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Review article

Oriental herbal medicine for generalized anxiety disorder: A systematic review of randomized controlled trials

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ABSTRACT

Introduction: Generalized anxiety disorder (GAD) requires long-term pharmacotherapy, and its recurrence rate is high. Due to several limitations of Western medicine (WM), there are increasing needs for complementary and alternative medicine. The purpose of this review is to examine the effectiveness and safety of Oriental herbal medicine (OHM), medicinal herbs or decoctions prescribed based on Eastern Asian medicine, for GAD.

Method: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) assessing the efficacy of OHM for GAD. Twelve electronic databases were searched from inception to 29 January 2018.

Results: A total 109 RCTs were included. Methodological assessments found unclear risks of bias in most the studies. OHM as an alternative monotherapy or adjunctive therapy showed favorable effects: 1) The OHM group had lower Hamilton Rating Scale of Anxiety (HAMA) score than the placebo group, with a mean difference (MD) of −8.35 (95% confidence interval: −12.21 to −4.49; P < 0.0001). 2) The OHM group had lower HAMA score than the WM group, with a MD of −1.46 (−2.25 to −0.66; P = .003). 3) The OHM plus WM group had lower HAMA score than the WM group, with a MD of −2.90 (−3.54 to −2.27; P < 0.00001). There were fewer adverse events in the OHM group than in the WM group.

Conclusions: The results suggest that OHM may have benefits for treating GAD, however, the reliability is severely limited by the overall low quality and marked heterogeneity of the included studies. RCTs of higher quality and longer follow-up periods should be performed.

1. Introduction

Generalized anxiety disorder (GAD) is a common mental disorder with a high rate of relapse. Persons suffering from this condition feel uneasy about almost everything, experiencing feelings of anxiety extremely broadly along with various physical symptoms [1]. GAD has a lifetime prevalence of 4–12% and a 12-month prevalence of approximately 2–6% globally [2–4]. GAD is the most prevalent in high-income countries and has a high comorbidity with mood disorder, especially with major depressive disorder [2–6]. Additionally, the economic burden associated with GAD is becoming a serious problem [7,8].

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitor (SNRIs) are recommended as first-line treatment for GAD in many clinical practice guidelines (CPGs), and benzodiazepines and buspirone as second-line treatments. However, long-term pharmacotherapy lasting more than 6 to 12 months is needed to avoid relapse [9–12]. Early discontinuation of SSRIs and SNRIs is related with high risk of relapse, and high dosage of benzodiazepines is associated with a number of adverse events (AEs) and risk of abuse [11,13]. GAD has a high recurrence rate, and AEs associated with pharmacotherapy lead to poor compliance [14].

Considering these limitations of Western medicine (WM), there are increasing needs for complementary and alternative medicine (CAM) [15]. In Korea, Oriental medicine treatment is a broadly applicable and common treatment option, and 92% of Koreans have received such treatment at least once in their lifetime [16]. Oriental herbal medicine

Abbreviations: AE, adverse event; AER, adverse event rate; CAM, complementary and alternative medicine; CCMD, Chinese classification of mental disorders; CI, confidence interval; CPG, clinical practice guideline; DSM, diagnostic and statistical manual of mental disorders; GAD, generalized anxiety disorder; HAMA, Hamilton anxiety rating scale; HAMD, Hamilton depression rating scale; ICD, international classification of disease; IRB, institutional review board; MD, mean difference; MIR, marked improvement rate; OHM, oriental herbal medicine; RCT, randomized controlled trial; RR, risk ratios; SAS, Zung self rating anxiety scale; SCL-90-R, symptom checklist-90-revised; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAI, state-trait anxiety inventory; TCM, traditional Chinese medicine; TCM-SI, syndrome index of traditional Chinese medicine; TER, total effective rate; TESS, toxic exposure surveillance system; TKM, traditional Korean medicine; WM, western medicine

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(OHM) is one of the Oriental medicine treatment approaches prescribing medicinal herbs or decoctions based on Eastern Asian medicine such as traditional Chinese medicine (TCM), Kampo medicine, and traditional Korean medicine (TKM). However, due to the lack of evidence for this approach, there are no official recommendations for the Oriental medicine treatment in clinical practice, especially in CPGs.

In this systematic review, we investigate the safety and effectiveness of OHM as a monotherapy or adjunctive therapy for GAD.

2. Methods

The protocol of this systematic review is registered in the PROSPERO database, registration number CRD42016050026 (available at www.crd.york.ac.uk/prospero/display_record.asp?ID = CRD42016050026).

2.1. Search strategy

Two authors (CYK and EJC) searched the following 12 electronic bibliographic databases: MEDLINE via PubMed, EMBASE via Elsevier, Cochrane Central Register of Controlled Trials (CENTRAL), the Allied and Complementary Medicine Database (AMED), PsycINFO, China National Knowledge Infrastructure (CNKI), Japan Science and Technology Information Aggregator, Electronic (J-STAGE), Oriental Medicine Advanced Searching Integrated System (OASIS), Korean Traditional Knowledge Portal (KTKP), Korean Studies Information Service System (KISS), Research Information Sharing Service (RISS), and National Digital Science Library (NDSL).

