probability was ranked as follows: GK + CT (74.7%) > SXN + CT (69.7%) > DGMI + CT (68.8%) > FT + CT (64.1%) > DM + CT (38.5%) > EGb + CT (33.7%) > CT (5%). 2) In terms of NIHSS scores, the cumulative probability ranking was: DGMI + CT (71.9%) > GD + CT (68.9%) > SXN + CT (62.3%) > EGb + CT (57.9%) > FT + CT (44.6%) > GK + CT (43.5%) > CT (1%). (iii) In terms of the Barthel Index, the cumulative probability was ranked as SXN + CT (98.2%) > GD + CT (83.3%) > GK + CT (57.4%) > FT + CT (48.5%) > EGb + CT (35.9%) > DGMI + CT (26.6%) > CT (0%). Conclusion Current evidence suggests that GK + CT is more focused on enhancing clinical effectiveness; DGMI + CT is more focused on reducing NIHSS scores; and SXN + CT is more focused on enhancing BI index. The efficacy of Ginkgo biloba-based herbal injections combined with conventional Western medicine in the treatment of AIS was better than conventional Western medicine in all cases, and the conclusions need to be validated by more high-quality RCTs due to the limitations of the quality and quantity of literature included in the study.***

Keywords: Ginkgo biloba, Traditional Chinese medicine injection, Acute ischemic stroke, RCT, Reticulation Meta-analysis, Efficacy, Safety**.**

1. Introduction

AIS is one of the major causes of human death and disability [1] AIS is the ischemic and hypoxic necrosis of blood-supplying brain tissues due to various causes of local blood supply disorders in brain tissues, which accounts for about 70% of clinical strokes, and its high rate of disability and mortality also poses a serious burden on society [2-4]. The high rate of disability and death has also caused a serious burden on the society. Nowadays, people's living standard is improving, the risk factors of IS are also exposed, the age of onset is gradually decreasing, but the number of onset is increasing, which has become a problem that cannot be ignored.

More and more clinical trials have shown that the use of Ginkgo biloba-based herbal injections combined with CT in the treatment of AIS has more obvious therapeutic effects than CT alone. Compared with oral proprietary Chinese medicines and Chinese medicine soup, Chinese medicine injection is characterized by shorter onset of action and better therapeutic effect. Thus, in this study, we collected RCTs of ginkgo biloba-based herbal injections for the treatment of AIS, and finally screened out six herbal injections, namely, Shuxu Xuning Injection, Ginkgo Damo Injection, Ginkgo Biloba Extract Injection, Ginkgolide Injection, Ginkgolide Diterpene Lactone Dextran Injection, and Apricot Rhizoma Ligustrum Sodium Chloride Injection. Through reticulated Meta-analysis, the efficacy rates of the six oral pCms for the treatment of AIS were comprehensively compared and ranked according to the efficacy, NIHSS score, and BI index, with a view to providing evidence-based medical evidence for the rational use of drugs in the clinic.

1.1 Inclusion Criteria

1.1.1 Types of research

RCT of Ginkgo biloba-based herbal injections for the treatment of AIS, language restricted to Chinese and English.

1.1.2 Subject of the study

Patients with a definite diagnosis of AIS, aged 30-80 years, with onset within 14 days, race and gender were not restricted.

1.1.3 Interventions

Control group: CT (including antiplatelet, anticoagulation, good cerebral circulation, blood pressure lowering, lipid

regulation, etc.) recommended by the Chinese Guidelines for Diagnosis and Treatment of Ischemic Stroke in the Acute Phase of Ischemic Stroke or with placebo; the experimental group was coadministered with Ginkgo biloba-based traditional Chinese medicine injections on the basis of the control group (including Shuxu Xuning injection, Ginkgundamo injection, Ginkgoloderma injection, Ginkgoloderma injection, Ginkgoloderma injection, Ginkgo diterpene glucosamine injection, and Ginkgoloderma injection). Lactone Glucosamine Injection, see Table 1 for specific information). The course of treatment for both the test and control groups was 14-15 days.

1.1.4 Indicators of results

(i) Total effective rate, refer to the efficacy evaluation standard adopted by the 4th National Academic Conference on Cerebrovascular Disease. Basic cure: reduction of neurological deficit score by 91% to 100%; significant effect: reduction of neurological deficit score by 46% to 90%; progress: reduction of neurological deficit score by 18% to 45%; no change: reduction of neurological deficit score by 0 to 17%; deterioration: increase of neurological deficit score. Progress: decrease in neurologic deficit score by 18% to 45%; no change: decrease in neurologic deficit score by 0 to 17%; deterioration: increase in neurologic deficit score. (ii) Neurologic deficit score (NIHSS). (iii) BI index.

