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Systematic Review

Injections of ginkgo in the treatment of cerebral infarction: A systematic review and network Meta-analysis☆

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ABSTRACT

Objective: To assess the clinical effectiveness and safety of injections of ginkgo (GI) combined with Western Medicine (WM) for cerebral infarction (CI).

Methods: Randomized controlled trials (RCTs) of CI treated by GI were searched in China National Knowledge Infrastructure Database, Wanfang, China Science and Technology Journal Database, Web of Science, Cochrane library, Embase, PubMed and Chinese Biomedical Literature Database, with the publication data no later than April, 2016. The Cochrane risk of bias method was used to evaluate the methodological quality of the RCTs. The data were analyzed by Review Manager 5.3, Stata 13.0, and WinBUGS 14 software.

Results: Totally 37 RCTs involving 4330 patients were included. By direct comparison, the results of GI group were significantly superior to the routine WM group in the total effective rates [$OR = 3.61$, 95% CI (2.93, 4.44), $P < 0.0001$], the neural function defect score (NFDS) [$MD = -4.39$, 95% CI (-5.47, -3.32), $P < 0.0001$]. Network Meta-analysis (NMA) results showed that, between 5 GIs in efficacy, the difference comparing ginaton injections (GbE) to ginkgo-dipyidamolum injections (GD) [$OR = 1.74$, 95% CI (0.73, 3.65)], shuxuening injections (SXN) [$OR = 1.06$, 95% CI (0.609, 1.697)] or ginkgolides injections (GK) [$OR = 4.711$, 95% CI (1.178, 13.21)] reach statistical significance; the difference comparing GD to GK reach statistical significance [$OR = 2.791$, 95% CI (0.866, 6.908)]; the difference comparing SXN to GK reach statistical significance [$OR = 4.537$, 95% CI (1.203, 12.41)]. Besides, there was no difference between 4 GIs in NFDS. Probability ranking result showed a great possibility for GK [Surface under the Cumulative Ranking curve (SUCRA) = 80.3%] in improving the total effective rates, which were followed by GD (SUCRA = 73.34%), SXN (SUCRA = 46.59%), GbE (SUCRA = 45.46%), floium ginkgo extract and tertram ethypyrazine sodium chloride injections (FT) (SUCRA = 35.64%). However, GK (SUCRA = 80.3%) or GbE (SUCRA = 69.4%) was better than other GIs in reducing NFDS. GK + WM is the best treatment measures to reduce NFDS in cerebral infarction, which were followed by SXN + WM (SUCRA = 51.6%), GD + WM (SUCRA = 48.1%).

Conclusion: GIs was more effectiveness on CI than the routine Western Medicine. But based on the limitations of the study, more high-quality randomized controlled trials will be necessary.

1. Introduction

Cerebral infarction (*CI*), also known as ischemic stroke, refers to the local brain blood circulation disorders, ischemia, and hypoxia due to softening of necrosis. The clinical symptoms of cerebral infarction are complex. The occurrence of cerebral infarction is associated with parts of the damage, the severity of cerebral ischemia, and prior to the onset of other diseases, etc [1]. People usually suffer CI at the age of 50–60, but now this situation is becoming younger, so the incidence of cerebral infarction has severely influenced human health [2]. At present, the main way to treat cerebral infarction include: thrombolytic therapy, platelet aggregation therapy, anticoagulant therapy, reduced fiber treatment and Traditional Chinese Medicine therapy [3]. At now, a large number of clinical trials show that injections of ginkgo (GI) has a significant effect in treating cerebral infarction, including ginkgo-dipyidamolum injections (GD), shuxuening injections (SXN), gina-

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ton injections (GbE), ginkgolides injections (GK) and floium ginkgo extract and tertram ethypyrazine sodium chloride injections (FT). Total flavones of ginkgo biloba have the function of dilated coronary arteries and cerebrovascular, improvement in the symptoms of cerebral ischemia.

Some researchers performed systematic reviews and standard Meta-analyses on clinical effectiveness and safety of GI combined with Western Medicine in treatment of *CI*. However, standard Meta-analysis is unable to include all direct and indirect comparisons among five types of GI in one analysis, while network Meta-analysis (NMA) can conduct a more accurate ranking and precision for the current therapeutic strategies. We aimed to provide a clinically useful summary of the results of the multiple-treatments Meta-analysis that can be used to guide treatment decisions.

