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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

GSS-M have been approved as generic medicine by Korea Food and Drug Administration since 2000 (License no. 2101-253). They were packed identically and labeled with subject code according to randomization. In regard of dosage, we followed the dosage for the products approved by Korea Food and Drug Administration. Placebo was composed of lactose (50%) and starch (50%). In order to maintain double-blind procedure, we were supplied with three drugs; GSS-I, GSS-M and placebo, wrapped in identical charta.

2.3. Study design

Patients were treated with study medication; GSS-I, GSS-M or placebo for 8 weeks. Total six visits were made. On first visit, screening process was done. After signing an informed consent, subjects were selected through inclusion criteria; including Structured Interview for DSM-IV Axis I Disorder, SCID-I criteria for diagnosis of GAD, Instrument of Pattern Identification for 'JingJi and ZhengChong' and medical examinations; blood pressure, vital sign, blood chemistry, chest PA, urine analysis, and electrocardiography. Urine pregnancy test was conducted for women of childbearing age.

Subjects were assigned to GSS-I, GSS-M or placebo group, by randomization. Manufacturer was given a randomization allocation table provided by the person in charge of statistics, and collectively labeled serial numbers on each experimental drugs and placebo. Then they were handed over to drug manager. Drug manager gave out either experimental drugs or placebo at research doctor's request. All treatment arms were delivered in a blinded fashion. Chief research officer safekept the randomization allocation table throughout the study. On second visit, scores for 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), and Instrument of Pattern Identification for 'JingJi and ZhengChong' were evaluated before starting intervention. We used HAM-A as our primary outcome measure to assess objective anxiety level of GAD. As for secondary outcome measure, K-STAI, PSWQ, K-BDI, SCL-90-R, WHOQOL-BREF were used to evaluate anxiety experience, overanxiousness, depression, and serenity level respectively. Patients received two weeks' worth of either GSS-I 23.01 g/day, GS-M 23.01 g/day or placebo 23.01 g/day and were instructed to intake drugs three times per day (each 7.67 g). Drugs were handed out every two weeks; from 2nd to 5th visit. Final visit was made two weeks after the 5th visit. Scores for HAM-A, K-STAI, PSWQ, K-BDI, SCL-90-R and WHOQOL-BREF were collected on 2nd, 4th, and 6th visit (Fig. 1).

2.4. Efficacy measures

Primary efficacy assessment was score change of HAM-A (Hamilton, 1959). The HAM-A consists of 14 items (each rated 0–4), with higher scores indicating more severe symptoms. HAM-A scores were measured before intervention, after 4 weeks, and after 8 weeks. Secondary efficacy assessment was evaluated measuring rate of treatment responders based on a 50% or greater reduction from

