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Effect of Sihogayonggolmoryeo-Tang on Hwa-byung: A Multicenter, Randomized, Double-Blinded, Placebo-Control Trial

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Objectives: Hwa-byung is a mental illness. It is also known as a Korean culture-related syndrome. In traditional Korean medicine, Sihogayonggolmoryeo-tang is used to treat Hwa-byung related neuropsychiatric symptoms. The purpose of this research was to examine the effect of Sihogayonggolmoryeo-tang on Hwa-byung.

Methods: A multicenter, randomized, double-blinded, placebo-controlled study was performed for 160 patients with Hwa-byung. Patients were divided into a Sihogayonggolmoryeo-tang group and a placebo group. Treatment period was 8 weeks. Hamilton Rating Scale for Anxiety (HAM-A), Likert scale for major symptoms of Hwa-byung, Hwa-byung Scale (HBS), Korean Beck Depression Inventory (K-BDI), Korean State-Trait Anxiety Inventory (K-STAI), Korean State-Trait Anger Expression Inventory (K-STAXI), and Korean WHO Quality of Life Scale Abbreviated Version (WHOQOL-BREF) were used to evaluate the effect of Sihogayonggolmoryeo-tang on Hwa-byung. We also used an Instrument of Pattern Identification for Hwa-Byung to evaluate different responses for six patterns of patients.

Results: Scores of all the measurements improved significantly for each group, showing no significant differences between the two groups. In the case of deficiency of both Qi and blood pattern, the Sihogayonggolmoryeo-tang group showed a significant decrease in the HAM-A score compared to the placebo group.

Conclusions: The effect of Sihogayonggolmoryeo-tang on Hwa-byung did not exceed that of the placebo. Further studies involving more elaborate pattern identification are needed.

Key Words: Hwa-byung, Sihogayonggolmoryeo-tang, Clinical trial, Randomized, Placebo-control study.

I. INTRODUCTION

Hwa-byung (HB), which literally means 'fire disease', is a Korean culture-related syndrome related to anger[1,2]. HB was listed in DSM-IV as a culture-bound syndrome of Korea in 1994 and a suppression of anger was pointed to be its major cause[3].

HB can be diagnosed as major depression, dysthymic disorder, and generalized anxiety disorder in the DSM-IV diagnostic criteria. However, HB has its classified diagnosis, as it is expressed in a complicated form of unique symptoms including a heat sensation, a feeling of being mortified, the sensation of a mass in the epigastrium, the feeling of something rising in the chest, and the feeling of 'Haan' meaning a collective feeling of oppression and isolation in Korean[4]. Major emotional symptoms of HB are anger, depression, and anxiety[5]. In the early stage, anger and anxiety are major symptoms and in the late stage, depression becomes more apparent[6].

Recently, amid increasing interest in HB, a clinical guideline for HB was published by the Korean Society of Oriental Neuropsychiatry[7] in 2013. However, quality clinical studies of HB still lacks. Clinical trials of HB were mainly reported in Korea, and the number of publicized researches was only 1 to 2 annually[8]. There was a non-randomized controlled trial, demonstrated the effectiveness of Yuldahanso-tang on HB[9]. A case series reported improvements in 5 patients accompanying HB symptoms with postmenstrual climacteric syndrome[10]. There was one randomized controlled trial that evaluated the efficacy of Bunsimgi-eum on hwa-byung, but showed no significant differences compared with the placebo[11].

Sihogayonggolmoryeo-tang (SYM) is a widely used prescription in the Traditional Korean Medical field. SYM originates from 'Shanghan Lun', a famous Chinese traditional medical book wrote by Zhang Zhongjing in A.D 200-205. It is mainly used to treat neurosis and psychosis such as insomnia, anxiety, headaches, dizziness, and tremors[12]. Several studies on SYM showed an anti-depressive effect and anti-epileptic effect in rat models[13,14]. But there are no clinical trials using SYM in Korea yet. In one case series of 5 patients with the climacteric syndrome, SYM showed evident effectiveness relieving neuropsychiatric symptoms when patients chiefly complain palpitation and heating sense[15].

The Clinical Guidelines for HB suggests using Bunsimgi-eum gami, Soyo-san gami, Banhasasimtang gami, and SYM on HB, among the most frequently used prescriptions in the clinical field[7]. As above, SYM is empirically one of the most commonly administered prescriptions to treat various neurosis and psychosis. Still, there has been no clinical research demonstrating its efficacy on HB, which made us conduct this study.

In this multicenter, randomized, double-blinded, placebo-controlled study, we examined the effect of SYM on HB. For the primary efficacy assessment, the Hamilton Rating Scale for Anxiety (HAM-A)[16] was evaluated. The Likert scale[17] for major symptoms of HB, HB Scale (HBS)[18], Korean Beck Depression Inventory (K-BDI)[19], Korean State-Trait Anxiety Inventory (K-STAI)[20], Korean State-Trait Anger Expression Inventory (K-STAXI)[21], and Korean WHO Quality of Life Scale Abbreviated Version (WHOQOL-BREF)[22] were used for the secondary assessment.

In addition, we used an Instrument of Pattern Identification for HB[23] to examine the effect according to the pattern identification. Pattern identification is a comprehensive process of analyzing and systemizing symptoms considering the relation between the clinical data obtained by physical examinations. It is commonly used in western pacific traditional medicine to determine the location, cause, and nature of the disease[23,24].

