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The comparative clinical study of efficacy of *Gamisoyo-San* (*Jiaweixiaoyaosan*) on generalized anxiety disorder according to differently manufactured preparations: Multicenter, randomized, double blind, placebo controlled trial

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ABSTRACT

Ethnopharmacological relevance: Gamisoyo-San (GSS) is a well-known Traditional Korean Medicine shown to be effective on mood disorders. *Aim of the study:* The purpose of this research is to examine the effect of Gamisoyo-San on generalized anxiety disorder by its differently manufactured preparations. *Materials and methods:* Multicenter, randomized, double-blinded, placebo-controlled study was set for 147 patients with generalized anxiety disorder recruited from November 1st 2009 to December 16th 2010. They were given Gamisoyo-San individual extract mixture (extraction done for each crude materia medica separately) or Gamisoyo-San multi-compound extract (extraction done for whole materia medica at once) or controlled medication. Hamilton Rating Scale for Anxiety (HAM-A), Korean State-Trait Anxiety Inventory (K-STAI), Penn State Worry Questionnaire (PSWQ), Korean Beck Depression Inventroy (K-BDI), Symptom Checklist-90-Revised (SCL-90-R), and Korean WHO Quality of Life Scale Abbreviated Version (WHOQOL-BREF) were evaluated. We also applied Pattern Identification tool for 'JingJi and ZhengChong (驚悸怔忡, Traditional Korean Medicine term which correlates with generalized anxiety disorder)' to patients to evaluate different responses among 9 patterns.
Results: HAM-A scores of Gamisoyo-San multi-compound extract group showed greater decrease compared to Gamisoyo-San individual extract mixture group and placebo group, but the difference was insignificant. WHOQOL-BREF scores of Gamisoyo-San multi-compound extract group showed significant increase compared to Gamisoyo-San individual extract mixture group and placebo group. In Heart blood deficiency pattern, the Gamisoyo-San multi-compound extract group showed significant decrease in K-BDI compared to the Gamisoyo-San individual extract mixture group.
Conclusion: Gamisoyo-San did not improve anxiety level of GAD patients. However, it can be useful to improve quality of life, and reduce depressive, obsessive–compulsive, somatic symptoms of generalized anxiety disorder. Gamisoyo-San multi-compound seemed more effective than Gamisoyo-San individual extract mixture, especially in Heart blood deficiency pattern.

1. Introduction

Generalized anxiety disorder (GAD) is a chronic psychiatric condition with excessive anxiety, irritability, and a variety of associated physical symptoms (Min, 2004). In Traditional Korean Medicine, internal medicine disorder; 'JingJi and ZhengChong' or 'fright palpitations and fearful throbbing' or '驚悸怔忡', is the closest term which correlates with GAD (Kwon et al., 2005). In translation, JingJi is palpitation ascribed to being frightened, and ZhengChong is a severe case of palpitation (World Health Organization, 2007). Amid diverse clinical studies of GAD being done in conventional medicine, quality clinical studies in Traditional Korean Medicine field are lacking.

Gamisoyo-San (GSS) is a well-known herbal formula, widely used to treat neurosis in Traditional Korean Medical field. It is suggested by

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the National Health Service medical care benefit standard, to be prescribed on 'JingJi and ZhengChong (U26.3)' and phobic anxiety disorder (F40) classifications among the Korean Standard Classification of Diseases (Ministry of Health and Welfare, 2009). GSS formula originates from 'Neikezhaiyao', which is a classic Traditional Chinese Medicine book written by Xuelizhai, in Ming dynasty era (Xue, 1999). It is mentioned to treat neuropsychiatric symptoms derived from pattern of 'liver depression and blood deficiency' (Lee, 1999). In recent clinical trials (Lee et al., 2007; Yamada and Kanba, 2007; Terauchi et al., 2011), GSS is reported to be effective on sleep disturbances, headache, dizziness in postmenopausal women, depressive symptoms in premenstrual dysphoric disorder, and on tardive dyskinesia derived from antipsychotic drug. Experimental studies (Choi and Lee, 1996; Hwang, 2001; Kim et al., 2004; Lee et al., 2010) and case studies (Ko et al., 2004; Je and Yoo, 2011) proved anti-stress, anti-depressive, antioxidant effect of GSS. Considering the traditional usage and earlier studies, authors reasoned that GSS may also be effective on GAD.

Meanwhile, as scientific technology evolves, diverse formulations are being developed and applied in conventional medicine. There are over 30 different types of formulations mentioned in The Korean Pharmacopoeia. As for herbal formula, traditional formulation is by hot water extraction done for entire materia medica at once and thus anticipating interactions among different matria medica in the course of simultaneous extraction. However, most likely due to convenience in manufacturing, many herbal products are being made in the form of extracts which are manufactured by extracting individual herb separately and then later on combined according to prescribed composition. This individual extract mixtures prescribed in traditional Korean Medical field are showing a decrease. Many attribute the tendency to doubtful efficacy of the products (Choi et al., 2004). Clinical physicians of Korean Medicine are concerned about the efficacy gap between multi-compound extract and individual extract mixture. They prefer traditional way of extraction, which is multi-compound extract. The present authors postulated that there might be some difference in efficacy between individual extract mixtures and multi-compound extract.

