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Original Article

Effect of herbal medicine (*Huanglian-jie-du* granule) for somatic symptoms and insomnia in patients with *Hwa-byung*: A randomized controlled trial

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ABSTRACT

Background: Huanglian-jie-du (HJD) granule, which is composed of representative "heat-clearing" herbs has been used for *Hwa-byung*. *Hwa-byung* is a culture-bound syndrome in Korea, characterized by distinct somatic symptoms such as chest congestion and heat sensation resulting from suppressed anger. We investigated the effect of HJD in patients with *Hwa-byung*.
Methods: Forty-four patients with *Hwa-byung* were recruited, and HJD or placebo granules were administered orally three times daily for seven days. The two primary outcomes were somatic symptoms, which were measured by Patient Health Questionnaire of physical symptoms (PHQ-15), and insomnia, which was measured by Insomnia Severity Index (ISI) at post-treatment.
Results: Between July 10 and October 31, 2017, 44 patients with *Hwa-byung* (mean age 36.68 years; and 38 female) were randomly assigned to HJD (n = 22) or placebo (n = 22) group. After administration of HJD or placebo granule for seven days, ISI score was lower in the HJD group compared to placebo group at post-treatment (adjusted mean difference -2.56 [95% CI -4.72 to -0.39], p = 0.0208). Meanwhile, there was no difference in PHQ-15 score between HJD group and placebo group at post-treatment (adjusted mean difference -0.50 [95% CI: -3.02–4.02], p = 0.7812).
Conclusions: Our results suggest that the administration of HJD granule has a potential to improve insomnia in *Hwa-byung* patients. Effect of HJD granule for general somatic symptoms in *Hwa*-byung patients is unclear, and further researches are needed.
Trial registration: Clinical Research Information Service, KCT0002379.

1. Introduction

Hwa-byung is one of the cultural concepts of distress in Korea, which is believed to result from accumulation of suppressed anger.[1,2] In Korea, *Hwa-byung* literally means both fire disease and anger disease. As the name suggests, the major emotion in *Hwa-byung* is anger, and the symptoms of *Hwa-byung* are characterized by heat sensation around the chest, chest congestion, and flush of anger, which are suggestive of fire.[3] This syndrome is comprehensible in the Confucian cultural context, which discourages people from expressing anger or negative emotions socially to maintain stable relationships.[4] As a result, suppressed anger accumulated inside the body develops into *Hwa-byung*, presenting characteristic somatic symptoms of chest congestion, and heat sensation; as well as psychological symptoms of anger, and frustration.[5,6] Structured and reliable diagnostic criteria of *Hwa-byung* were developed and it includes symptoms of *Hwa-byung* such as chest congestion, heat sensation, resentment/anger, anxiety, insomnia, dry mouth, headache/dizziness, and palpitation.[7] The prevalence of *Hwa-byung* based on these criteria has been reported to be 5.4% in the local Korean population.[8]

Huanglian-jie-du (HJD, *Hwangryunhaedok*-tang in Korean; and *Oren-gedoku-to* in Japanese) decoction is popular heat-clearing and detoxicating formula in traditional oriental medicine.[9,10] HJD has been reported to have potential pharmacological effects on hyperlipidemia, tumor, arthritis, liver injury, Alzheimer's disease, and depression.[10,11] There are a few previous studies about HJD

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for the *Hwa-byung* patients. A case report about the effect of HJD pharmacopuncture on heat sensation around chest has been reported.[12] Also, approved indication of HJD granule by Korea Food & Drug Administration (KFDA) includes insomnia, neurosis, dizziness, and palpitation of a relatively healthy but red-faced person with flushing. Heat sensation, insomnia, and palpitation is one of the representative somatic symptoms of *Hwa-byung*. Textbook of Korean medicine in neuropsychiatry suggests that HJD granule is the first line therapy in *Hwa-byung* with predominant heat sensation and insomnia,[13] but the clinical evidence is limited.

Hwa-byung has four stage of clinical course; anger, conflict, resignation (giving-up), and symptom stages, and each stage has distinct characteristics.[14] In the early stage of *Hwa-byung*, expression of anger and acute stress reaction including chest discomfort, flushing, and insomnia are predominant.[13] In this study, we mainly focused on this early stage of *Hwa-byung* to explore the proper intervention for relieving the alarmed response in acute stressed circumstance. Somatic symptoms and insomnia were selected for the primary outcomes, which are typical symptoms in early stage *Hwa-byung*. The objective of this randomized clinical trial was to explore the potential effect of HJD granule for relieving somatic symptoms and insomnia in patients with *Hwa-byung* in early stages.