II. METHODS

1. Study design

Participants visited 6 times in total. On the first visit, a screening process was done. After signing the consent. Participants were screened by the inclusion/exclusion criteria. The Structured Interview Criteria for HB Diagnosis[25] and an Instrument of Pattern Identification for HB were carried out as well as medical examinations which included blood pressure, vital signs, blood chemistry, chest PA, urine analysis, and electrocardiography. A urine pregnancy test was conducted for women in childbearing age.

The person in charge of statistics performed the randomization and supervised the assignment sheet. The selected participants were randomly assigned to the SYM or placebo group. The manufacturer labeled serial numbers on the experimental drug and placebo and handed over to the drug manager. The drug manager offered them to the research doctor's request. The person in charge of statistics independently kept the randomization allocation table throughout the study. The authenticity of the drug was maintained confidential to the participants and the researchers until the end.

On the second visit, HAM-A, Likert scale for major symptoms of HB, HBS, K-BDI, K-STAI, K-STAXI, WHOQOL-BREF, and Instrument of Pattern Identification for HB were evaluated.

Participants took the encapsulated drugs three times per day (2.5 g each) for eight weeks. Every week, participants were checked for compliance and adverse effects by telephone. Drugs were handed out every two weeks from the 2nd visit to the 5th visit. On the 6th visit, medical examinations and questionnaires were done. The HAM-A, Likert scale for major symptoms of HB, HBS, K-BDI, K-STAI, K-STAXI, and WHOQOL-BREF were evaluated on the 2nd, 4th, and 6th visit (Table 1).

Table 1. Timeline of the Clinical Trial

	Visit 1 (Screening)	Visit 2 (0-week)	Visit 3 (2-week)	Visit 4 (4-week)	Visit 6 (6-week)	Visit 6 (8-week)
Consent	✓					
Demographic information	✓					
Medical history	✓					
Medical Examinations	✓	✓	✓	✓	✓	✓
Chest PA	✓					
Electrocardiography	✓					
Lab tests	✓					✓
Urine pregnancy test	✓			✓		✓
Screening	✓					
Pattern identification	✓	✓				
HAM-A		✓		✓		✓
K-STAI		✓		✓		✓
Likert scale		✓		✓		✓
HBS		✓		✓		✓
K-BDI		✓		✓		✓
K-STAXI		✓		✓		✓
WHOQOL-BREF		✓		✓		✓
Medication administration		✓	✓	✓	✓	
Drug Adherence			✓	✓	✓	✓
Adverse events			✓	✓	✓	✓

HAM-A: The Hamilton Rating scale for Anxiety, K-STAI: Korean State-Trait Anxiety Inventory, Likert scale: Likert scale for major symptoms of Hwa-byung, HBS: Hwa-byung Scale, K-BDI: Korean Beck Depression Inventory, K-STAXI: Korean State-Trait Anger Expression Inventory, WHOQOL-BREF: WHO Quality of Life Scale Abbrevieated Version.

2. Participants

160 participants were recruited from January 4, 2011, to September 26, 2012, in three centers: Daejeon Oriental Hospital of Daejeon University, Dunsan Oriental Hospital of Daejeon University, and Dongguk University Bundang Oriental Hospital. The study was approved by the Institutional Review Board at each institution (Authorization number: Daejeon Oriental Hospital of Daejeon University DJOMC-57-1, Dunsan Oriental Hospital of Daejeon University 10-3-2, Dongguk University Bundang Oriental Hospital 20100001). This trial was registered at clinicaltrials.gov (NCT01362114).

After given full explanations about the purpose, method, randomization odds, inconvenience, guaranteed secrecy, compensation, and right for withdrawal, participants signed the consent as agreement.

Male or female aged 20~65 years meeting the interview criteria for HB Diagnosis were included[20]. The exclusion criteria were as follows: (1) current or past history of delusion or hallucination (2) past history of manic episode, hypomanic episode, or mixed episode (3) current or past history of alcohol abuse or dependence (4) taking substances (e.g., antianxiety drugs, antipsychotic drugs, steroids, digitalis, L-dopa) which might affect symptoms (5) medical conditions (e.g., hyperthyroidism, hypothyroidism, and heart disease) that might affect symptoms (6) diagnosed with hepatoma, hepatic cirrhosis, chronic renal failure, congestive heart failure (7) pregnant or lactating women (8) women in childbearing age not using medically accepted means of birth control (9) considered inappropriate to carry out the study.

