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Chinese herbal medicine Dengzhan Shengmai capsule as adjunctive treatment for ischemic stroke: A systematic review and meta-analysis of randomized clinical trials

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ABSTRACT

Objective: The existing eligible randomized controlled trials (RCTs) were critically appraised for the effectiveness and safety of Chinese herbal medicine Dengzhan Shenmai for ischemic stroke.
Design: Systematic review and meta-analysis (CRD42016042914, http://www.crd.york.ac.uk/PROSPERO).
Methods: Six electronic databases were searched from inception to May 2016. Risk ratio (RR) and mean difference (MD) with a 95% confidence interval (CI) were used as effect estimates using RevMan 5.3. Meta-analysis was performed where data were available. A summary of finding table was generated by the GRADEpro (version 3.6).
Results: We identified 14 RCTs involving 5206 participants. Majority of the included trials were of high risk of bias in methodological quality. For acute ischemic stroke, adding DZSM capsule to conventional therapy achieved higher Barthel Index scores (MD 22.37, 95% CI 21.34–23.40), lower neurological function deficit scores (MD – 3.73, 95% CI −5.27 to −2.19) and lower recurrence rate (RR 0.22, 95% CI 0.10, 0.46). For patients in their convalescence (or sequelae) stage of ischemic stroke, DZSM capsule was superior in improving quality of life (MD 28.8, 95% CI 7.10–50.50) and recurrence rate (RR 0.71, 95% CI 0.51–0.99) compared to placebo. No trials reported serious adverse events.
Conclusion: DZSM capsule appears to improve neurological function, quality of life, and reduce recurrence rate based on conventional therapy for ischemic stroke. DZSM capsule seems generally safe for clinical application. However, the findings of benefit are inconclusive due to generally weak evidence, and further large, rigorous trials are still warranted.

1. Introduction

Strokes are caused by disruption of the blood supply to the brain.[1] It is now the second most common cause of death and a major cause of disability worldwide.[2] According to the World Health Organization, 15 million people suffer a stroke worldwide every year: 5 million people die and another five millions are left permanently disabled, placing a heavy burden on family and community.[1] Approximately 67% of all strokes are ischemic in Asian populations.[3] In china, the prevalence rate of stroke is 1.23% until 2013, the mortality is 1.88 million per year, cumulative recurrence rate during 5 years more than 30%, and stroke survivors suffer serious neurological disorders (loss of vision, speech or both, paralysis, and confusion).[4]

According to its natural course, ischemic stroke can be divided into 3 stages: the acute stage (less than two weeks from symptom onset), convalescence stage (2 weeks to 6 months from symptom onset), and sequelae stage (6 months or longer from symptom onset).[5] At present, available therapies for acute ischemic stroke are reperfusion-based strategies, including intravenous fibrinolysis and endovascular intervention.[5] Because of their limitations of time or indications, they are only available for few patients and have a moderate effect.[6,7] In addition, the anti-platelet drugs were reported to have a high risk of

Abbreviations: DZSM, dengzhan shengmai; RCTs, randomized clinical trials; BI, Barthel Index; mRS, the modified Rankin Scale; NIHSS, national institutes of health stroke scale; NFDS, neurological function deficit score; SS, QOL Stroke Specific Quality of Life Scale

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intracranial bleeding and the anticoagulants do not improve the long-term outcomes.[8] Despite aggressive control of known risk factors, the recurrence rate of stroke remains high.[9]

We searched PubMed and identified 2 systematic reviews.[10,11] of Chinese patent medicine for ischemic stroke. Both reviews included randomized controlled trials (RCTs) and showed that Chinese patent medicine Xingnaojing (13 RCTs, 1514 participants, searched up to Nov 2013) and Ligustrazine (3 RCTs, 643 participants, searched up to Dec 2012) might be beneficial for the treatment of stroke, but more high quality RCTs are needed to confirm the positive findings. In China, Dengzhan Shengmai (DZSM) capsule was commonly used for cardiovascular diseases, and it was approved for sequelae stage of stroke on market by the China Food and Drug Administration (CFDA) in 2002. As a Chinese patent herbal medicine, developed from the traditional classical prescription (Powder for Restoring Pulse Beat), it consists of ingredients from four herbs, including *Erigeron breviscapus, Panax ginseng, Ophiopogon japonicas* and *Schisandra chinensis*. It may augment the immunity through supplementing 'Qi', nourishing 'Yin', and promoting blood circulation based on traditional Chinese medicine theory[12] *Erigeron breviscapus* has been shown to have an anti-oxidative and neuroprotective effect and reduce blood viscosity.[13] This review aimed to systematically collect all relevant randomized trials and critically appraise the effectiveness and safety of DZSM capsule for ischemic stroke.