2. Material and methods

2.1. Searching strategy

Literature search was conducted in several databases including the China National Knowledge Infrastructure Database (CNKI), the Chinese Scientific Journals Database (VIP), Wanfang Database, Web of Science, the Chinese Biomedical Literature Database (CBM), PubMed, Embase, and the Cochrane Library, with the publication data no later than April, 2016. Chinese search terms include: English search terms include: Shuxuening injections, brain infarction, ischemic stroke, cerebral infarction, ginaton injections, ginkgo leaf extract and dipyridamole injections, ginkgolide injections, floium ginkgo extract and tertram ethypyrazine sodium chloride injections. In PubMed, for example, the specific search strategies of PubMed as following:

#1 "brain infarction"[Mesh]
#2 "ischemic stroke [Abstract/Title]" OR "cerebral infarction [Abstract/Title]"
#3 #1 OR #2
#4 “Ginkgo Leaf Extract and Dipyridamole Injection [Abstract/Title]" OR " Ginaton Injection [Abstract/Title]" OR " Shuxuening Injection [Abstract/Title]" OR " Ginkgolide injection [Abstract/Title]" OR " Floium Ginkgo Extract and Tertram Ethypyrazine Sodium Chloride Injection [Abstract/Title]"
#5 #3 AND #4

2.2. Inclusion criteria

Studies meeting the following criteria were included: (a) Randomized controlled trials (RCTs) used GI as an adjuvant treatment of CI, regardless of blinding. (b) The diagnosis of CI was according to the fourth national cerebrovascular diseases conferences in 1995 [4]. No limitation was placed on age, gender, race or severity of disease. (c) The control group and experimental group were both given WM therapy, including neuroprotective agents, anticoagulants, dehydration, thrombolysis, energy mixture, and calcium antagonists. On the basis of that, experimental group was added one type of CI. (d) The primary outcomes were the total effectiveness of CI. Basic heal was determined when the neurological deficit score decreased by between 90% and 100%, and the level of Sick is "0". Significant progress was determined when the neurological deficit score decreased by between 46% and 90%, and the level of Sick is between "1" and “3". Progress was determined when the neurological deficit score decreased by between 18% and 45%. No change was determined when the functional deficit score decreased by $<$17%. Worsen was determined when the functional deficit score increase. The secondary outcomes were the changes of neural function defect score (NFDS) and adverse drug reactions /adverse drug events (ADRs/ADEs).

2.3. Exclusion criteria

Data were incorrect, incomplete or not available and without separate evaluation of the individual drug were excluded. Besides, reviews, conference abstracts, comments, and research proposal were excluded.

2.4. Data extraction and quality assessment

Two investigators (Tan Di, Liu Shi) independently conducted the literature searching, study selection, data extraction, and assessment of risk of bias. Information extraction included authors, year of publication, study size, participants' age and gender, intervention measurements, outcomes and ADRs by the use of predesigned forms.

The quality assessment was conducted by The Cochrane Risk Assessment Tool, which included random sequence generation, blinding of outcome assessment, blinding of participants and personnel, allocation concealment, selective reporting, incomplete outcome data, and other biases. Each study was rated "high", "unclear", or "low". "High" refers to the random method is not correct, or no allocation concealment or no blinding. "Unclear" means the results are not described in this paper. "Low" means correct random methods, appropriate blinding without being violated through implementation, and a detailed description in the article. Any disagreements were resolved by a third researcher (Wu Jiarui).

2.5. Statistical analysis

Systematic review methods: Review Manager Software (version 5.3), provided by the Cochrane Collaboration was, used for the data analysis. Data were summarized by using relative risk (*RR*) or mean difference (*MD*) with 95% confidence interval (*CI*). The heterogeneity of original studies was evaluated with χ^2 test and *I*-squared statistic. When $P > 0.1$ and $I^2 < 50\%$, a fixed-effect model was used to pool the results; otherwise, a random-effect model was used.

NMA methods: results are reported as odds ratios (*OR*) or standard mean difference (*SMD*) with 95% *CI* for all comparisons of interventions. Initially, the data were analyzed by Stata13.0 software which to draw network diagram. Then, we used the WinBUGS14 software (MRC Biostatistics Unit, Cambridge, UK) to conduct Bayesian network Meta-analyses [5,6]. We calculated 95% *CI* for *OR* using the Markov Chain Monte Carlo methods. Besides, in order to check the consistency of the NMA results, we conducted the inconsistency analysis by using the Stata software. These ranking probabilities were used to calculate the Surface under the Cumulative Ranking curve (SUCRA), which is expressed as percentage (100% for the best intervention and 0% for the worst intervention and approximately 50% for equivalent interventions) [7].

3. Results

3.1. Searching and filtering results

The initial search yielded 1740 studies, and then 321 studies were excluded. With further text reading, 37 studies [8–44] were selected after removing case studies and literatures that did not meet the inclusion criteria. All 37 papers were in Chinese and published no later than April, 2016 (Fig. 1).

3.2. Characteristics of included studies

In total 4330 patients were involved in the Meta-analysis. The average age of the patients was approximately between 50 and 70

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