1.2 Exclusion Criteria

(i) duplicated published literature; (ii) non-RCTs, such as animal experiments, reviews, guidelines, meta-analyses, and theoretical experiences; (iii) studies that included non-CTs in the control measures, such as herbal preparations, acupuncture, and other TCM therapies; and (iv) studies with unavailable literature and missing data. (vi) Literature with unclear treatment course. (vii) Sample size of less than 30 cases per group.

1.3 Search Strategy

Computerized search of SinoMed, VIP, Wan Fang Data, CNKI, Pub Med, EMbase, The Cochrane Library, Web of Science databases, screening for RCTs with efficacy and safety of Ginkgo biloba-based herbal injections for the treatment of AIS, with a timeframe of the search from the library's construction to December 2022 The time frame of the search was from library construction to December 31, 2022. The search was conducted by combining subject terms and free terms, adjusted according to the search characteristics of different databases, as well as searching clinical trial registration websites. The Chinese search terms included: cerebral infarction, stroke, ischemic stroke, cerebral infarction, shuxuenin injection, ginkgolodamo injection, apricot rhizome sodium chloride injection, ginkgolodendrolactone dextran injection, and so on; and the English search terms included: ischemic stroke, Stroke, Acute Ischemic, traditional Chinese medicine, Shuxuu medicine, and clinical trial registration website. medicine, Shuxuening Injection, Ginkgo Leaf Extract and Dipyridamole Injection, randomized controlledtrial, and so on.

1.4 Literature Screening and Data Management

The studies were screened independently by 2 researchers according to the NERC criteria, and after the screening was completed, the information was extracted and eventually cross-checked, and if inconsistencies arose during the data organization process, they could be determined by discussion or by a 3rd party. Using Note Express Literature Manager to check the imported studies, the initial screening is to read the titles and abstracts of the literature, and exclude the literature that obviously does not meet the criteria, and then read the full text of the literature when rescreening to determine whether the literature meets the inclusion criteria. When encountering the inability to obtain the full text or important information, it can be obtained by contacting the author of the article via e-mail or telephone. The final included literature used Excel to extract the content, which mainly included: title, publication date, 1st author, intervention, course of treatment, and outcome indicators.

1.5 Quality Assessment and Bias Analysis of Included Studies

This study was evaluated for quality according to the Jadad Quality Rating Scale, in which 2 researchers independently evaluated the quality of the included studies, including the generation of random sequences, randomization concealment, execution of the blinding method, and whether to describe withdrawal and exit, and cross-checked after the independent evaluation, and in case of inconsistency, it was possible to discuss the results or have a 3rd party judge the results. A score of 1 to 3 was considered low quality, and a score of 4 to 7 was considered high quality.

1.6 Statistical Analysis

This study was statistically analyzed using Stata 16.0 software. Mean difference (MD) was used for continuous data, and risk ratio (RR) was used for the statistical effect analysis of dichotomous variables, and 95% confidence intervals (CI) were used. The network group command was used for data preprocessing in the retrospective meta-analysis, and network evidence diagrams and "compare-correct" funnel plots were drawn for each outcome indicator, and two-by-two comparisons of different interventions were performed, and efficacy was ranked according to the cumulative area under the working curve (SUCRA). Inconsistency test was performed when there was a closed loop, and the P value and inconsistency factor (IF) of the 95% CI and Z test were calculated; when $P>0.05$ and the lower limit of the 95% CI of the IF value was equal to 0, it was regarded as a better consistency of the results of the direct and indirect comparisons, and conversely, it was regarded that there was a significant inconsistency in the closed loop.

2. Results

2.1 Literature Search Process and Results

A total of 4792 relevant papers were obtained from the initial review, and 148 RCTs were finally included after checking, reading the title, abstract, and full text [5-152]. After the screening process, 148 RCTs were finally included.

2.2 Basic Characteristics of the Included Literature

A total of 148 papers were included in this study, with a total

sample size of 16,809 cases, including 8,426 cases in the experimental group and 8,383 cases in the control group. The maximum sample size was 760 cases and the minimum sample size was 60 cases. A total of six traditional Chinese medicine injections were included: shuxinin injection, ginkgoloderm injection, ginkgo biloba leaf extract injection, ginkgolide injection, ginkgolide diterpene lactone glucosamine injection, and apricot rhizome sodium chloride injection, and a table of the basic characteristics of the included studies is shown in Table 1.

