Meta-Analysis of Traditional Chinese Patent Medicine for Ischemic Stroke

Bo Wu, MD, PhD; Ming Liu, MD; Hua Liu, MD; Wei Li, MD; Song Tan, MD, PhD; Shihong Zhang, MD; Yuan Fang, MD

Background and Purpose—A large number of traditional Chinese patent medicine (TCPM) are widely used for ischemic stroke in China. The aim of this study was to systematically review the existing clinical evidence on TCPM for ischemic stroke.

Methods—We identified all TCPM that were listed in the Chinese National Essential Drug list of 2004 and those commonly used TCPM in current clinical practice for ischemic stroke. Fifty-nine TCPM were identified for further evaluation. We applied Cochrane systematic review methods. We searched for reports of randomized controlled trials and controlled clinical trials on any of the 59 TCPM for ischemic stroke comparing one TCPM with control. Primary outcomes included death or dependency at the end of follow-up (at least 3 months) and adverse events. Effects on neurological impairments were a secondary outcome.

Results—One-hundred ninety-one trials (19,338 patients) on 22 TCPM were available and included, of which 120 were definite or possible randomized controlled trials and 71 were controlled clinical trials. The methodological quality of included trials was generally “poor.” Few trials reported methods of randomization. Three trials were randomized, double blind, and placebo-controlled. Primary outcomes: one trial on Puerarin and one trial on Shenmai injection assessed death or dependency at the end of long-term follow-up (at least 3 months) and found no statistically significant difference between 2 groups. The reported adverse events including allergic reaction, headache, nausea, diarrhea, bellyache, blood pressure change, and subcutaneous ecchymosis. Most of the adverse events were not severe. Secondary outcomes: analysis of the secondary outcome, “marked improvement in neurological deficit,” showed apparent benefits of about the same magnitude for all the TCPM studied. Of the 22 TCPM, 8 drugs (Milk vetch, Mailuoning, Ginkgo biloba, Ligustrazine, Danshen agents, Xuesetong, Puerarin, and Acanthopanax) had relatively more studies and patient numbers.

Conclusions—There was insufficient good quality evidence on the effects of TCPM in ischemic stroke on the primary outcome (death or dependency). We considered the apparent benefit on neurological impairment was as likely to be attributable to bias from poor methodology as to a real treatment effect. However, because the agents assessed appeared potentially beneficial and nontoxic, further randomized controlled trials are justified. Eight drugs could be further research priorities. (Stroke. 2007;38:1973-1979.)

Key Words: ischemic stroke ■ meta-analysis ■ systematic review ■ traditional Chinese patent medicine

Stroke is a major cause of death and disability in the world.1 Prevention and effective treatment of stroke is of utmost importance in China and in the West. The most appreciable distinction between China and the West in treating stroke is the use of acupuncture and traditional Chinese patent medicine (TCPM).2 In China, acupuncture and at least one TCPM that may ameliorate the microcirculation are regularly used in stroke patients in either Western medicine hospitals or traditional Chinese medicine hospitals. Several systematic reviews on the efficacy of acupuncture for ischemic stroke have been published in English.3,4,5 In contrast, few studies have been published in English reporting the effectiveness and safety of many commonly used TCPM,2,6,7 even though they have been widely accepted as a standard treatment for ischemic stroke in China for >30 years.8 Currently, there is as yet no routine effective, generally accepted, specific treatment for ischemic stroke, except for aspirin and thrombolytic treatment with recombinant tissue plasminogen activator for highly selected patients.9 Therefore, confirmation of the effectiveness of TCPM could have a great impact on stroke management in the world.

Pharmacological studies indicated that some TCPM can be used for dilating the cardiocerebral vessels, suppressing the aggregation of platelets, improving circulation, removing...
blood stasis, protecting against ischemic reperfusion injury, and enhancing the tolerance of ischemic tissue to hypoxia.\textsuperscript{10} The most commonly used formulations of TCPM for stroke include injections and tablets. It is uncertain whether there is robust evidence on the clinical effects of TCPM and whether TCPM can be recommended either for routine treatment or considered as a standard treatment in the control group in clinical trials. We are aware of some relevant trials reported in China.

