Meta-analysis of traditional Chinese patent medicine for ischemic stroke  

CRD summary
This review investigated the efficacy and safety of traditional Chinese patent medicines in the treatment of ischaemic stroke. The lack of good-quality evidence led the authors to state that no conclusions could be drawn. Given concerns about the synthesis and poor quality of the data, the authors’ reluctance to draw any conclusions from the evidence appears appropriate.

Authors’ objectives
To systematically review the evidence on the use of traditional Chinese patent medicine (TCPM) for ischaemic stroke.

Searching
The Cochrane Library (Issue 1, 2005), MEDLINE (1966 to March 2005), EMBASE (1980 to March 2005) and the Chinese Biomedical Database (1979 to March 2005) were searched; the search terms were not reported. The bibliographies of relevant articles were screened. The company manufacturing TCPM was contacted for information on other published and unpublished studies. No mention was made of whether language restrictions were applied to the search.

Study selection
Randomised controlled trials (RCTs) and non-randomised controlled trials with at least 3 months' follow-up were eligible for inclusion.

Trials of patients of any age or gender treated for ischaemic stroke were eligible for inclusion. Ischaemic stroke was defined as studies in which patients met the World Health Organization or Chinese National criteria for stroke; the latter involves a confirmatory computed tomography (CT) or magnetic resonance imaging (MRI) scan. Studies of patients with unspecified stroke (haemorrhagic or ischaemic) in which no CT or MRI scan was performed were also eligible for inclusion, although all the patients in the included studies had a confirmatory CT or MRI scan. In the included studies, the patients were aged from 18 to 90 years and 56 to 72% were male.

Intervention inclusion criteria were medicines listed in the Chinese National Essential Drug (2004) and those used in current clinical practice for the treatment of ischaemic stroke. All formulations (tablet or injection) and dosage or treatment regimen were eligible for inclusion. In the included trials, 22 TCPM were studied, the most common being milk vetch injection. No inclusion criteria were given for the control group. The included studies were either placebo-controlled or a comparison was made between a TCPM with another treatment and the same other treatment in the control group. In the majority of included studies, treatment began within 14 days and lasted from 14 to 60 days. All of the trials were conducted in China.

Studies that reported death, adverse effects or dependency were eligible for inclusion. The secondary outcomes were neurological deficit improvement after treatment, all-cause mortality and quality of life. In the included studies, dependency was defined as a score of 60 or less on the Barthel Index.

Six reviewers independently selected the studies, but the authors did not report how any disagreements were resolved.

Assessment of study quality
The reviewers stated that study quality was assessed, but did not explain what scale was used. The criteria assessed were randomisation, allocation concealment, blinding, intention-to-treat analysis and number of patients lost to follow-up.

Six reviewers performed the quality assessment, but the authors did not state how any disagreements were resolved.

Data extraction

Database of Abstracts of Reviews of Effects (DARE)
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Six reviewers independently extracted the data, but the authors did not report how any disagreements were resolved. Where possible, the authors of included trials were contacted to obtain missing data.

**Methods of synthesis**

Meta-analyses were used to compute pooled odds ratios (ORs) with 95% confidence intervals (CIs) using the Peto method for dichotomous outcomes. The authors did not state whether the reported results were derived from fixed-effect or random-effects models. Continuous outcomes were pooled using weighted or standardised mean differences. Heterogeneity between the studies was investigated using a $\chi^2$ test. It appears from the results that the reviewers used meta-analysis to pool the results of studies of different TCPM. However, it is unclear how different studies of the same TCPM were pooled for the primary outcomes.

**Results of the review**

One hundred and ninety-one trials (19,338 participants), 120 of which were definite or possible RCTs and 71 of which were controlled trials, were included in the review.

The authors rated most of the trials as poor quality. One hundred and fifteen possible RCTs failed to describe methods of randomisation, only 4 trials used blinded outcome assessment, and only one trial described using an intention-to-treat analysis and reported the number of participants lost to follow-up.

Death and dependency: one trial of Puerarin and one of Shen Mai found no statistically significant difference in dependency between the intervention and control groups. There were no deaths in either of these trials.

Adverse events (38 trials, including 14 TCPM): treatment with the intervention was associated with a statistically significant higher risk of adverse events compared with control (OR 2.55, 95% CI: 1.88, 3.45, $p<0.001$). There was no evidence of statistical heterogeneity ($p=0.26$). Specific TCPM for which there were significantly higher adverse events than placebo were Ginkgo biloba (OR 5.70, 95% CI: 2.17, 14.98), Ligustrazine (OR 2.30, 95% CI: 1.40, 3.78), Mailuoning (OR 5.76, 95% CI: 1.40, 23.74), Puerarin (OR 4.58, 95% CI: 1.78, 11.80), Sheng Mai (OR 7.81, 95% CI: 1.07, 56.97) and Xue Shuan Xin Mai Ling (OR 7.55, 95% CI: 1.03, 55.24).

Neurological benefit (189 trials, including 22 TCPM): treatment with the intervention was associated with a significantly greater benefit in neurological state compared with control (OR 3.39, 95% CI: 3.14, 3.65, $p<0.001$). There was no evidence of statistical heterogeneity ($p=0.07$). Each individual compound other than Da Huo Luo was associated with improved neurological benefit.

All-cause mortality (10 trials, including 7 TCPM): treatment with the intervention was associated with a significantly lower all-cause mortality compared with control (OR 0.46, 95% CI: 0.23, 0.93, $p=0.03$). There was no evidence of statistical heterogeneity ($p=0.75$).

No trial assessed quality of life.

**Authors' conclusions**

Given the lack of good-quality evidence, no conclusions about efficacy or safety could be drawn.

**CRD commentary**

The review addressed a clear but broad research question. Attempts were made to identify both published and unpublished studies, but it is difficult to assess the reliability of the search without further details of the search terms used. Efforts were made to minimise bias and errors during the study selection, quality assessment and data extraction processes.

The methods of synthesis are not clear. In the forest plots for the meta-analysis, there is one row per TCPM rather than per trial; it is therefore unclear how the pooled OR per TCPM were derived. The included studies did not describe what the control intervention was for any trial other than the few placebo-controlled trials. In addition, there were few details about the intervention regimens, study populations and study designs, which makes it difficult to assess whether it was appropriate to combine the data, although little or no statistical heterogeneity was reported. The authors also highlighted a number of other concerns about the study data and their reliability.
Despite the concerns about the review methodology and given the poor quality of the included studies, the authors' decision not to draw any conclusions because of the lack of good-quality evidence is appropriate.

**Implications of the review for practice and research**

Practice: There is currently no evidence to support the routine use of TCPM for ischaemic stroke.

Research: Further high-quality RCTs that conform to the CONSORT (Consolidated Standards of Reporting Trials) guidelines, and which investigate the efficacy of TCPM in ischaemic stroke patients, are warranted. These should focus, in particular, on Milk vetch, Mailuoning, Ginkgo biloba, Ligustrazine, Danshen agents, Xuesetong, Puerarin and Acanthopanax.

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