3. Preparation of drugs

Drugs were manufactured by Kyoungbang Pharmaceutical (Gyeonggi-do, Korea) using good manufacturing practices (GMP). SYM has been approved as a generic medicine by the Korea Food and Drug Administration since 2000. It is composed of eleven medicinal plants: Bupleurum falcatum Linne (Bupleuri Radix) 1.67 g, Pinellia ternata (Thunb.) Breit. (Pinelliae Rhizoma) 1.33 g, Poria cocos (Schw.) Wolf (Poria Sclerotium) 1 g, Cinnamomum cassia Blume (Cinnamomi Ramulus) 1 g, Zizyphusjujuba var. inermis Rehder (Zizyphi Fructus) 0.83 g, Panax ginseng C. A. Mey (Ginseng Radix) 0.83 g, Elephas Species (Fossilia Ossis Mastodi) 0.83 g, Ostreagigas Thunb. (Ostreae Concha) 0.83 g, Zingiber Officinale Rosc. (Zingiberis Rhizoma Recens) 0.33 g, Scutellariabaicalensis Georgi (Scutellariae Radix) 0.83 g, and Rheumpalmatum L. (Rhei Rhizoma) 0.33 g. The proportion follows the prescription described in the book 'Encyclopedia of Traditional Korean Medicine[26].' The dosage was determined based on the approval of the Korea Food and Drug Administration. Validation of the raw materials was carried out based on the 'Korean Pharmacopoeia' and 'National Standard of Traditional Medicinal (Herbal and Botanical) Materials' published by the Ministry of Food and Drug Safety, Korea.

Refined water was added as much as 8~10 times that of the herbs. The herbs were extracted at 80~100°C for 4 hours. After filtration (100 mesh), the extract was dried in a vacuum dryer. Lactose (22.0%) and cornstarch (22.0%) were used as excipients. A scanning test for heavy metals (cadmium, lead, arsenic, and mercury) and pesticide residues was done for each crude herbal medicine. Quantitative analysis of marker compounds (cinnamic acid ($C_9H_8O_2$), ginsenoside Rb1 ($C_{54}H_{92}O_{23}$), and baicalin glucuronide ($C_{21}H_{18}O_{11}$)) was also carried out (Fig. 1). The placebo was composed of lactose and cornstarch. SYM and placebo were encapsulated in identical capsules.

4. Efficacy measures

The primary outcome measure was the score change of the HAM-A[16]. The HAM-A consists of 14

items each rated 0-4 that higher scores indicating more severe symptoms. The secondary outcome measures were the Likert scale for major symptoms of HB, HBS, K-BDI, K-STAI, K-STAXI, and WHOQOL-BREF.

5. Sample size

The sample size was calculated based on the results of the independent two-sample t-test using the change in the HAM-A observed after 8 weeks. The score change and its standard deviation were assumed based on existing studies[27,28]. The expected score changes in the experimental and control groups were 12.0 and 8.4, respectively. And the standard deviation was estimated by the square root of the joint sample variance observed in an existing clinical trial[27]. The required number of participants in each group (n) was calculated according to the fol-

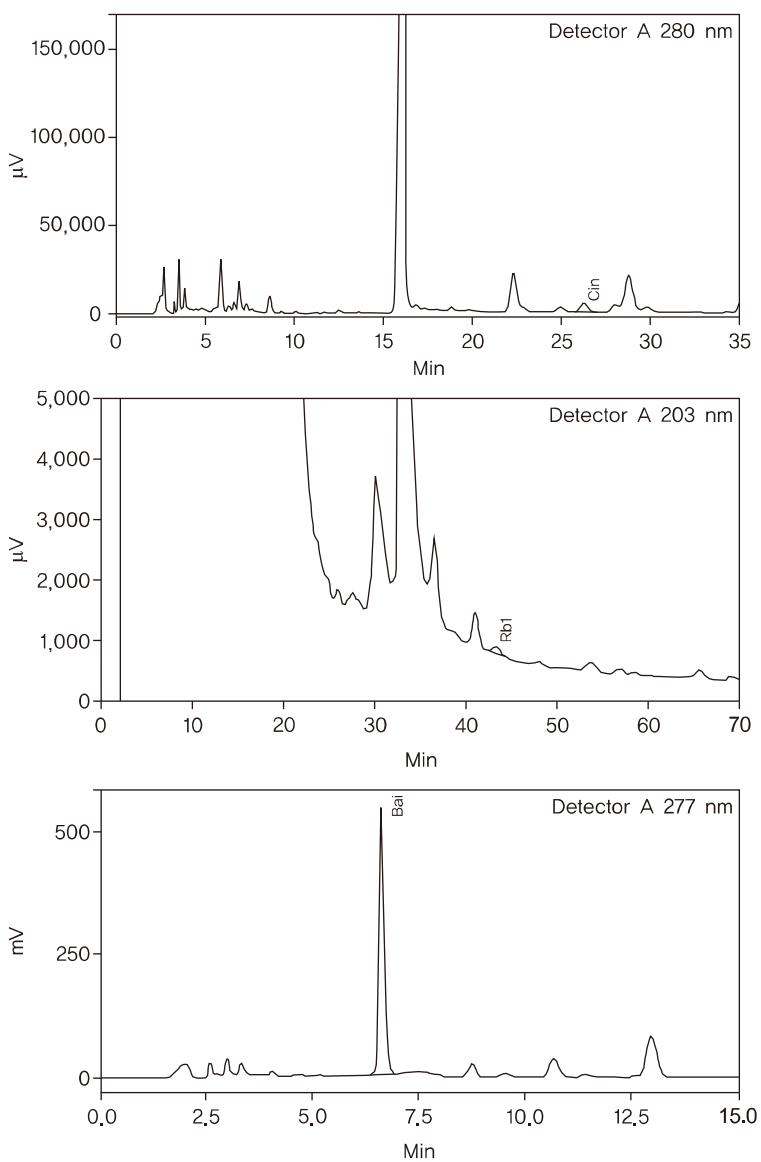

Fig. 1. Chromatograms of cinnamic acid, ginsenoside Rb1 and baicalin glucuronide.

lowing formula[29,30] (Fig. 2). In the formula, the significance level (α) is 5%; the power of the test ($1-\beta$) is 80%; the expected difference in score between the control and experimental group (1-d) is 3.6; the standard deviation (δ) is 7.3; the divided ratio between the groups is 1:1, and the expected rate of compliance (1-r) is 90%.