The aim of this study was therefore to assess the quantity, quality and overall strength of the evidence on TCPM in the treatment of ischemic stroke and to identify whether any TCPM appeared sufficiently promising to justify further large-scale randomized trials.

Materials and Methods
We restricted this review to the TCPM listed in the Chinese National Essential Drug (CNED) of 2004 (http://www.sda.gov.cn) and those commonly used TCPM in current clinical practice for ischemic stroke. The drugs in the CNED represent the most important listed by the Chinese government. Commonly used TCPM had more clinical studies reported. Fifty-nine TCPM were identified for further evaluation. Cochrane systematic review methods were applied as much as possible.

Study Identification
Six researchers (B.W., H.L., W.L., S.T., S.Z., Y.F.) independently identified studies on the 59 TCPM through searches of the Cochrane Library (issue 1, 2005), MEDLINE (1966 to March 2005), EMBASE (1980 to March 2005), and the China Biological Medicine Database (CBM-disc 1979 to March 2005), which is a database of Chinese biomedical research literature.

The reference lists of all relevant articles were searched for further studies and the pharmaceutical company manufacturing TCPM was contacted to identify further published and unpublished studies.

Study Selection
Definite or possible randomized controlled trials (RCTs; trials with clear method of randomization were defined as definite RCTs; those allegedly “RCTs” but with unknown methodology were defined as possible RCTs) and controlled clinical trials (studies evaluating a treatment that included an intervention and a control group, in which treatment allocation was not necessarily randomized) on any of the 59 TCPM for ischemic stroke comparing one TCPM with control were eligible.

Trials that included patients of any age or sex with ischemic stroke were eligible. Ischemic stroke was defined if the patients met the World Health Organization or the similar Chinese National criteria (demanding a CT/MRI scan as confirmation) of stroke\textsuperscript{11,12} and hemorrhagic stroke was excluded by CT/MRI scanning. Possible ischemic stroke in which CT/MRI were not performed were also to be included.

Trials evaluating any formulation of TCPM (injection or tablet) were included regardless of length of treatment period and dosage of treatment. The primary outcome measures were death or dependency controlled.\textsuperscript{16–18} One trial on Puerarin\textsuperscript{14} and one trial on Shenmai\textsuperscript{15} had grade A level of adequate concealment of randomization because it allocated patients according to random numbers sealed in the opaque envelopes. The remaining 115 possible RCTs did not describe the methods of randomization. Four trials blinded the assessment of outcome.\textsuperscript{16–19} Only one trial on Puerarin reported the number of patients lost to follow-up and whether they had used intention to treat analysis.\textsuperscript{14} The remaining trials did not mention blinding or intention to treat analysis.

Data Analysis
Heterogeneity between trials results was tested using a standard $\chi^2$ test. The results were reported as Peto ORs with corresponding 95% CI for dichotomous data.\textsuperscript{13} If continuous data were available, weighted mean difference or standardized mean difference was to be calculated. The figures were obtained from the statistical software provided by the Cochrane Collaboration (RevMan 4.2).

Results

Study Identification and Characteristics
Of the 59 TCPM, we found reports of definite or possible RCTs and controlled clinical trials for 22. For the remaining 37 TCPM, we found only uncontrolled observational studies. One-hundred ninety-one trials (19 338 patients) on 22 TCPM were included, of which 120 were definite or possible RCTs and 71 were controlled clinical trials. All trials were conducted in China (1992 to 2004; Table).

The age of patients in the included studies ranged from 18 to 90 years. Each trial included more males (56% to 72%) than females. All included trials applied standard western medicine diagnostic criteria for ischemic stroke although many trials used TCM criteria in addition. All studies reported the need for all patients to have had CT/MRI scanning to confirm the diagnosis.

The timing of the start of treatment after stroke onset was within 14 days in 118 trials. The patients received the treatment within 30 days of stroke onset in the remaining trials. The total duration of treatment with TCPM varied from 14 to 60 days.

