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Oral Chinese herbal medicine for kidney nourishment in Alzheimer's disease: A systematic review of the effect on MMSE index measures and safety

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Summary
Objective: To evaluate the effectiveness and safety of the Chinese herbal medicine for kidney nourishment (CHMK) assessed with the Mini-Mental Status Examination (MMSE) index objective outcome measures in individuals with Alzheimer's disease.
Methods: Searches were conducted in 7 medical databases from their inceptions until July 19, 2014 for randomized controlled trials (RCTs) that compared the oral administration of CHMK plus conventional pharmacotherapy with the same conventional pharmacotherapy alone with MMSE index measures as outcomes. Relevant resources were also manually retrieved. Two reviewers screened the citations of the reports, assessed the risk of bias and extracted data independently. Data analysis was carried out with Cochrane Collaboration's RevMan5.2.6 software and evidence quality grading evaluation of the systematic review was conducted with Grades of Recommendations Assessment Development and Evaluation (GRADE) profiler software.
Results: A total of 20 studies involving 1682 participants were included in the meta-analysis. There were 15 trials that compared CHMK with conventional pharmacotherapy and 5 trials that compared CHMK plus conventional pharmacotherapy with conventional pharmacotherapy alone. The main meta-analysis results showed relative benefits in effective rates in five studies (odds ratio [OR] 2.74, 95% confidence interval [CI] 1.55—4.85) and cure rate/clinical-control rates in five studies (OR 1.91, 95% CI 1.27—2.88) in favor of the CHMK plus conventional pharmacotherapy group. As for CHMK compared with conventional pharmacotherapy, no significant

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differences were noted in the effective rate (OR 1.09, 95% CI 0.82—1.46; cure rate (OR 1.06, 95% CI 0.81—1.38) and detailed sub-group of MMSE scores from the onset time to 4 weeks (weighted mean difference [WMD] 0.31, 95% confidence interval [CI] —0.81 to 1.42, 8 weeks WMD 1.12, 95% CI —0.54 to 2.78, 12 weeks (WMD 0.43, 95% CI —1.62 to 2.48, or 24 weeks WMD 1.92, 95% CI —1.60 to 5.44) follow-up and the overall effect (WMD 0.79, 95% CI —0.11 to 1.69). Moreover, weaknesses in methodological quality were identified in most studies according to Cochrane Risk of Bias tool assessment, while the quality level of GRADE classification indicated ''very low''. The incidence of adverse events with CHMK (0.87%) was lower than in the conventional pharmacotherapy group (4.08%), which revealed use of CHMK was relatively safer than conventional pharmacotherapy alone.

Conclusion: The effectiveness and safety of oral administration of CHMK cannot be currently determined because of publication bias and the low quality level of the included trials. Further studies on a larger scale and with more rigorous designs are required to define the role of CHMK in the treatment of AD.

Introduction

Alzheimer's disease (AD) is a disorder characterized by the progressive development of cognitive dysfunction syndrome involving different degrees of damage in patients' language, visual space, and memory function, which are associated with reduced cognitive ability, personality disorder, and significant recession of work, social and daily life ability.[1—3] A recent survey in Shanghai indicated that the prevalence of AD dementia occurring in 55-year-old and 65-year-old people in China was 2.57% and 4.6% respectively.[4,5] AD is considered as the fourth most frequent cause of death in the world. The aim of current routine pharmacotherapy for AD is to control disease progression, improve cerebral blood circulation and the metabolism of brain cells by administering duxil, piracetam, hydergine and pentoxifylline.[6,7] However, the treatment outcomes have remained less than satisfactory and some pharmacotherapy has been associated with adverse events such as cardiovascular events and risk of mental disorders.[8,9]

Since there is a series of problems with current pharmacotherapy, such as the existence of large contraindications, side effects, high costs or addictions, the use of the complementary and alternative medicine (CAM) such as the Chinese herbal medicine for kidney nourishment (CHMK) has been relatively common among AD dementia sufferers because of their curative effects, fewer adverse reactions, low cost and wide-range of applications. It has been reported that many people with AD have used some form of CAM to improve their health, compensate for dietary deficiencies and counteract the side effects of medications.[3,8]

The domains of CHMK mainly consist of radix rehmanniae praeparata, fructus cnidii, ginseng, fructus ligustri lucidi and the fruit of Chinese wolfberry. At present, CHMK either used alone or integrated with conventional pharmacotherapy has been widely chosen for the treatment of AD dementia in China. Moreover, CHMK can be administered as oral decoctions or prepared into capsules, powders or pills. They are commonly combined with routine pharmacotherapy in an attempt to improve outcomes. Although some studies have reported CHMK effectiveness for AD dementia, the conclusions have been inconsistent and adverse effects in the treatment of AD dementia still remain uncertain. Also, no systematic review specifically addressing CHMK for the treatment of AD dementia is available. The aim of this review was to evaluate the evidence for the efficacy of therapies using CHMK versus conventional pharmacotherapy or CHMK plus conventional pharmacotherapy versus the same conventional pharmacotherapy alone in AD dementia based on randomized-controlled trials (RCTs) that used Mini-Mental Status Examination (MMSE) index objective outcome measures. In addition, the analysis aimed to compare the adverse effects of oral administration of CHMK and determine the safety of CHMK in the treatment of AD dementia.

Methods

Criteria for considering studies for this review

Types of studies

Studies included in this review were RCTs that were published in English or Chinese. The trials that did not present any outcome data or with data not available from the original authors, were excluded.

Types of participants

Participants were males or females who were diagnosed AD dementia. Studies that adopted AD diagnostic criteria based the International Classification of Diseases (ICD-10)[10], Diagnostic and Statistical Manual of Mental Disorders (DSM-III, DSM-IIIR and DSM-IV)[11,12], National Institute of Neurological and Communicative Disorders and Stroke and the AD dementia and Related Disorders Association (NINCDADRDA)[13,14], Chinese Classification of Mental Disorders (CCMD-3)[15] or other well-recognized AD diagnostic criteria at home and abroad were included in the analysis. Moreover, the diagnostic criteria included neuroimaging verification of pathological alterations in the brain such as with CT or MRI.

Types of interventions

The intervention in the experimental group was ''kidney-nourishing'' as the core principle and priority was given for use of CHMK. Either comparison of oral CHMK with placebo,