6. Statistical analysis

Continuous data were summarized as the mean± the standard deviation. Categorical data were described by frequencies and percentages (%). All statistical analyses were done with an ITT (intention-to-treat). The missing values for the efficacy variables were imputed by the LOCF method (the last observation carried forward). The difference in the continuous data between the groups was analyzed with independent two-sample t-test or generalized linear mixed models, while the difference within groups was done with paired-samples t-test. The difference in the categorical data between the groups was analyzed with Fisher's exact test or Pearson chi-square test. A p-value of less than 0.05 was considered statistically significant.

$$\sigma=\sqrt{\frac{88*7.26^2+86*7.28^2+\cdots+84*7.28^2}{88+86+\cdots+84}}=7.30$$

$$n=\frac{2*\sigma^2(Z_{\alpha/2}+Z_{\beta})^2}{\alpha^2(1-r)^2}=\frac{2*7.3^2(1.96+0.84)^2}{3.6^2*0.9^2}\approx 80$$

Fig. 2. Formula for standard deviation and number of subjects.

III. RESULTS

1. Subject demographics

160 patients were enrolled in total: 45 from the Daejeon Oriental Hospital of Daejeon University (site 1), 52 from the Dunsan Oriental Hospital of Daejeon University (site 2), and 63 from Dongguk University Bundang Oriental Hospital (site 3). 21 patients dropped out, and 139 patients completed the study. 10 patients dropped out for personal reasons without any adverse effects, 5 due to nonattendance, 3 due to poor compliance, 1 due to protocol violation (other concurrent treatments), and 2 due to adverse effects (Fig. 3). There were no statistical differences between the two groups (SYM and placebo) in the ratio for gender, age, height, weight, blood pressure,

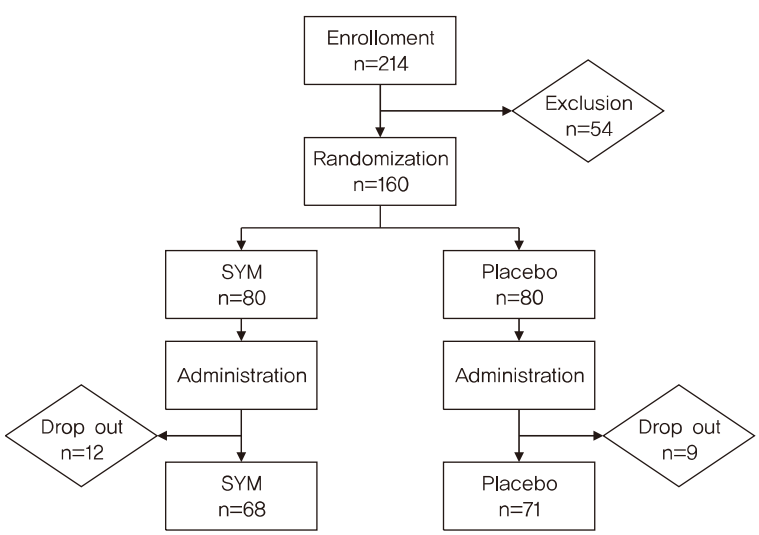

Fig. 3. Patient flow of the study.

body temperature, and respiration rate (Table 2).

2. Distribution of the pattern identification

In the SYM group, the most common pattern was the disharmony between the heart and kidney pattern (28; 36.36%) followed by the stagnation of the liver Qi pattern (18; 23.38%), malfunction of the gallbladder due to phlegm stagnation (15; 19.48%), the flare-up of the liver fire pattern (12; 15.58%), and a deficiency of both Qi and blood (4; 5.19%). In the placebo group, the disharmony between the heart and kidney pattern (27; 36.00%) took up the largest proportion, followed by the stagnation of the liver Qi pattern (22; 29.33%), the flare-up of the liver fire pattern (14; 18.67%), the malfunction of the gallbladder due to phlegm stagnation (9; 12.00%), and a deficiency of both Qi and blood (4; 5.19%). There was no significant difference in the distribution of the patterns between the two groups.

3. HAM-A

HAM-A scores before the treatment and after 4 and 8 weeks of the treatment for each group were as follows: the SYM scores were 21.07±5.41, 15.71±6.48 ($p<0.001$), and 12.79±6.37 ($p<0.001$), and the control group scores were 21.99±5.85, 16.04±5.51 ($p<0.001$), and 13.49±5.57 ($p<0.001$), respectively. Within all groups, a significant decrease in the HAM-A scores was observed. However, the HAM-A scores between the SYM and the placebo group showed no significant difference (Fig. 4). The change in scores for the HAM-A after the intervention was compared among the patterns. The SYM group showed a significant decrease compared to the placebo group for the deficiency of both Qi and blood pattern (Fig. 5), whereas there were no significant changes in other patterns.