Only 2 trials\textsuperscript{14,15} assessed ability of daily living through Barthel Index at 3 months or at 6 months after stroke onset. The remaining 189 trials measured neurological deficit, of which 2 trials used the European Stroke Scale, 1 trial the Canadian Neurological Scale, 186 trials the Modified Edinburgh-Scandinavian Stroke Scale, which was recommended at the Second and revised at the Fourth National Cerebrovascular Diseases Conference in China.\textsuperscript{12} Injection and tablet were studied in these included trials. Only 3 trials were randomized, double blind, placebo-controlled.\textsuperscript{16–18} The remaining 188 trials were designed comparing TCPM plus other treatment in trial group with the same other treatment in control group.

Study Quality
The methodological quality of most included trials was generally “poor.” Few trials reported the method of randomization. Three trials were randomized, double blind, placebo-controlled.\textsuperscript{16–18} One trial on Puerarin\textsuperscript{14} and one trial on Shenmai\textsuperscript{15} had grade A level of adequate concealment of randomization because it allocated patients according to random numbers sealed in the opaque envelopes. The remaining 115 possible RCTs did not describe the methods of randomization. Four trials blinded the assessment of outcome.\textsuperscript{16–19} Only one trial on Puerarin reported the number of patients lost to follow-up and whether they had used intention to treat analysis.\textsuperscript{14} The remaining trials did not mention blinding or intention to treat analysis.
<table>
<thead>
<tr>
<th>Drug</th>
<th>RCT</th>
<th>CCT</th>
<th>Outcome Measures</th>
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<td>Definite, Double Blind, Placebo, Method Clear</td>
<td>Definite, Method Clear</td>
<td>Possible, Method unclear</td>
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<td>Milk vetch injection</td>
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<tr>
<td>Qing Kai Ling injection</td>
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<tr>
<td>Shen Mai injection</td>
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<tr>
<td>Xing Nao Jing injection</td>
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<tr>
<td>Da Huo Luo tablet</td>
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<td><strong>120</strong></td>
<td><strong>71</strong></td>
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**37 TCPM with no Eligible Clinical Trials**

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<tr>
<th>Drug</th>
<th>RCT</th>
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<td>Hua Tuo Zhai tablet</td>
<td>An Gong Jiang Ya tablet</td>
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<td>Er Shi Wu Wei Zhen Zhi tablet</td>
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<td>Niu Huang Qing Xing tablet</td>
<td>Er Shi Wu Wei Shan Hu tablet</td>
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<td>Zhong feng Hui Chun tablet</td>
<td>Xi Xian Tong Shuan tablet</td>
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<td>Nao An tablet</td>
<td>Qiang Li Tian Ma Du Zhong tablet</td>
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<td>Long Deng tablet</td>
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**CCT** indicates clinical controlled trial.
Primary Outcomes

Death or Dependency

One trial on Puerarin (98 patients) assessed death or dependency through Barthel Index at 6 months after stroke onset.14 Dependency was defined as Barthel Index scored 60 or less. There was no statistically significant difference between 2 groups (Peto OR, 0.86; 95% CI, 0.35 to 2.11). One trial on Shenmai (50 patients) injection also assessed death or dependency at 3 months after stroke onset.15 It recorded the mean score and the standard deviation before and after treatment by using Barthel Index. No statistically significant difference was found between the 2 groups (weighted mean difference, 11.58; 95% CI, 9.04 to 32.20). No deaths occurred in these 2 trials.

Adverse Events

No obvious adverse events occurred in 96 trials. Fifty-seven trials did not mention adverse events. Thirty-eight trials on 14 TCPM reported adverse events. It included allergic reaction, headache, nausea, diarrhea, bellyache, blood pressure change, and subcutaneous ecchymosis. Most of the adverse events were not severe. They disappeared without special treatment. The adverse events in trial group were higher than that of the control group on Ginkgo biloba (Peto OR, 5.70; 95% CI, 2.17 to 14.98), Ligustrazine (Peto OR, 2.30; 95% CI, 1.40 to 3.78), Mailuoning (Peto OR, 5.76; 95% CI, 1.40 to 23.74), Puerarin (Peto OR, 4.58; 95% CI, 1.78 to 11.80), Sheng Mai (Peto OR, 7.81; 95% CI, 1.07 to 56.97), and Xue Shuan Xin Mai Ling (Peto OR, 7.55; 95% CI, 1.03 to 55.24). There was no statistically significant difference between 2 groups on the remaining 8 TCPM (Figure 1).