The following search terms were used: (“anxiety disorders” OR “anxiety” OR “generalized anxiety” OR “generalized anxiety” OR GAD) AND (“medicinal plants” OR “Chinese herbal drugs” OR “traditional Chinese medicine” OR “Kampo medicine” OR “Korean traditional medicine” OR “traditional Oriental medicine” OR “herbal medicine” OR “prescription drugs” OR “alternative medicine” OR “complementary medicine” OR “herb*” OR “decoction*” OR “botanic*”) AND (“randomized” OR “randomly” OR “placebo” OR “groups”). Further, these search terms were translated into other languages, including Chinese and Korean, in the non-English databases. The initial search date was 31 August 2016, and update search was performed on 29 January 2018. Trials published from inception to the final search date were retrieved. We also conducted manual searches of the reference lists of eligible trials.

2.2. Inclusion criteria

The inclusion and exclusion criteria of this review were as follows: (1) Randomized controlled trials (RCTs) were included. There were no restrictions on publication status, blinding, publication date, or language. (2) Patients diagnosed with GAD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), International Classification of Disease (ICD), Chinese Classification of Mental Disorders (CCMD), or other equivalent standards were included. GAD patients with comorbid diseases or pathological conditions were excluded. (3) Interventions using any form of oral herbal medicine based on Eastern Asian medicine were included, such as TCM, Kampo medicine, and TKM, alone or along with WM. (4) Controls could be either placebo or a WM pharmacotherapy used to relieve symptoms of GAD.

Two authors (CYK and EJC) independently screened titles and abstracts to identify trials that potentially met the criteria, and they assessed full texts of screened trials for eligibility. Any disagreement between the two authors over eligibility was resolved through discussion with a third reviewer (JWK).

2.3. Outcome measures

The primary outcomes were the anxiety scores post-treatment, measured using valid assessment tools including the Hamilton Anxiety Rating Scale (HAMA), the Zung Self-Rating Anxiety Scale (SAS), and the State-Trait Anxiety Inventory (STAI). AE score measured using the Toxic Exposure Surveillance System (TESS) was also set as a primary outcome.

The secondary outcomes were the other symptom scores post-treatment, measured using the Syndrome Index of Traditional Chinese Medicine (TCM-SI), Hamilton Depression Rating Scale (HAMD), Symptom Checklist-90-Revised (SCL-90-R), and similar scales. Clinical efficacy including total effective rate (TER) and marked improvement rate (MIR) were calculated using HAMA (TER [HAMA] and MIR [HAMA], respectively), SAS, STAI, TCM-SI, HAMD, and SCL-90-R. Clinical efficacy and the adverse event rate (AER) were also set as secondary outcomes.

2.4. Data extraction

A standardized form was used by two independent authors (CYK and EJC) to extract data from the included studies. Extracted informations included publication year, approval from an institutional review board (IRB), consent form, sample size, information for assessment of the risk of bias, diagnostic criteria, TCM pattern identification, details of the intervention and control conditions, components of the OHM, outcomes, and time points of measurement. Any discrepancy between the two authors was resolved through discussion with a third reviewer (SYC).

2.5. Assessment of risk of bias

Two authors (CYK and HWS) independently assessed the risk of bias of eligible trials following the criteria described in the Cochrane Handbook version 5.1.0 [17]. The following domains were assessed as “Low risk,” “Unclear,” or “High risk”: (1) random sequence generation; (2) allocation concealment; (3) blinding of the participants and personnel; (4) blinding of the outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other biases. In case of other biases, when the study reported the approval from Institutional Review Board (IRB), it was considered the study with scientific and ethical appraisal and rated it as a low risk. Any disagreement between the two authors over the risk of bias was resolved through discussion with a third review author (SYC).

2.6. Data analysis

Data synthesis was performed using Review Manage Software (RevMan 5.3) for those trials containing sufficient data for meta-analysis. In the meta-analysis, a random-effect model was used when there were more than four trials in the comparison and when they had significant heterogeneity ($I^2 > 50\%$). Otherwise a fixed-effect model was used, with mean differences (MDs) for continuous outcomes and risk ratios (RRs) for binary outcomes. We calculated 95% confidence intervals (CI) and two-sided P values for each outcome. In addition to the meta-analysis, we qualitatively analyzed the recurrence rates of GAD in the trials, as well as the kinds and frequency of administration of the herbs and the TCM patterns.

2.7. Subgroup analysis

For primary outcomes, subgroup analysis by recruitment criteria with or without TCM pattern identification was performed to explore the heterogeneity and the differences in efficacy and safety between the two subgroups. Furthermore, subgroup analysis by treatment period was also performed.