2. Methods

The review protocol was registered at PROSPERO (NO: CRD42016042914). The format of this review follows the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Additional file 1).

2.1. Eligibility criteria

2.1.1. Type of study randomized controlled trials

2.1.1.1. Type of participants. People with ischemic stroke were included and should have been diagnosed by brain Computed Tomography or Magnetic Resonance Imaging to confirm infarction in brain and exclude hemorrhage regardless of their sex, age, and race or disease stage.

2.1.1.2. Type of intervention. DZSM capsule was tested as intervention regardless of its dosage or treatment duration. The control included placebo or conventional therapy. Co-interventions were allowed as long as all arms received the same co-intervention(s).

2.1.1.3. Type of outcomes. For acute stage, the primary outcomes were all-cause mortality, dependence defined as Barthel Index (BI) scores < 60 or the modified Rankin Scale (mRS) scores > 3[14] and serious adverse events including fatal, life threatening, requiring hospitalization or change of treatment regimen.[15] The secondary outcomes were changes of neurological function deficit assessed by validated scales such as the National Institute of Health Stroke Scale (NIHSS) or the nationally approved Neurological Function Deficit Score (NFDS), treatment failures defined according to the nationally approved criteria,[16] we regarded no change (function defect score decreased by 18%–45%), deterioration (function defect score decreased by about 17%) and death as treatment failures, quality of life, and non-serious adverse events. For convalescence (or sequelae) stage, the primary outcomes were dependence, recurrence rate of ischemic stroke, quality of life, and serious adverse events, and the secondary outcomes were all-cause mortality, neurological deficit, treatment failure, and non-serious adverse event.

2.2. Search strategy

We comprehensively searched the Cochrane Library, PubMed, Chinese Biomedical Database (SinoMed), China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Wanfang Database; from their inception to May 2016 (Additional file 2). References of all included trials were hand searched for additional eligible trials.

2.3. Study selection and data extraction

Two authors (XY Yang and JG Li) independently and in duplicate examined the titles and abstracts identified potentially eligible trials and then review the full text to identify the trials meeting eligibility criteria. And we extracted the data from included trials on the first authors and year of publication, detail of randomization, characteristics of participants (such as age, sex and clinical stage), sample size, descriptions of intervention/control and outcomes. The discrepancies were resolved through consensus and if necessary, arbitrated by the third author (Liu JP).

2.4. Quality assessment

Two authors (XY Yang and LQ Wang) independently assessed the methodological quality of RCTs using risk of bias tool provided by the Cochrane Hand-book for Systematic Reviews of Interventions.[17] Any disagreements were resolved by discussion with third author (JP Liu). We assessed the following quality items: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias based on imbalance of the baseline information here. The quality of included trials was categorized to low/unclear/high risk of bias. Trials which met all criteria were categorized to low risk of bias, trials which met none of the criteria were categorized to high risk of bias, and other trials were categorized to unclear risk of bias if insufficient information acquired to make judgment.

2.5. Data analysis

The statistical analyses were carried out using Review Manager 5.3 software from the Cochrane Collaboration. Data were summarized using risk ratio (RR) with 95% confidence intervals (CI) for binary data or mean difference (MD) with 95% CI for continuous data. Meta-analysis was done if the trials had a good homogeneity on study design, participants, interventions, control, and outcome. Statistical heterogeneity was tested by examining both the Chi-squared test and the I-squared statistic (I^2)[18], meaning that an I^2 larger than 50% and P less than or equal to 0.1 indicated the possibility of statistical heterogeneity and random-effects model was adopted. We planned to perform a sensitivity analysis to test the robustness of the results by excluding study with unclear random sequence generation. We conducted intention to treat analysis for the missing data. Funnel plots were used to assess the publication bias if more than 10 RCTs tested the same outcome in one meta-analysis.

We would perform subgroup analyses by disease stage or by different neurological function deficit measurements if data were available. Quality of evidence was assessed across important outcomes using GRADE approach to support management recommendations by the GRADEpro software (version 3.6).

3. Results

3.1. Description of studies

The initial search yielded 253records from the six databases, and an unpublished article was identified by contacting principal investigator. Full texts of 37 articles were read, and 18 trials were eligible. However, four trials,[19–21] did not report the disease stages, so we excluded them from this review. Therefore, fourteen trials [22–35] with a total 5206 participants were included in this review. Details of the study selection