Secondary Outcomes

Neurological Deficit Improvement After Treatment

One-hundred eighty-nine trials (19 190 patients) measured neurological deficit, of which 2 trials used the European Stroke Scale,20,21 1 trial the Canadian Neurological Scale,22 and 186 trials the Modified Edinburgh-Scandinavian Stroke Scale.12 The latter classifies effect on neurological deficit into six categories of “cure,” “significant improvement,” “improvement,” “no improvement,” “deterioration,” and “death” in terms of the change of score before and after the treatment.12 To permit at least some overall analysis, we converted these outcomes into dichotomous data. We grouped together “cure,” “significant improvement,” and “improvement” as “effective” and “no improvement,” “deterioration,” and “death” as “ineffective.” There was no significant heterogeneity among trials on every TCPM (P range from 0.18 to 0.97). Meta-analysis of these trials showed that the improvement of neurological deficit at the end of treatment between the 2 groups was significantly increased with TCPM except for Da Huo Luo (Peto OR, 1.37; 95% CI, 0.29 to 6.56). Eight drugs, Milk vetch, Mailuoning, Ligustrazine, Ginkgo biloba, Xuesetong, Danshen agents, Puerarin, and Acanthopanax, had more studies and >1000 patients, respectively (Figure 2).

Death From Any Cause

Deaths were reported in only 10 trials.14,23–31 No death occurred in the remaining trials. Two trials on Qingkailing injection reported death at the end of treatment,23,24 and treatment was associated with a substantial reduction in the odds of death, although the numbers of events was very small (Peto OR, 0.24; 95% CI, 0.06 to 0.91). No statistically significant difference was found between 2 groups in 1 trial on Acanthopanax (Peto OR, 0.13; 95% CI, 0.01 to 2.15),25 1 trial on Xuesetong injection (Peto OR, 0.13; 95% CI, 0.00 to 6.39),26 1 trial on Ligustrazine (Peto OR, 0.48; 95% CI, 0.05 to 4.74),27 2 trials on Compound Dan Shen injection (Peto OR, 0.63; 95% CI, 0.11 to 3.67),28,29 1 trial on Puerarin14 (Peto OR, 1.04; 95% CI, 0.25 to 4.41), and 2 trials on Milk vetch30,31 (Peto OR, 0.66; 95% CI, 0.11 to 3.83; Figure 3).

Quality of Life

No trial assessed quality of life.
Discussion

This is the first comprehensive review of the most commonly used and Government-approved TCPM for ischemic stroke. In many years, Western medicine has made tremendous progress and had become the dominating medical treatment worldwide. However, it has been increasingly recognized that Western medicine may sometimes fail to treat an illness, whereas such illness is reportedly improved by the so-called complementary medicine based on a different theory. Western doctors often find this difficult to understand. Few relevant articles on TCPM for stroke have been published in the English medical journals, and the limited evaluation of TCPM outside of China reduces its external validity. However, TCPM for stroke are very popular in China, not least because there are few effective, generally accepted, low-cost, specific treatments for the routine treatment of acute ischemic stroke. Currently, there are >100 TCPM used for stroke. These TCPM have been used in clinical practice for 30 years in China and approved by the Chinese State Food and Drug Administration for stroke. However, few researchers evaluated their effectiveness according to current rigorous international standards. Although there have been a few systematic reviews on selected TCPM, no single study has assessed the majority of the commonly used TCPM for ischemic stroke. This review aimed to assess the quantity, quality, and overall strength of evidence of TCPM for stroke.

In this systematic review, there was very limited evidence from RCTs on the effect of TCPM on the primary efficacy outcome (death or dependency); there were just 2 truly randomized controlled trials (of Puerarin and Shenmai injection) that assessed long-term outcome after stroke onset. No definite conclusion can be drawn because of the limited numbers of patients in these 2 trials. Nonetheless, they demonstrate that TCPM can be evaluated with RCT. Furthermore, for the other primary outcome, adverse effects, the data were reassuring. Although adverse events in the intervention groups were generally higher than in controls for 6 TCPM, the adverse reactions were mild and needed no further treatment.