In this multicenter, randomized, double blinded, placebo-controlled study, we examined the effect of Gamisoyo-San on GAD by its differently manufactured preparations. We used a Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959) as primary outcome measure, Korean State-Trait Anxiety Inventory (K-STAI) (Hahn et al., 1996), Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990), Korean Beck Depression Inventroy (K-BDI) (Rhee et al., 1995), Symptom Checklist-90-Revised (SCL-90-R) (Kim and Kim, 1984), and Korean WHO Quality of life Scale Abbreviated Version (WHO-QOL-BREF) (Min et al., 2000) as secondary outcome measure.

In addition, we used an Instrument of Pattern Identification for 'JingJi and ZhengChong' (Park et al., 2010) to examine the effect according to different patterns. Pattern identification (syndrome differentiation) is a unique process in western pacific Traditional Medicine, of overall analysis of clinical data to determine the location, cause and nature of a patient's disease and achieving a diagnosis of a pattern/syndrome (World Health Organization, 2007).

To our knowledge, this is the first published study comparing efficacy of differently manufactured preparations of Traditional Korean Medicine.

2. Methods

2.1. Patients

Total 147 participants were recruited from November 1st 2009 to December 16th 2010 in two centers: Daejeon Oriental Hospital of Daejeon University and Dunsan Oriental Hospital of Daejeon University. The study was approved by Institutional Review Board at each study site (Authorization number: DJOMC-2009-28, DJOMC-2010-05). Participants agreed a written informed consent stating purpose, method, randomization odds, inconvenience, guaranteed secrecy, compensation, and right for withdrawal of this trial. This trial was also registered at clinicaltrials.gov (NCT01285115).

Inclusion criteria for the study were male or female aged 20–65 years, who met Structured Interview for DSM-IV Axis I Disorder, SCID-I criteria for diagnosis of GAD (Kim et al., 2004). Exclusion criteria were as follows: current or past history of delusion or hallucination, past history of at least one manic episode, hypomanic episode, or mixed episode, current or past history of alcohol abuse or alcohol dependence history, intake of substances (e.g. antianxiety drugs, antipsychotic drugs, steroids, digitalis, L-dopa) which might affect symptoms, medical conditions (e.g. cerebrovascular disease, cancer, hyperthyroidism, hypothyroidism, heart disease) that might affect symptoms, current with hepatoma, hepatic cirrhosis, chronic renal failure, congestive heart failure, pregnant or lactating, and subjects concluded not suitable to follow the study process.

2.2. Preparation of drugs

Every materia medica was purchased from Daeyeon Pharmaceutical (Incheon, Korea). Each herb underwent a close examination of any hazardous substance from the Korea Pharmaceutical Test & Research Institute. Drugs were manufactured by Kyoungbang Pharmaceutical (Gyeonggi-do, Korea) as good manufacturing practices (GMP). We requested three products; Gamisoyo-San individual extract mixture (GSS-I), Gamisoyo-San multi-compound extract (GSS-M) and placebo from the company. GSS-I and GSS-M share the same composition of 10 materia medica: Atractylodes japonica Koidz. ex Kitam., rhizome (Atractylodis Rhizoma Alba) 1 g, Bupleurum falcatum Linne., radix (Bupleuri Radix) 1 g, Polypori umbellati Polyporaceae (Poria (Hoelen)) 1 g, Mentha arvensis Linne var. piprascens Malinvaud., herba (Mentha Herba) 0.33 g, Angelica gigas Nakai., radix (Angelicae Gigantis Radix) 1 g, Glycyrrhiza uralensis Fischer., radix and rhizome (Glycyrrhizae Radix et Rhizoma) 0.67 g, Zingiber officinale Roscoe., rhizome (Zingiberis Rhizoma Recens) 0.33 g, Paeonia lactiflora Pallas., radix (Paeoniae Radix) 1 g, Gardenia jasminoides J.Ellis., fructus (Gardeniae Fructus) 0.67 g, and Paeonia suffruticosa Andrews., cortex radices (Moutan Cortex Radicis) 0.67 g (in single dosage of 7.67 g). The proportion follows the prescription described in the book 'Neikezhaiyao' (Xue, 1999). Difference between GSS-I and GSS-M, is in an extraction method. While extraction of GSS-I product is done for each crude material medica separately, GSS-M is done as a whole.

As for GSS-I, refined water was added as much as 8–10 times than that of each medical plants. Extraction was executed under 95–100 °C and 0.70–0.75 kg/cm^2 of pressure for 4 h. It was then transferred to storage tank for filtration. After filtration, concentration procedure was done under steam pressure 0.70–0.75 kg/cm^2, steam temperature below 60 °C, tank temperature 60 °C, and internal decompression 60–65 mm bar. After yield check (97–103%), excipients; lactose (33%) and corn starch (4%) were combined with the extract under agitator speed 120 rpm and chopper 320 rpm for 3 min. After the combination, the extract was dried in a vacuum dryer under 90 ± 5 °C for 30 min. Granulation was done under 100–200 mesh. Then all individual extracts were added up in high speed mixer of 160 rpm for 15 min. Lactose and cornstarch were used as excipients. As for extraction of GSS-M, extraction of 10 materia medica was done at once under identical condition to that of GSS-I.

In regard of quality control, scanning test of heavy metal (lead, arsenic) and pesticide residues was done for each crude herb medicine. They also passed grain size analysis, mass/weight variation test, and microbial limit test. Quantitative analysis of marker compounds (paeoniflorin (C23H28O11), geniposide (C17H24O10), glycyrrhizin (C42H62O16)) was also carried out. Both GSS-I and