4. Likert scale for major symptoms of HB

The Likert scale scores were compared in each group, before the treatment and after 4 and 8 weeks

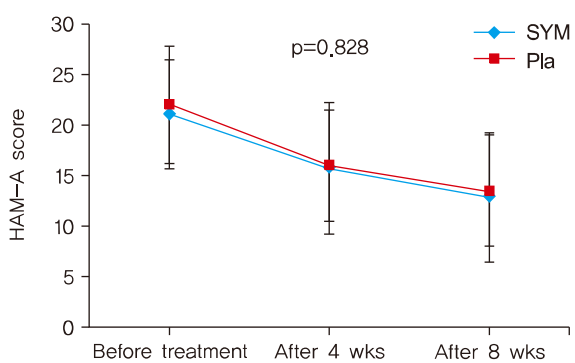

Fig. 4. Comparison of the HAM-A scores between the groups.

Table 2. Clinical Characteristics of the Hwa-Byung Groups Treated with SYM and Placebo

Classification	SYM	Placebo	p[a]	p[b]
Total number	77	75		
Gender				
Male (%)	8 (10.39)	7 (9.33)	0.827	
Female (%)	69 (89.61)	68 (90.67)		
Mean Age (y)	46.87±9.14	47.95±8.17		0.448
Height (cm)	159.22±5.38	159.22±6.30		0.998
Weight (kg)	60.76±10.47	59.68±8.46		0.486
Blood pressure (mmhg)				
Systolic	118.94±16.36	120.85±14.57		0.447
Diastolic	78.55±11.08	78.12±9.76		0.802
Pulse (rate/min)	71.27±10.20	69.08±9.32		0.169
Temperature (℃)	36.69±0.37	36.66±0.40		0.651
Respiration (rate/min)	19.91±1.13	19.88±1.11		0.873

SYM: Sihogayonggolmoryeo-tang, [a]Pearson chi-square test, [b]Independent two samples t-test, Data were presented as mean±standard deviation.

of the treatment: the SYM scores were 13.27±6.06, 8.57±5.67 ($p<0.001$), and 6.66±5.09 ($p<0.001$), and the control group scores were 12.75±5.89, 8.72±5.35 ($p<0.001$), and 6.84±4.92 ($p<0.001$). In both groups, there were significant decreases in the Likert scale scores by the time sequence. The change in the Likert scale scores between the SYM and the placebo group was not statistically significant (Fig. 6).

5. HBS

The HBS personality traits (HBS-P) scores before the treatment and after 4 and 8 weeks of the treatment for each group are described as in the following: the SYM scores were 37.75±8.43, 34.71±9.23 ($p<0.001$), and 33.30±9.02 ($p<0.001$), and the control group scores were 38.68±9.21, 35.47±8.16 ($p<0.001$), and 33.63±7.15 ($p<0.001$), respectively. HBS-P scores improved significantly within all groups.

The HBS symptoms (HBS-S) scores before the treatment and after 4 and 8 weeks of the treatment were as follows: the SYM scores were 34.95±11.34, 29.83±11.51 ($p<0.001$), and 27.12±11.73 ($p<0.001$), and in the control group, scores were 35.85±10.94, 32.37±10.11 ($p<0.001$), and 28.56±10.19 ($p<0.001$), each. In all groups, there was a meaningful decrease in the HBS-S scores. The change in the HBS scores between the SYM and the placebo group was not noticeable in both categories (Fig. 7).

6. K-BDI

The K-BDI scores of each group were evaluated

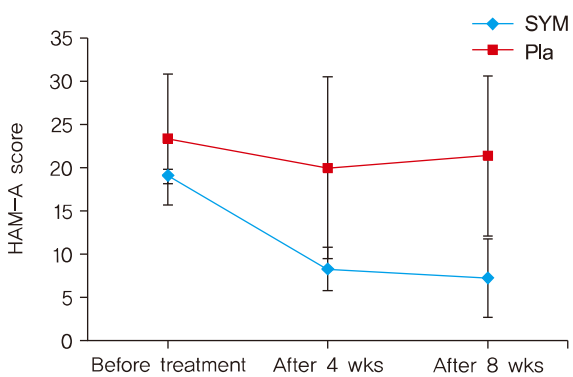

Fig. 5. Comparison of the HAM-A scores between the groups for the deficiency of both Qi and blood pattern.
SYM: Sihogayonggolmoryeo-tang.

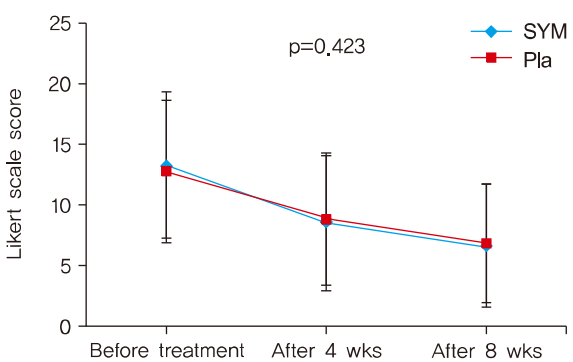

Fig. 6. Comparison of the Likert scale scores between the groups.
SYM: Sihogayonggolmoryeo-tang.