Table 1: Basic information about the included literature

Inclusion of studies	Sample size T/C	intervention T	C	treatments (d)	outcome indicator	Jadad Rating
Li Dongwei [5] 2006	34/31	SXN 20mL + CT	CT	14	①	1
Zhang Rili [6] 2007	67/62	SXN 20mL + CT	CT	15	①	1
Wang Jieming [7] 2008	56/40	SXN 20mL + CT	CT	14	①	1
Chen Junhong [8] 2008	115/114	SXN 40mL + CT	CT	15	①④	6
Li Lijuan [9] 2009	75/75	SXN 5mL + CT	CT	14	③④	1
Yan Xingya [10] 2010	30/30	SXN 20mL + CT	CT	14	①④	0
Yang Essence [11] 2010	48/48	SXN 20mL + CT	CT	14	①④	1
Du Xianlan [12] 2010	104/102	SXN 20mL + CT	CT	14	②	0
TAN PENG TEN [13] 2011	37/36	SXN 20mL + CT	CT	14	②	1
Wu Yan [14] 2011	30/30	SXN 10mL + CT	CT	14	①	1
Shao Jingen [15] 2011	43/43	SXN 20mL + CT	CT	14	①④	1
Xuehui Li [16] 2011	120/120	SXN 20mL + CT	CT	14	①	1
Zhang Yijun [17] 2012	80/80	SXN 20mL + CT	CT	14	①	2
Zhang Wei [18] 2012	60/60	SXN 20mL + CT	CT	14	①	0
Zhou Shenghua [19] 2012	45/45	SXN 20mL + CT	CT	14	①	1
Schuco [20] 2013	30/30	SXN 10mL + CT	CT	14	②	1
Guo Wenjie [21] 2013	35/35	SXN 20mL + CT	CT	14	①	1
Wang Huirong [22] 2014	40/40	SXN 20mL + CT	CT	14	②	2
Qin Deyou [23] 2014	30/30	SXN 20mL + CT	CT	14	①	1
Han Yafei [24] 2014	36/36	SXN 10mL + CT	CT	14	①	1
Lan Chaoyang [25] 2015	100/100	SXN 20mL + CT	CT	14	①	2
Cushman's Pavilion [26] 2016	40/40	SXN 20mL + CT	CT	14	①	1
Ching Chiu Lin [27] 2016	40/40	SXN 10mL + CT	CT	14	①	2
Li Yun [28] 2018	65/65	SXN 20mL + CT	CT	14	②	1
Duan Hechun [29] 2018	35/35	SXN 20mL + CT	CT	14	①②③	1
Catherine Yin [30] 2020	34/34	SXN 20mL + CT	CT	14	①②	2
Yang Baohua [31] 2020	43/43	SXN 20mL + CT	CT	14	①②	2
Li Zhentao [32] 2020	40/40	SXN 25mL + CT	CT	15	② ④	1
Chen Dong [33] 2020	74/74	SXN 20mL + CT	CT	14	①②	2
Xu Mingchang [34] 2021	47/46	SXN 20mL + CT	CT	14	②	2
Peng Jie [35] 2021	37/37	SXN 20mL + CT	CT	14	①②	2

T-test group; C-control group; CT-conventional Western medicine treatment;
① Overall effective rate ② NIHSS score ③ BI index ④ Number of cases of adverse events

2.3 Evaluation of the Quality of the Included Literature

Of the 148 papers included, 70 studies [8, 11, 22, 25, 28, 30, 31, 33] used the randomized table of numbers method, The studies mentioned blinding, of which 1 was blinded to patients, medical staff, and researchers and operated using the randomized envelope method; the other 1 was double-blind and implemented allocation concealment and reported cases of shedding. None of the remaining studies mentioned blinding, allocation concealment, reporting of lost visits, or dropout cases. According to Jadad scale, 1 study scored 6 points and 1 study scored 5 points as high quality literature, 75 studies scored 2 points, 64 studies scored 1 point and rest of the literature scored 0 points as low quality literature as shown in Table 1.

2.4 Evidence Networks

A total of 6 herbal injections were involved in this study, with 4 direct comparisons and no closed-loop formation. The results showed that GD+CT vs CT had the largest number of studies (30 RCTs) and the control group had the largest sample size (n = 1756). The reticulation between interventions is shown in Figure 1.

