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Review article

Meta-analysis of clinical trials of oral Chinese herbal prescriptions for treatment of vascular dementia based on mini mental state examination scores

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Summary

Introduction: Chinese Herbal Medicine has been used for centuries to treat diseases associated with the brain. The objective of this study was to assess the clinical efficacy and safety of oral Chinese herbal prescriptions (CHP) for patients with vascular dementia (VD) by conducting a systematic review and meta-analysis.

Methods: Databases in English and Chinese were searched for randomized controlled trials (RCTs) including patients with VD comparing CHP to Hydergine or Piracetam and placebo. The main outcomes were the changes in the weighted mean difference (WMD) and 95% confidence interval (CI) for mini mental state examination (MMSE) or activities in daily living (ADL) score.

Results: Twenty-four trials with 2043 patients were identified and analyzed. In the meta-analysis, CHP treatment increased MMSE score (versus Piracetam WMD: 1.16, 95% CI: 0.56–1.76; versus placebo WMD: 3.39, 95% CI: 1.77–5.01, separately). CHP treatment reduced ADL score (versus Piracetam WMD: −5.51, 95% CI: −10.7, −0.32; versus placebo WMD: −7.40, 95% CI: −10.64, −4.16, separately). However, there was no statistically in MMSE score (WMD: 2.12; 95% CI: −0.026, 4.27) and ADL score (WMD: −1.95; 95% CI: −5.41, 1.51) between the CHP and Hydergine group.

Conclusions: CHP treatment appears to have beneficial effects for patients with VD. However, high-quality studies are needed to provide clear evidence for the future use of CHP in treatment of VD.

Keywords: Meta-analysis; Vascular dementia; Chinese herbal prescription.

Introduction

Vascular dementia (VD) is defined as the loss of cognitive function resulting from ischemic, ischemic-hypoxic, or hemorrhagic brain lesions as a result of cardiovascular disease and cardiovascular pathologic changes [1].VD has been estimated to account for 0.9% in people aged 60 years [2] and 1.50% for people aged 65 years or older [3] in China. VD increases the morbidity, disability, and healthcare costs of older people, and decreases their quality of life and survival [4].

Current therapeutic approaches include controlling the underlying risk factors for cerebrovascular disease, such as hypertension and diabetes mellitus, with the primary goal of slowing clinical progression [5]. Western drug therapy for VD mainly includes expanding cerebral blood vessels and improving cerebral metabolism. However, these treatments have not achieved satisfactory results [6,7] and side effects of the drugs are common [8]. Therefore, complementary and alternative medicines may provide potential candidates.

Traditional Chinese herbal medicine (TCM) has been used practiced in the Chinese health care system for many years. TCM is widely used in the treatment VD in China [9] and many clinical trials have been conducted to explore its efficacy [10,11]. Stagnation of blood and kidney deficiency have become two important concepts in Chinese medicine to explain the origin of dementia

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[12]. The static blood obstructing the brain is the main syndrome of VD [13]. Therapeutic strategies of Chinese medicine on VD are mainly focused on the blood stasis, kidney deficiency and phlegm turbidity. A principal feature of these TCM prescriptions is that they consist of multi-herb formula comprising two or more herbs. Therefore, formula should be the primary target of this investigation. Considering small sample sizes may be of insufficient power to provide a robust conclusion, a meta-analysis may help clarify this issue. In the present meta-analysis, we evaluated the findings from recent randomized controlled trials (RCTs) on the efficacy and safety of Chinese herbal prescription (CHP) used in the treatment VD to determine whether CHP is beneficial to VD patients.

Materials and methods

Literature search

Systematic literature searches were performed in following electronic databases: PubMed database, EMBASE, Wanfang, China National Knowledge Infrastructure, and Weipu databases published prior to August 2013. All databases were searched without language limitations. We used Medical Subject Heading (MeSH) terms: traditional Chinese medicine (TCM); Chinese herbal medicine, herbs; ergoloid mesylates or Hydergine; Piracetam; placebo; randomized controlled trials; RCT; and clinical study/trial. We also searched the existing reviews and scanned the cited references in published studies to identify additional trials.

Study selection

Following criteria were used to select trials: (1) RCTs with testing orally administration fixed Chinese herbal prescription (CHP) compared to placebo or Western medicine (Hydergine or Piracetam) treatment or for VD were included; (2) patients, male or female of any age, with a diagnosis of VD; (3) trials had to report at least one of the following outcome measures: changes in mini mental state examination (MMSE) or activities in daily living (ADL) score; and (4) patients number more than 50 cases. CHP composed of combinations of herbs, animal parts, and minerals, and prepared as either decoctions, granules, pills, or capsules. Studies were excluded if: (1) patients with specific types of non-vascular dementia; (2) abstracts, case reports, and reviews; and (3) duplicate publication. In addition, trials based on injections of CHP or on combination preparation also containing Western medicine were also excluded.

Data extraction

Two reviewers (DD Gong and J Xu) independently extracted the data using standardized data forms. Items on the forms included: (1) baseline demographics (author and year of publication); (2) participants (sample size and age); (3) CHP intervention; (4) control intervention; (5) duration of intervention; (6) outcome measures; and (7) adverse events. Where discrepancies were identified, reviewers resolved these by discussion.

Assessments bias risk

The methodological quality was assessed according to the Cochrane reviewers' Handbook [14] in combination with TCM diagnosis according to the guidance, Principles of Clinical Research on New Chinese Medicines for Treatment of Dementia [15] by two reviewers independently using a grading scheme for each of following aspects: adequate sequence generation; allocation concealment; blinding; incomplete outcome data addressed; and free of selective reporting. In addition, if subjects were recruited for trials according to the different TCM patterns and Western approach to disease diagnosis, the study was classified as low risk bias.

Statistical analysis

Included trials were categorized by the treatment interventions, and the following comparisons were made as CHP versus controls (Hydergine or Piracetam or placebo). Continuous data were calculated as weighted mean difference (WMD) with 95% confidence interval (CI). Homogeneity of WMD across studies was assessed by using the Cochrane Q statistic and the I^2 statistic. When a significant Q statistic ($p < 0.10$) or $I^2 > 50\%$ indicated heterogeneity across the studies, pooled effect sizes were calculated by the random-effects model; otherwise, a fixed-effects model was used [16]. To clearly describe herbs used in these included trials, we performed a simple statistical analysis of the frequency. Publication bias was assessed by Begg's rank correlation test and Egger's linear regression test with $p < 0.10$ indicating statistical significance. All the meta-analyses were performed by STATA statistical software. $p < 0.05$ was considered as statistically significant.

Results

Study characteristics

A total of 253 potentially relevant publications were identified from the initial search strategy. After screening the full texts, 24 trials [17–40] met the inclusion criteria (Fig. 1). In total, the 26 trials were comprised of 2043 patients, including 1071 who had received CHP, 545 who had received Hydergine, 323 who had received Piracetam, and 104 who had received a placebo. All the included trials were conducted in China. Treatment duration ranged from 1 to 3 months. Characteristics of 24 RCTs are listed in Table 1. Of 24 trials, seven [17,22–24,28,29,31,32] used patent prescription. The most commonly used herbs were *Szechuan lovage Rhizome*, *Tuber Fleeceflower Root*, *Grassleaf Sweelflag Rhizome*, and *Milkvetch Root*. Distribution of frequency (≥ 5) herbs was listed in Table 2. All of the included trials were classified as having moderate or high risk of bias according to the methodological quality assessment (Table 3).