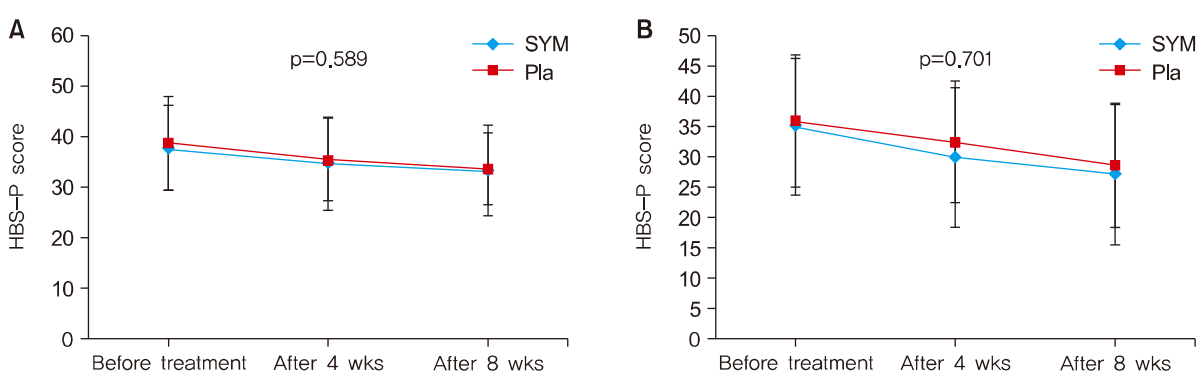

Fig. 7. Comparison of the HBS scores between the groups. (A) HBS personality traits. (B) HBS symptoms.
SYM: Sihogayonggolmoryeo-tang.

before the treatment and after 4 and 8 weeks of the treatment: the SYM scores were 22.66±10.88, 18.48±11.26 ($p<0.001$), and 15.81±11.18 ($p<0.001$), and the control group scores were 23.87±10.23, 18.23±10.62 ($p<0.001$), and 15.67±10.78 ($p<0.001$). Both groups showed significant improvement in the K-BDI scores. In neither comparative analysis, the K-BDI scores was not significantly different between the SYM and the placebo group (Fig. 8).

7. K-STAI

The K-STAI State scores in each group before the treatment and after 4 and 8 weeks of the treatment were as follows: the SYM scores were 55.75±9.98, 50.30±9.89 ($p<0.001$), and 48.91±10.02 ($p<0.001$), and the control group scores were 55.72±9.03, 51.77±8.98 ($p<0.001$), and 49.20±9.98 ($p<0.001$), respectively. Within all groups, a significant decrease in the K-STAI State scores was observed. In the case of K-STAI Trait scores, it was observed as follows before the treatment and after 4 and 8 weeks of the treatment for each group: the SYM scores were 58.53±10.37, 55.05±11.17 ($p<0.001$), and 53.05±10.48 ($p<0.001$), and the control group scores were 58.15±8.85, 55.67±9.05 ($p=0.007$), and 53.32±9.54 ($p<0.001$), respectively. The improvement in K-STAI Trat scores was statistically meaningful within all groups. The change in the K-STAI scores between the SYM and the placebo group showed no significant difference in all categories (Fig. 9).

8. K-STAXI

The K-STAXI State scores before the treatment and after 4 and 8 weeks of the treatment for each group were as follows: the SYM scores were 18.87±7.52, 15.49±5.67 ($p<0.001$), and 14.62±5.33 ($p<0.001$), and the control group scores were 19.84±7.61, 16.48±6.77 ($p<0.001$), and 15.12±5.81 ($p<0.001$). All groups presented a significant improvement in the K-STAXI State.

The K-STAXI Trait scores before the treatment and after 4 and 8 weeks of the treatment for each

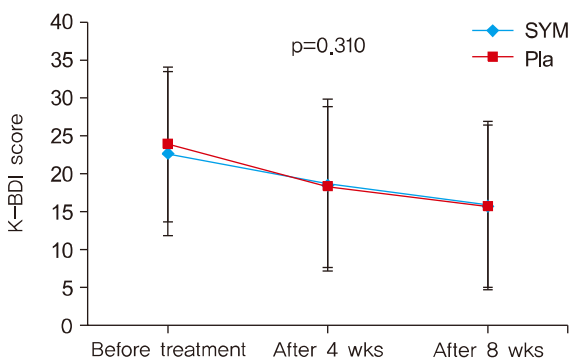

Fig. 8. Comparison of the K-BDI scores between the groups.
SYM: Sihogayonggolmoryeo-tang.