2. Methods

2.1. Study design

This study is a randomized, double-blind, prospective, placebo-controlled trial with two parallel groups to explore the efficacy and safety of HJD granule on *Hwa-byung*. Details of the study protocol have been published on May 2018.[15] Using a protocol approved by the Kyung Hee University Korean Medicine Hospital Institutional Review Board (Approval Number KOMCIRB-170217-HR-004), this trial was conducted in a single center, Kyung Hee University Medical Center, in Seoul, Korea. Written informed consent was obtained from all participants before the procedures. This trial was registered with clinical research information service, registration number of KCT0002379. We submitted our trial protocol to registry site on 19 June 2017, and it was registered on 20 July 2017 after the review process. The date of first participant recruitment was 10 July 2017, which was after the submission of the protocol.

2.2. Participants

Forty-four eligible participants were recruited through advertising via hospital notice boards, and subways. Participants aged between 19 and 65 were included. Eligible patients required a diagnosis of *Hwa-byung*, with symptom onset within the prior 4 weeks. The diagnosis of *Hwa-byung* was carried out by a qualified specialist using structured clinical interview for *Hwa-byung* based on the diagnostic criteria of *Hwa-byung*.[13] The validity and reliability of the diagnostic criteria for *Hwa-byung* have been reported to be high in Korean populations.[7] The diagnostic criteria of *Hwa-byung* is available at previously published protocol of this study, and clinical guideline for *Hwa-byung*.[13,15] Participants were excluded if they had high risk of suicide; current or lifetime bipolar disorder, schizophrenia; current or previous intake of psychotropic drugs within 30 days; non-psychotropic drugs having psychiatric adverse effect within 14 days; psychotherapy, electroshock treatment, or transcranial magnetic therapy within 30 days; or oriental medical treatment within 14 days; serious unstable medical condition; uncontrolled diabetic or hypertension; hepatic or renal disease; hyperthyroidism or hypothyroidism; and likelihood of pregnancy.

2.3. Randomization and blinding

After screening, eligible participants were randomly assigned to the HJD group or the placebo group in a 1:1 ratio. The randomization sequence was generated by an independent investigator who was not involved in the recruitment or enrollment of participants. R (version 3.3.3) statistical software was used to generate randomization sequence with block size of four. Kyungjin pharmaceutical Co., Ltd (Icheon, Korea), which is not involved in the performance of this clinical trial, packed numbered containers based on random allocation sequence. Each identical drug container was labeled with a random allocation number. The participants and investigators involved in the enrollment, assignment, treatment, and outcome assessment were blinded to the treatment allocation. Until completion of the statistical analysis, the group information (whether HJD or placebo group) was replaced with “A” or “B” as blind codes.

2.4. Procedures

All participants orally ingested 2.5 g of granules with 150 mL of warm water, three times a day (7.5 g for 1 day), for 7 consecutive days. The HJD granule is composed of following four crude drugs: Root of *Scutellaria baicalensis* 3.0 g, Fruit of *Gardenia jasminoides* 2.0 g, Rhizome of *Coptis chinensis* 2.0 g, Bark of *Phellodendrom amurense* 1.5 g. The HJD granule, powdered and freeze-dried water extract, was manufactured by the Tsumura & Co, Ltd. in Japan. Placebo granule, which was nearly identical to the experimental granules in shape, color, scent, and taste and containing no effective ingredients, was manufactured by Kyungjin Pharmaceutical Co., Ltd (Icheon, Korea). The manufacturing numbers were UGR901 for HJD granule and 17001 for placebo. Both drugs were packaged in identical drug containers. Clinical outcomes were measured at baseline, post-treatment (1 week after baseline), and follow-up (5 weeks after baseline). The Korean Medicine Clinical Trial Center at the Kyung Hee University Korean Medicine Hospital monitored this study. The monitoring procedures followed the standard operating procedures (SOPs) and the Korean good clinical practice (KGCP). Monitoring was done twice: initially, when the first participant completed the whole experiment, and second when the last participant completed.

2.5. Outcome measurements

The primary outcomes were the score of Patient Health Questionnaire of Physical Symptoms (PHQ-15)[16,17] and Insomnia Severity Index (ISI)[18,19] at the post-treatment, after 7 days of administration. PHQ-15 measures unspecific somatic symptoms caused by mental problems; stomach pain, back pain, pain in arms, legs, or joints, menstrual problems, headaches, chest pain, dizziness, fainting spells, palpitation, shortness of breath, sexual problems, constipation or diarrhea, indigestion, feeling tired, and sleeping problems.[17] ISI measure the severity of insomnia, which score range from 0 to 28, higher score means severe insomnia.[20]

The secondary outcomes include the Stress Response Inventory (SRI),[21] Visual Analogue Scale for *Hwa-byung* Symptoms (VAS-HS),[13] State Trait Anger Expression Inventory-State Anger (STAXI-S).[22] Subscales of SRI includes stress response symptoms of tension, aggression, somatization, anger, depression, fatigue, and frustration.[21] VAS-HS were based on fifteen *Hwa-byung* symptoms listed in diagnostic criteria of Hwa-byung.[23] 100 mm Visual analogue scale of each *Hwa-byung* symptoms were measured, and mean score was calculated. Mean score of every *Hwa-byung* symptoms which range from 0 to 100 was used for main analysis, and *each Hwa-byung* symptoms were additionally analyzed. STAXI-S were adopted to measure state anger, which major emotion of *Hwa-*

byung.[22] Every adverse event that occurred during the treatment and follow-up phases was carefully documented.