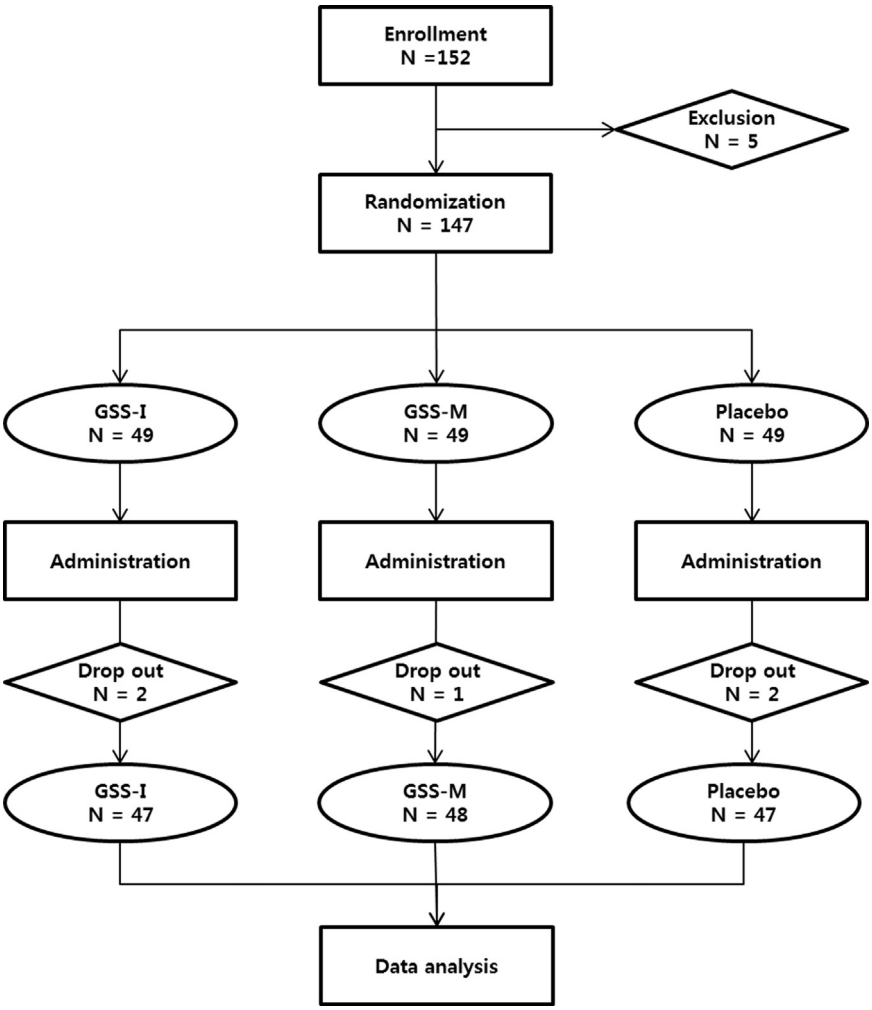

Fig. 1. Patient flow of study.

baseline HAM-A scores to 4 weeks/8 weeks after intervention. Subjects were also evaluated on additional secondary outcome measures, including score change of K-STAI, PSWQ, K-BDI, SCL-90-R and WHOQOL-BREF.

2.5. Statistical analysis

Continuous data were summarized in Mean ± Standard deviation. Categorical data were described by frequencies and percentages (%). ANOVA was used for comparison of continuous clinical characteristics between groups, while Fisher's exact test or Pearson chi-squared test was carried out for categorical characteristics. All statistical analyses were performed with ITT (intention-to-treat) data set containing all of 147 patients who were initially randomized to the groups. The missing values in efficacy variables were imputed by the method of LOCF (the last observation carried forward). Since some efficacy outcomes were measured twice (at 4 weeks, 8 weeks), we used linear mixed models for continuous outcomes and generalized linear mixed models for dichotomous outcomes. In linear mixed model, we presumed covariance structures having compound symmetric matrix and used the sandwich estimator (Liang and Zeger, 1986) to obtain the standard error of parameter estimates. The p-Value less than 0.05 was considered statistically significant.

3. Results

3.1. Subject demographics

A total of 147 patients were enrolled; 117 from Daejeon Oriental Hospital of Daejeon University (site 1), 30 from Dunsan Oriental Hospital of Daejeon University (site 2). Five patients dropped out, and 142 patients completed the study. 3 dropped out of personal reasons without any adverse effect, 1 due to poor compliance, and 1 due to nonattendance. Demographic and clinical characteristics were similar across treatment groups (Table 1).

3.2. Distribution of pattern identification

In GSS-I group, most common was the Heart qi deficiency pattern (16, 32.65%), followed by the Heart blood deficiency pattern (12, 24.49%), and the Heart deficiency with timidity pattern (11, 22.45%). In GSS-M group, most common was the Heart qi deficiency pattern (16, 32.65%), followed by the Heart deficiency with timidity pattern (14, 28.57%), and the Heart blood deficiency pattern (10, 20.41%). In placebo group, most common was the Heart deficiency with timidity pattern (20, 40.82%), followed by the Heart qi deficiency pattern (10, 20.41%), and the Heart blood deficiency pattern (8, 16.33%). There was no significant difference in the distribution of patterns between three groups.

3.3. Hamilton Rating Scale for Anxiety (HAM-A)

HAM-A scores before treatment, after 4 weeks, and 8 weeks for each group were; GSS-I 29.10 ± 6.63, 23.27 ± 8.00 ($p < 0.001$), 19.55 ± 8.52 ($p < 0.001$); GSS-M 27.06 ± 7.60, 21.88 ± 8.15 ($p < 0.001$), 17.08 ± 6.55 ($p < 0.001$), and control group, 27.86 ± 6.92, 23.65 ± 8.18 ($p < 0.001$), 19.29 ± 7.88 respectively ($p < 0.001$). Within all groups, significant decrease of HAM-A scores was observed.

Greatest decrease of HAM-A scores after 4 weeks and 8 weeks of intervention, was observed in GSS-M group, followed by GSS-I and placebo groups. However, the difference was insignificant (Fig. 2). In regard of treatment response rate, GSS-I group showed greater response than placebo group and GSS-M group, but the difference was insignificant (Table 2).