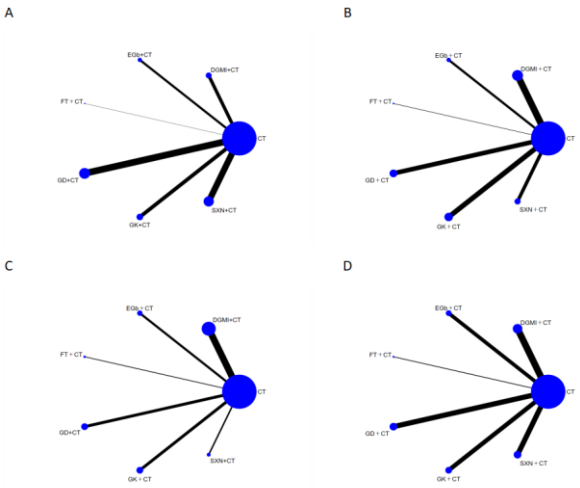

Figure 1: Evidence network for each outcome indicator A - Effectiveness rate B - NIHSS score C - BI score D - Incidence of adverse effects

2.5 Publication Bias Assessment

Publication bias was assessed for each outcome indicator, and the comparison-corrected funnel plot showed poor symmetry and some possible publication bias in the results, see Figure 2.

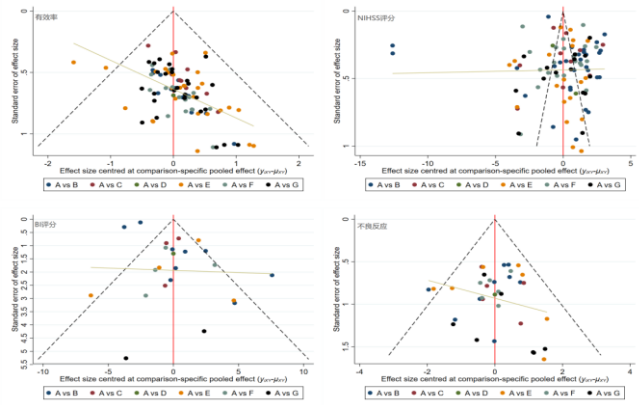

Figure 2: Funnel plot for each outcome indicator

2.6 Net Meta-Analysis

2.6.1 Efficient

2.6.1.1 Net Meta-Analysis

The results of the reticulated Meta-analysis of effectiveness yielded a total of 21 two-by-two comparisons, suggesting that in terms of increasing effectiveness Shu Xuning injection (OR=3.54, 95% CI [2.86, 4.39]), Ginkgolides injection (OR=3.72, 95% CI [2.72, 5.08]), Ginkgoloderma injection (OR=2.90, 95% CI [2.36, 3.56]), Ginkgo biloba extract injection (OR=2.76, 95%CI [2.06, 3.69]), and Ginkgo diterpene lactone glucosamine injection (OR=3.56, 95% CI [2.58, 4.91]) combined with CT were more effective than CT alone, and the difference of the comparisons was statistically significant (P<0.05), which showed that the results showed that GK + CT was more focused on improving the clinical effectiveness. See Table 2.

Table 2: Meta-analysis of efficient netting

intervention	OR [95% CI]						
	SXN + CT	GK + CT	GD + CT	FT + CT	EGb + CT	DGMI + CT	CT
SXN + CT	0						
GK + CT	0.95 [0.65,1.39]	0					
GD + CT	1.22 [0.91,1.64]	1.28 [0.88,1.87]	0				
FT + CT	0.93 [0.24,3.64]	0.98 [0.25,3.89]	0.76 [0.20,2.97]	0			
EGb + CT	1.28 [0.89,1.84]	1.35 [0.88,2.07]	1.05 [0.74,1.50]	1.38 [0.35,5.46]	0		
DGMI + CT	1.00 [0.68,1.47]	1.05 [0.67,1.64]	0.82 [0.56,1.20]	1.07 [0.27,4.26]	0.78 [0.50,1.20]	0	
CT	3.54 [2.86,4.39]	3.72 [2.72,5.08]	2.90 [2.36,3.56]	3.80 [0.99,14.58]	2.76 [2.06,3.69]	3.56 [2.58,4.91]	0

2.6.1.2 SUCRA probability ranking

With regard to the enhancement of clinical efficiency by Ginkgo biloba herbal injection combined with CT regimen, the probability of SUCRA was ranked as GK + CT (rank=2.5)>SXN + CT (rank=2.8)>DGMI + CT (rank=2.9)>FT + CT (rank=3.2)>GD + CT (rank=4.7)>EGb + CT (rank=5.0)> CT (rank=7.0), as shown in Figure 4. 5.0)> CT (rank=7.0), see Figure 3.