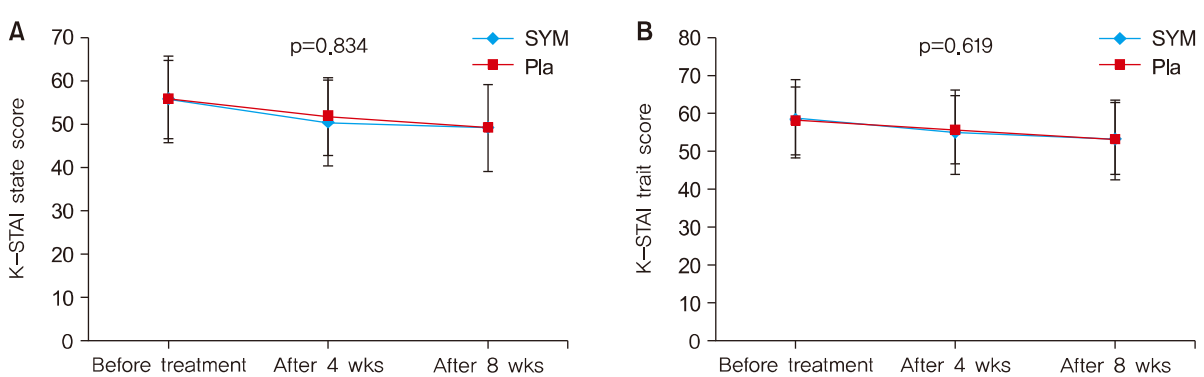

Fig. 9. Comparison of the K-STAI scores between the groups. (A) K-STAI state. (B) K-STAI trait.
SYM: Sihogayonggolmoryeo-tang.

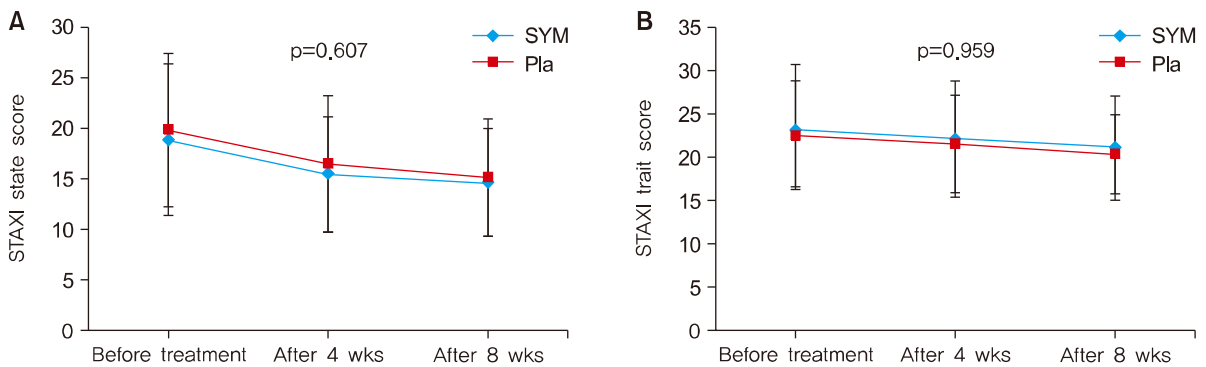

Fig. 10. Comparison of the K-STAXI scores between the groups. (A) K-STAXI state. (B) K-STAXI trait.
SYM: Sihogayonggolmoryeo-tang.

group were as in the following: the SYM scores were 23.43±7.22, 22.31±6.68 (p=0.009), and 21.30±6.06 (p<0.001), and in the control group, the scores were 22.67±6.10, 21.77±5.67 (p=0.031), and 20.57±4.54 (p<0.001), respectively. Within all groups, a significant decrease in the K-STAXI Trait scores was observed. When comparing the change in the K-STAXI scores, no significant variation was seen between the SYM and the placebo group in all categories (Fig. 10).

9. WHOQOL-BREF

The WHOQOL-BREF scores were assessed before the treatment and after 4 and 8 weeks of the treatment and are mentioned as below: the SYM scores were 38.75±12.65, 41.41±12.79 (p=0.001), and 43.94±13.54 (p<0.001), and the control group scores were 36.80±12.03, 39.39±11.53 (p=0.003), and 42.46±11.91 (p<0.001), each. It was observed that there was a significant decrease in the WHOQOL-BREF scores in both groups. The change in the WHOQOL-BREF scores between the SYM and the placebo group did not show any significant difference (Fig. 11).

10. Adverse effects

Adverse effects appeared in two cases. One case of facial edema and one case of BPPV (benign paroxysmal positional vertigo) were reported. After a medical examination by the research doctor, symptoms were concluded to be irrelevant to the intervention. The facial edema disappeared naturally, and the BPPV disappeared after hospitalization.

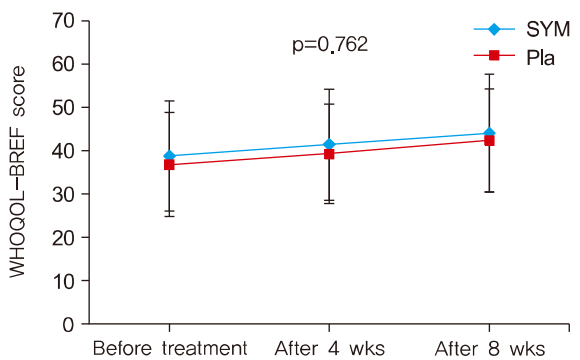

Fig. 11. Comparison of the WHOQOL-BREF scores between the groups.
SYM: Sihogayonggolmoryeo-tang.

IV. DISCUSSION

This was a meaningful clinical trial in that we could evaluate the efficacy of SYM on HB in various aspects.

In both the SYM group and the placebo group, HB symptoms were observed to be improved gradually by the treatment period. Nonetheless, we could not find any evidence that SYM is better than placebo in the treatment of HB.