3.4. Korean State-Trait Anxiety Inventory (K-STAI)

K-STAI State scores before treatment, after 4 weeks, and 8 weeks for each group were; GSS-I 60.76 ± 8.64, 54.73 ± 8.82 ($p < 0.001$), 51.35 ± 9.44 ($p < 0.001$); GSS-M 61.47 ± 8.20, 54.20 ± 9.02 ($p < 0.001$), 50.43 ± 9.90 ($p < 0.001$), and control group, 59.82 ± 8.07, 54.49 ± 9.44 ($p < 0.001$), 49.78 ± 9.83 ($p < 0.001$) respectively. Within all groups, significant decrease of K-STAI State scores was observed. K-STAI Trait scores before treatment, after 4 weeks, and 8 weeks for each group were; GSS-I 62.55 ± 6.78, 57.43 ± 8.76 ($p < 0.001$), 53.90 ± 9.31 ($p < 0.001$); GSS-M 62.98 ± 8.35, 56.98 ± 9.53 ($p < 0.001$), 51.84 ± 10.58 ($p < 0.001$), and control group, 61.33 ± 7.97, 57.53 ± 10.11 ($p < 0.01$), 52.55 ± 10.42 ($p < 0.001$) respectively. Within all groups, significant decrease of K-STAI Trait scores was observed.

Compared between three groups, GSS-M group showed the greatest decrease in K-STAI State score after 4 weeks and 8 weeks, followed by placebo group and GSS-I group. GSS-M group also showed the greatest decrease in K-STAI Trait score, followed by GSS-I group and placebo group. In both cases the difference was insignificant.

Table 1
Clinical characteristics of generalized anxiety disorder in groups treated with GSS individual extract mixture, GSS multi-compound extract and placebo.

Classification		GSS-I	GSS-M	Pla	p^a	p^b
Gender	Male (%)	12(24.49)[c]	11(22.45)	12(24.49)	0.963	
	Female (%)	37(75.51)	38(77.55)	37(75.51)		
Mean age (y)		40.96 ± 11.50[d]	37.24 ± 10.66	39.51 ± 12.03		0.271
Height (cm)		160.69 ± 8.15	162.19 ± 7.38	162.33 ± 7.52		0.506
Weight (kg)		60.03 ± 10.82	61.32 ± 11.57	60.83 ± 12.79		0.861
Blood pressure (mmHg)	Systolic	120.35 ± 15.36	118.37 ± 14.22	118.02 ± 15.18		0.708
	Diastolic	77.98 ± 10.54	74.78 ± 10.42	75.31 ± 12.31		0.314
Pulse (rate/min)		75.80 ± 14.48	72.92 ± 9.41	74.84 ± 11.82		0.489
Temperature (°C)		36.36 ± 0.38	36.33 ± 0.39	36.38 ± 0.39		0.766
Respiration (rate/min)		20.12 ± 0.95	20.00 ± 0.74	20.31 ± 0.96		0.233

GSS-I: Gamisoyo-san individual extract mixture.
GSS-M: Gamisoyo-san multi-compound extract.
Pla: Placebo.
Statistically significant value ($p < 0.05$).

[a] Pearson chi-square test.
[b] ANOVA for the values.
[c] Number (%).
[d] Mean ± standard deviation.

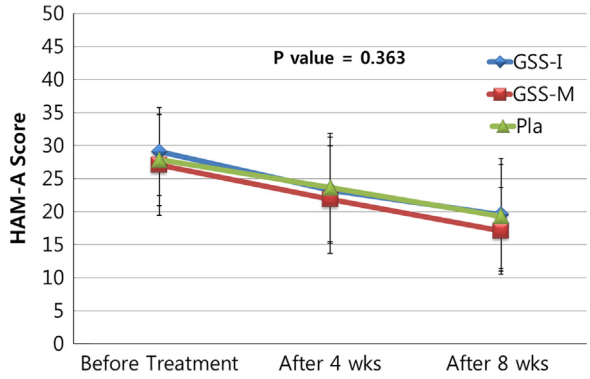

Fig. 2. Comparison of HAM-A score between groups. GSS-I: Gamisoyo-san individual extract mixture. GSS-M: Gamisoyo-san multi-compound extract. Pla: Placebo. *p*: Comparisons between groups in the linear mixed models. Statistically significant value ($p < 0.05$).