The most striking finding in this review was that the estimate of effect on the secondary outcome, "neurological deficit improvement," for all the TCPM was similar. This size of effect could be real or could just be attributable to bias, because lack of randomization or allocation concealment in a trial of a truly ineffective compound could yield similar estimates. Publication bias could also be a factor. However, because the methodological details for many of these trials were lacking, we tried to contact authors to get further information by telephone, letter, or e-mail. Unfortunately, we got replies from only 8 investigators (on trials of Milk vetch, Mailuoning, Dan Shen agents, Ginkgo biloba, and Puerarin). This extra data allowed us to reclassify 8 "allegedly" randomized studies as quasi-RCTs or controlled clinical trials. We inferred that the remaining trials were unlikely to be true RCT, although there was also no definite evidence to confirm this inference. Therefore, the results should be interpreted cautiously because of the unclear methodology of these trials. Similarly, no definite conclusion can be drawn from these trials. At this level of outcome measure, 8 drugs (Milk vetch, Mailuoning, Ginkgo biloba, Ligustrazine, Danshen agents, Xuesetong, Puerarin, and Acanthopanax) had relatively more studies and patients number (>1000 patients) and perhaps were worthy of further research.
Another striking finding was the very low case fatality rate. Death occurred in only 10 trials. There are a number of possible explanations: a truly low case fatality rate for stroke in China; the patients with severe stroke were not sent to hospitals (admission bias); a reluctance on the part of Chinese stroke physicians to include severe strokes in research studies (selection bias); or failure to report major outcome events (reporting bias) and only trials with low mortality rates submitted their results for publication (publication bias). We were unable to determine which of these factors pertained.

We did not regard the evidence on the effects on death in the small number of trials that reported deaths as reliable. The observed positive results on death might be attributable to lack of true randomization and/or chance. However, based on these 2 uncertain findings on neurological deficit improvement and low case fatality rates, the general lack of reporting of methodology in these trials publication is not consistent with the CONSORT statement on the reporting of the results of randomized trials (http://www.consort-statement.org/); this requirement is being highlighted in many journals around the world but clearly needs additional emphasis in China.

Although some TCPM fell outside of our selection criteria, this review provided the current status on the evidence for the approved TCPM for ischemic stroke in China. The methodological quality of most included trials was generally “poor” because they did not describe their methods in detail. How-
ever, because we sought to report on overall quality, we did not arbitrarily simply exclude them. The limitations of most trials were as follows. In the majority, we could not be sure that treatment allocation was truly randomized and well concealed, or not (this could have led to selection bias); measures at the level of activities of daily living were our primary outcome and the preferred primary outcomes for stroke trials, yet most trials were focused on effects on neurological deficit and impairment (our secondary outcome measure); it was unclear whether most trials had used a blinded method to assess outcome; and, finally, some trials did not report the frequency of adverse events.

In conclusion, a definite conclusion on efficacy and adverse events associated with TCPM cannot be drawn from this review because of the unclear methodological quality of these identified trials. We found no evidence of a beneficial effect on the primary measure of efficacy to support the routine use of TCPM for ischemic stroke. However, the agents appeared to be relatively free of major adverse effects and if the apparently beneficial effects on neurological impairment were confirmed in methodologically rigorous trials, they would lead to many useful treatments for stroke being identified and used outside China. Therefore, further high-quality, large-scale, randomized trials of TCPM for stroke are justified to confirm or refute the effects reported here. We suggest Milk vetch, Mailuoning, Ginkgo biloba, Ligustazine, Danshen agents, Xuesetong, Pueroarin, and Acanthopanax had relatively more studies and patient numbers should be priorities for further research. Future trials should overcome the limitations of the trials presented in this review; in particular, they should assure adequate concealment of allocation, blinding of outcome assessors, and use functional outcome as the primary outcome measured at long-term follow-up. Reports of the trials should conform to the recommendations of the CONSORT statement. If such RCTs designed reliably confirmed that certain TCPM are beneficial for ischemic stroke, this would contribute greatly to the treatment of ischemic stroke worldwide. However, if RCTs did not provide evidence of benefit, this would challenge the whole concept of TCPM. We hope this article will stimulate proper evaluation of TCPM.

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References
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