The primary outcome, HAM-A showed a signifi-

cant decrease at each time point when compared within both groups. However, when compared between the groups, the difference was not significant (Fig. 4).

As for both the Likert scale for major symptoms of HB and HBS, there was a meaningful improvement at each time point within both groups. But when compared between the groups, there was no statistically significant difference between the SYM and the placebo group (Fig. 6, 7).

The K-BDI was significantly improved when compared within both groups by time period. However, when compared between the groups, the difference was not noticeable (Fig. 8). This suggests SYM has no significant effect on the depressive symptoms of HB.

The K-STAI results were much the same. Both groups showed a significant decrease at each time point individually while there were no obvious differences between the groups (Fig. 9). The results from the HAM-A and K-STAI implicate that SYM does not have a distinctive effect over the placebo on the anxiety symptoms of HB.

Likewise, the K-STAXI and WHOQOL-BREF results were also compared within and between the groups. When compared within both groups, the changes in scores were statistically significant; however, when compared between the groups, the differences were not noticeable (Fig. 10, 11).

Meanwhile, we analyzed the effect of SYM on different patterns and discovered one remarkable finding. Only for the deficiency of both Qi and blood pattern, the SYM group showed a significant improvement in the HAM-A score compared to the placebo group (Fig. 5) other than the rest of the patterns. However, only a few subjects belonged to the deficiency of both Qi and blood pattern. Therefore, additional research is needed using the pattern identification method.

In Korean traditional medicine, HB is regarded to be developed by the stagnation of the liver Qi, the flare-up of the liver fire, disharmony between the heart and kidney, deficiency of both Qi and blood, or malfunction of the gallbladder due to phlegm stagnation[23]. SYM is generally used for the malfunction of the gallbladder due to phlegm stagnation pattern[7].

One research analyzed the trends of clinical trials using Chinese medicine treatment for depression to apply it to HB. In this research, HB was considered similar to the depression caused by stagnation transforming into the fire and Danchisoyo-san appeared to be used most often[31].

Likewise, when comparing the number of the patients diagnosed as each pattern in this study, disharmony between the heart and kidney pattern (28; 36.36%) was the most, followed by the stagnation of the liver Qi pattern (18; 23.38%), malfunction of the gallbladder due to phlegm stagnation (15; 19.48%), the flare-up of the liver fire pattern (12; 15.58%) and a deficiency of both Qi and blood (4; 5.19%). The top four of the five patterns ware the excess types of patterns and are mostly related to the stagnation.

Nevertheless, in this study, SYM showed a significant improvement only in the deficiency of both Qi and blood pattern which makes it quite inconsistent with the basic Korean medicine theories and precedented researches.

In a systematic review that analyzed 21 RCTs of SYM on post-stroke depression, five RCTs used pattern identifications. Among them, four RCTs used SYM associated with stagnation of the liver or Qi, and one RCT used SYM on the liver-kidney yin deficiency pattern. However, it is difficult to say that SYM was prescribed focused on the deficiency type symptoms because Ilgwan-jeon was used together, which is usually used on the liver deficiency.

On the other hand, in the case series referred before, SYM was prescribed considering that the post-

menstrual symptoms are caused by the stagnation of the liver Qi, which is originally generated by yin deficiency of liver and kidney and uncontrolled yin deficient fire[15]. Additionally, there was one case series that SYM showed significant improvements in 32 patients with hyperhidrosis accompanied by yin deficiency fire and the flare-up of the liver fire. Because the portion Rheumpalmatum L. (Rhei Rhizoma) and red lead in SYM granules of these days are lesser than in the original SYM in 'Shanghan Lun', this study proposes a probability that SYM granules are applicable on the deficiency conditions[32].

In the Instrument of Pattern Identification for HB, only one type of pattern is selected as representative by the symptom scores. Therefore, sometimes it is difficult to reflect a certain condition, especially when the excess state and deficiency state is complicated. In other words, a patient with apparent deficiency symptoms can be diagnosed as a deficiency of both Qi and blood pattern in the instrument, even if the base pathogenesis of HB was the malfunction of the gallbladder due to phelgm stagnation.

Nonetheless, in each group, there were only four participants who correspond to the deficiency of both Qi and blood pattern. Because of this small sample size, we cannot exclude the possibility that the effect size appeared to be inaccurate, thereby suggest further studies with a larger sample for clear assessment.

Besides, there was a noticeable difference only in HAM-A than other assessment measures. It can be inferred that in the treatment of HB, SYM can be effective on remarkable psychosomatic symptoms associated with anxiety.

Some limitations could have affected this clinical trial. First, the approved daily dose of the extraction product was only one-third of the amount of the decoction formula, the ordinary form in the clinical field. This difference may have hindered some effects. We suggest further research on SYM of various dosages and formulas. Second, in the diagnostic process of psychiatric disorders, history taking itself can act as a psychotherapeutic intervention. A rapport between the patients and the research doctor or nurse can produce a placebo effect, making it difficult to verify the drug efficacy. Additionally, variations in the scores assessed by questionnaires could be greater than in assessment tools for physical illnesses.

In conclusion, SYM did not significantly improve the symptoms of HB patients any better than that of the placebo. However, it is meaningful in the sense that our study suggests further clinical studies to involve more elaborate pattern identification.

CONFLICT OF INTEREST

None.

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