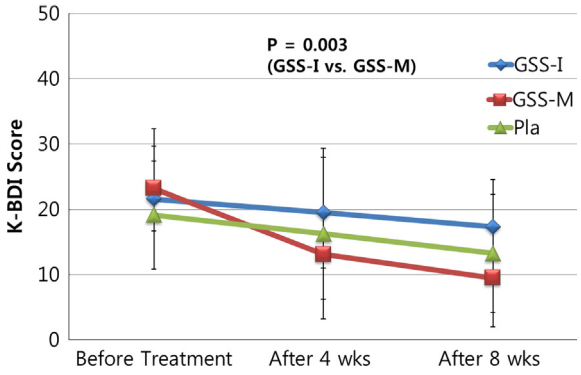

Fig. 3. Comparison of K-BDI score between groups in Heart Blood Deficiency Pattern. GSS-I: Gamisoyo-san individual extract mixture. GSS-M: Gamisoyo-san multi-compound extract. Pla: Placebo. *p*: Comparisons between groups in the linear mixed models. Statistically significant value ($p < 0.05$).

Table 2
Treatment response rate in groups treated with GSS individual extract mixture, GSS multi-compound extract and placebo.

Weeks		< 50%	≧50%	Total	*p*[a]
4 wks	GSS-I	42(85.71)[b]	7(14.29)	49	0.513
	GSS-M	45(91.84)	4(8.16)	49	
	Pla	45(91.84)	4(8.16)	49	
	Total	132	15	147	
8 wks	GSS-I	32(65.31)	17(34.69)	49	0.591
	GSS-M	36(73.47)	13(26.53)	49	
	Pla	36(73.47)	13(26.53)	49	
	Total	104	43	147	

GSS-I: Gamisoyo-san individual extract mixture.
GSS-M: Gamisoyo-san multi-compound extract.
Pla: Placebo.
Statistically significant value ($p < 0.05$).
[a] Pearson chi-square test.
[b] Number (%).

3.5. Penn State Worry Questionnaire (PSWQ)

PSWQ scores before treatment, after 4 weeks, and 8 weeks for each group were; GSS-I 60.14 ± 9.05, 57.29 ± 9.53 ($p < 0.05$), 51.10 ± 10.14 ($p < 0.001$); GSS-M 61.63 ± 10.14, 58.71 ± 9.48 ($p = 0.001$), 50.39 ± 10.80 ($p < 0001.$), and control group, 59.67 ± 10.48, 56.78 ± 9.88 ($p < 0.05$), 52.61 ± 10.28 ($p < 0.001$) respectively. Within all groups, significant decrease of PSWQ scores was observed. PSWQ score change compared between GSS-I, GSS-M and placebo group showed insignificant difference.

3.6. Korean Beck Depression Inventory (K-BDI)

K-BDI scores before treatment, after 4 weeks, and 8 weeks for each group were; GSS-I 23.16 ± 8.48, 16.14 ± 8.25 ($p < 0.001$), 13.80 ± 7.90 ($p < 0.001$); GSS-M 23.57 ± 8.25, 14.96 ± 7.95 ($p < 0.001$), 10.57 ± 7.42 ($p < 0.001$), and control group, 21.14 ± 9.52, 15.04 ± 8.73 ($p < 0.001$), 12.49 ± 8.13 ($p < 0.001$) respectively. Within all groups, significant decrease of K-BDI scores was observed.

Score change of K-BDI after intervention was compared between three groups. GSS-M group showed greater decrease after 4 weeks and 8 weeks, followed by placebo group and GSS-I. Statistical significance was borderline ($p < 0.094$). Compared between patterns, GSS-M group showed significant decrease compared to GSS-I group, in the Heart blood deficiency pattern (Fig. 3).

3.7. Symptom Checklist-90-Revised (SCL-90-R)

Compared within group, total SCL-90-R score at each points of time (after 4 weeks, after 8 weeks), decreased significantly in all three groups, comparing from that taken before the treatment ($p < 0.001$).

Compared between three groups, GSS-M group showed greater decrease in almost every categories, followed by GSS-I and placebo groups. However the difference was insignificant.

When compared by site, GSS-M group of site 2 showed significant decrease in total score ($p = 0.009$), somatization score ($p = 0.003$), obsessive–compulsive score ($p = 0.036$), phobic anxiety score ($p = 0.003$), global severity index score ($p = 0.012$), and positive symptom total score ($p = 0.015$) of SCL-90-R compared to placebo group.