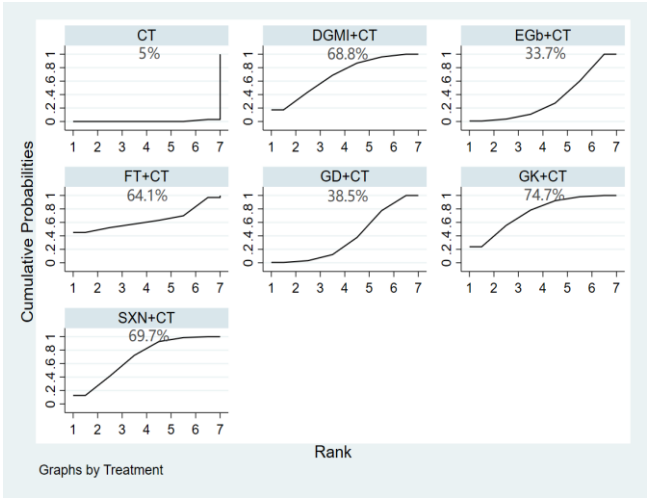

Figure 3: Efficient probabilistic ordering

3. Discussion

The efficacy of Chinese medicine in the treatment of stroke is well documented, and with the development of science and technology, the number of therapeutic measures and protocols in Chinese medicine has been increasing [36]. With the development of science and technology, the therapeutic measures and programs of Chinese medicine have been increasing. As a milestone in the process of modernization of Chinese medicine, Chinese medicine injection has become one of the characteristics of Chinese medicine, which has the advantages of fast onset of action and high bioavailability, and has been widely used in clinical treatment [37]. AIS belongs to the category of "Stroke Disease" in Chinese medicine, and it is believed that stroke is caused by a combination of positive deficiency and evil substance, with positive deficiency being the root cause of the disease, mostly due to insufficient qi and blood, and yin deficiency of the liver and kidney; and evil substance being the symptom of the disease, with stagnation of blood stasis, phlegm, wind, and fire being the main causes. The main causes of the disease are stasis, phlegm, wind and fire. Clinically, AIS is mostly caused by meridian stasis, and Ginkgo biloba has the efficacy of activating blood circulation and removing blood stasis, clearing the channels and relieving pain, resolving turbidity and lowering lipids, etc. Traditional Chinese medicine injections containing Ginkgo biloba have been playing a pivotal role in the clinical treatment of AIS. The Chinese medicine injections containing Ginkgo biloba have been playing a pivotal role in clinical treatment.

The results of this study showed that the efficacy of Ginkgolides herbal injection combined with CT was significantly better than that of CT alone, and GK + CT was the most efficacious in terms of enhancing the clinical efficiency. The main starting components of ginkgolide injection are ginkgolides A, B, and C and bilobalide [38] Ginkgolides A, B, C and bilobalide, which have the effects of promoting neurogenesis, reducing cerebral edema, antioxidant, improving energy metabolism, anti-inflammatory, and pro-angiogenesis [39]. The present study was conducted to determine the degree of neurological deficits. In this study, the degree of neurological deficits was used as an indicator to analyze and evaluate the efficiency, so the role of ginkgolide injection in enhancing the efficiency may be related to its neuroprotective and restorative effects.

DGMI + CT had the best efficacy in reducing the NIHSS score.

The results of reticulation meta-analysis showed that: (1) in terms of increasing clinical efficiency, the cumulative probability ranking was: GK + CT (74.7%) > SXN + CT > DGMI + CT > FT + CT > DM + CT > EGb + CT > CT. (2) in terms of decreasing NIHSS score, the cumulative probability ranking was: DGMI + CT > GD + CT > SXN + CT > EGb + CT. (3) in terms of increasing Barthel index, the cumulative probability ranking was: SXN + CT > GK + CT > FT + CT > GK + CT > CT. CT＞FT＋CT＞GK＋CT＞CT. 3) In terms of improving the Barthel Index, the cumulative probability ranking was: SXN＋CT＞GD＋CT＞GK＋CT＞FT＋CT＞EGb＋CT＞DGMI＋CT＞CT, and all of the above rankings were statistically significant. In terms of safety, a total of 68 RCTs reported adverse reactions, mostly headache, dizziness, gastrointestinal reactions and rash mainly, but no serious adverse reactions, and none of them were statistically significant, indicating that Ginkgo biloba-based herbal injections have a good safety profile for the treatment of AIS.

4. Summary

In summary, GK + CT is the best for improving clinical efficiency, DGMI + CT is effective in reducing NIHSS score, and SXN + CT is advantageous in improving BI index. Ginkgo biloba-based herbal injections are effective and safe in the treatment of acute AIS. Due to the limitation of the quality and quantity of literature included in the study, more high-quality RCTs are needed to verify the findings.

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