In Heart blood deficiency pattern, GSS-M group showed significant decrease in Positive Symptom Total score ($p = 0.036$) and a borderline decrease in Total score ($p = 0.054$), Obsessive–Compulsive score ($p = 0.087$), and Interpersonal Sensitivity score ($p = 0.054$) compared to GSS-I group. In Heart qi deficiency pattern, GSS-I group showed borderline decrease in Psychoticism score ($p = 0.054$) compared to placebo group.

3.8. WHO Quality of Life Scale Abbreviated Version (WHOQOL-BREF)

WHOQOL-BREF scores before treatment, after 4 weeks, and 8 weeks for each group were; GSS-I 35.03 ± 10.31, 40.27 ± 11.88 ($p < 0.001$), 43.74 ± 12.33 ($p < 0.001$); GSS-M 33.16 ± 9.77, 40.72 ± 11.50 ($p < 0.001$), 47.37 ± 12.26 ($p < 0.001$), and control group 37.01 ± 11.77, 42.50 ± 11.95 ($p < 0.001$), 44.66 ± 14.07 ($p < 0.001$), respectively. Within all groups, significant increase of WHOQOL-BREF scores was observed.

Score change of WHOQOL-BREF after intervention was compared between three groups. GSS-M group showed significant increase compared to GSS-I and placebo groups after 8 weeks of intervention (Fig. 4). Compared between patterns, GSS-M group showed borderline decrease compared to GSS-I group, in the Heart blood deficiency pattern (Fig. 5).

3.9. Adverse effects

There were five cases of slight adverse effects. Two cases of dyspepsia (4.08%), one case of diarrhea (2times/day, 2.04%), and one case of fatigue (2.04%) were reported. After conducting medical examination by research doctor, we concluded that the symptoms were irrelevant to the intervention. Drug intake was maintained, and the symptoms naturally disappeared.

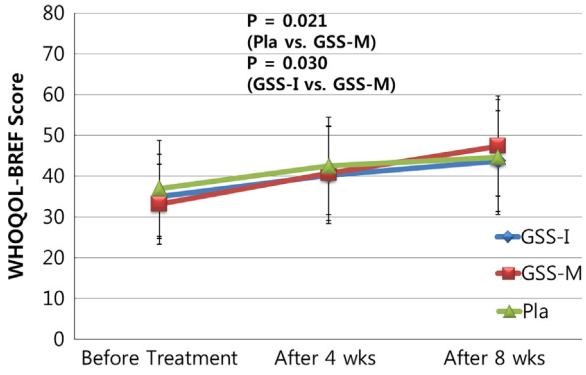

Fig. 4. Comparison of WHOQOL-BREF score between groups. GSS-I: Gamisoyo-san individual extract mixture. GSS-M: Gamisoyo-san multi-compound extract. Pla: Placebo. *p*: Comparisons between groups in the linear mixed models. Statistically significant value ($p < 0.05$).

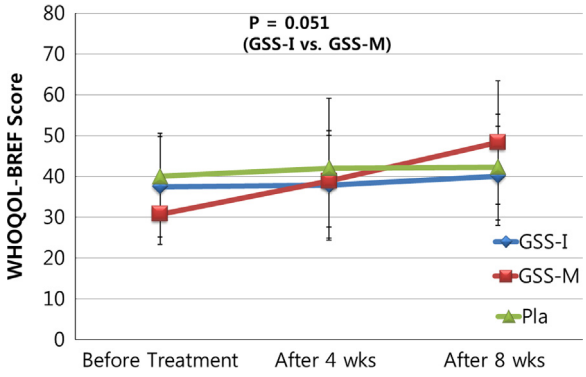

Fig. 5. Comparison of WHOQOL-BREF score between groups in Heart blood deficiency pattern. GSS-I: Gamisoyo-san individual extract mixture. GSS-M: Gamisoyo-san multi-compound extract. Pla: Placebo. *p*: Comparisons between groups in the linear mixed models. Statistically significant value ($p < 0.05$).

4. Discussion

This was a meaningful clinical study evaluating efficacy of herbal drug on GAD. Also, it was the first clinical trial comparing efficacy of differently manufactured preparations of Traditional Korean Medicine on GAD.

Pattern identification (辨證) is the process of overall analysis of clinical data to determine the location, cause and nature of a patient's disease (World Health Organization, 2007). It is also the process of recognizing and confirming mechanism of diseases based on Oriental Medical theory (Jeong and Ahn, 1998). We conducted pattern identification on patients before intervention, and examined assessment outcomes according to different patterns.

HAM-A, which is our primary outcome variable, showed significant decrease at each point of time comparing within all three groups. Compared between groups, GSS-M group showed greater decrease than GSS-I and placebo groups. However, the difference was insignificant (Fig. 2). Treatment response rate also showed insignificant difference compared between groups (Table 2).

As for both K-STAI and PSWQ, all three groups showed significant decrease at each point of time compared within group. However, there were insignificant differences of K-STAI and PSWQ scores compared between groups. Evaluating the scores for HAM-A, K-STAI, and PSWQ, which we used to measure anxiety, we can say that GSS has insignificant effect on anxiety symptoms of GAD.

K-BDI showed significant decrease compared within group. Compared between three groups, GSS-M group showed greater decrease of K-BDI score, followed by placebo group and GSS-I. Statistical difference was insignificant, yet there was a borderline ($p < 0.094$) difference between groups. Also, in the Heart blood deficiency pattern, GSS-M group showed significant decrease compared to GSS-I group (Fig. 3). This result suggests a certain efficacy of GSS on depressive symptoms.

Total SCL-90-R score decreased significantly in all three groups compared within group. Compared between groups, three groups showed insignificant difference. However, when compared by site, GSS-M group of site 2 showed significant decrease in total score ($p=0.009$), somatization score ($p=0.003$), obsessive–compulsive score ($p=0.036$), phobic anxiety score ($p=0.003$), global severity index score ($p=0.012$), and positive symptom total score ($p=0.015$) of SCL-90-R compared to placebo group. Obsessive–compulsive score was also significantly decreased compared to GSS-I group's ($p=0.042$). Speculating the different SCL-90-R outcome between two sites, we came across two probabilities. First, subjects from site 1 had a greater tendency of reporting efficacy than subjects from site 2. The tendency was also witnessed in other assessment indicators including SCL-90-R. Second, SCL-90-R categories seem to reflect change of symptoms more sensitively compared to other subjective assessment indicators.

WHOQOL-BREF scores increased significantly within all groups. Compared between three groups, GSS-M group showed significant increase compared to GSS-I and placebo groups after 8 weeks of intervention (Fig. 4). In the Heart blood deficiency pattern, GSS-M group showed borderline decrease of WHOQOL-BREF score compared to that of GSS-I group (Fig. 5). This suggests efficacy of GSS on improving quality of life in GAD patients.

Most results from HAM-A and secondary efficacy indicators show that score change was greater in GSS-M group, followed by GSS-I and placebo groups. It suggests GSS, especially GSS-M, to have a certain effect on depression, and quality of life.

In regard of pattern identification, the Heart blood deficiency pattern drew our attention. In the Heart blood deficiency pattern, GSS-M group showed significant improvement of K-BDI, Positive Symptom Total score of SCL-90-R, and a borderline improvement in WHOQOL-BREF, score, Obsessive–Compulsive score and Interpersonal Sensitivity score of SCL-90-R compared to GSS-I group. Given that blood deficiency transforming into fire is an indication for GSS prescription (Lee, 1999), and that 'JingJi and ZhengChong' manifests in Heart-liver blood deficiency pattern (Kwon et al., 2005), the significant efficacy of GSS in the Heart blood deficiency pattern leads us to the importance of referring to pattern identification when prescribing GSS.

Yet, there are some limitations that could have affected the study. When dealing with psychiatric disorders, including GAD, diagnostic process and history taking itself can act as a psychotherapeutic intervention. Rapport between patients and research doctor/nurse can act as a placebo, thus interrupting verification of drug efficacy. Also, due to the nature of the illness, assessment indicators had to be mainly questionnaires, therefore variation of score is expected to be greater compared to assessment tools for physical illness. Furthermore, evaluating with descriptive statistics, placebo effect of two sites was different in some assessment variables. We had difficulty verifying the effect in these assessment variables. Also, there can be a blinding issue since we used charta for packing drugs. Taste and fragrance could have affected blinding procedure.

In conclusion, Gamisoyo-San did not significantly improve anxiety level of GAD patients any better than placebo. However, our study was meaningful in a sense that Gamisoyo-San showed a certain effect on improving the quality of life, and reducing depressive, obsessive–compulsive, phobic anxiety, somatic symptoms in GAD patients. The significant efficacy of Gamisoyo-San in the Heart blood deficiency pattern provides evidence about the importance of pattern identification process when prescribing

herbal medicine. Also, we witnessed that multi-compound showed better efficacy than individual extract mixture. Our result will be useful in designing future clinical studies involving formulas of Traditional Korean Medicine and pattern identification.

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