2.6. Statistical analysis

As previously reported, a clinically relevant reduction in the ISI score was determined to be 5.[20] The results from a recent clinical trial of Korean medicine treatment for *Hwa-byung* demonstrated that the standard deviation of the change in ISI scores was assumed to be 5.73.[24] With a 5% significance level and 21 participants per group, we had 80% power to detect a mean difference of 5 in ISI score based on the standard deviations of the previous study. A total of 44 participants were recruited to account for an expected 5% dropout rate.

There were two primary outcomes in this study, and to adjust the error in multiple comparisons, significant level of 0.025 were applied for the two primary outcomes, respectively. Least square (LS) mean difference between HJD group and placebo group was calculated by analysis of covariance (ANCOVA) with baseline as the covariate and the group as the fixed factors. Additionally, LS mean difference by Mixed-effect Model for Repeated Measure (MMRM) was also examined. The paired sample *t*-test was also conducted to compare intra-group change of outcomes from baseline to post-treatment, and follow-up. Intention-to-treat analysis including all randomized participants' data was carried out, and multiple imputations were applied for replacing missing data in ANCOVA. Continuous variables were presented as mean (95% confidence interval), and categorical variables were presented as frequency (%). Comparing proportions between two groups were carried out by chi-square test or Fisher's exact test. Analyses were performed using SAS® Version 9.4 software (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participant flow

Eligible participants were recruited from July 10 to October 31, 2017. Participants attended clinic visits at the time of randomization, and later at 1-week, and 1-month follow-up visits. During the study period, 48 people were screened, and 44 (91.7%) were eligible to participate in the study. None of the eligible participants refused to participate in the study and finally 44 subjects (100% of eligible participants) were randomly assigned (Fig. 1) The ages ranged from 19 to 64 years and mean age was 36.68 (95% CI: 33.01, 40.36) years. 38 (86%) of total participants were female, which showed gender-related difference in prevalence similar with the previous report that majority of *Hwa-byung* patients are female.[13] All baseline demographics and characteristics showed no significant difference between groups (Table 1). Baseline PHQ-15 and ISI score seems to be different in two groups, which were not statistically significant, and ANCOVA with baseline data as the covariate was carried out.

A total of 2 participants, who declined to participate for personal reason which are not related to safety issue, dropped out before the 1-week follow-up (Fig. 1). The intention-to-treat primary analysis involved all patients who were randomly assigned. The medication compliance of the HJD group was 94.6%, and that of the placebo group was 91.2%. 42 participants showed a compliance rate above 70%.

3.2. Primary outcomes

Results of two primary outcomes are presented in Table 2. After administration of HJD or placebo granule for seven days, PHQ-15 score was decreased in both groups, from 21.23 (95% CI: 19.14, 23.32) to 13.95 (95% CI: 11.64, 16.27) in HJD group ($p < 0.0001$), and from 18.77 (95% CI: 16.31, 21.23) to 13.00 (95% CI: 10.08, 15.92) in placebo group ($p = 0.0048$). There was no significant difference between two groups in PHQ-15 score at post-treatment (LS mean difference −0.50 [95% CI: −3.02–4.02], $p = 0.7812$). ISI score was also decreased in both groups, from 14.91 (95% CI: 12.93, 16.89) to 9.05 (95% CI: 7.32, 10.77) in HJD group ($p < 0.0001$), and from 17.05 (95% CI: 14.83, 19.26) to 13.10 (95% CI: 10.32, 15.88) in placebo group ($p = 0.0001$). There was significant difference between two groups in ISI score at post-treatment (LS mean difference -2.56 [95% CI: −4.72 to −0.39]; $p = 0.0208$). LS mean differences calculated by MMRM are also presented in Table 2, which show the minor difference between the results of the two methods.

Table 1
Baseline characteristics.

Characteristic	HJD group (N = 22)	Placebo group (N = 22)	p-value
Gender			0.999
Male	3 (14%)	3 (14%)	
Female	19 (86%)	19 (86%)	
Age (year)	35.32 (31.13, 39.50)	38.05 (32.85, 43.24)	0.427
PHQ-15	21.23 (19.14, 23.32)	18.77 (16.31, 21.23)	0.121
ISI	14.91 (12.93, 16.89)	17.05 (14.83, 19.26)	0.143
SRI	86.77 (77.94, 95.61)	79.27 (67.22, 91.32)	0.303
VAS-HS	63.51 (57.54, 69.49)	58.01 (51.58, 64.45)	0.200
STAXI-S	22.59 (19.93, 25.25)	21.73 (18.38, 25.08)	0.677

Data are n (%) or mean (95% CI). PHQ-15, Patient health questionnaire- physical symptoms; ISI, Insomnia severity index; SRI, Stress response inventory; VAS-HS, Visual analogue scale for *Hwa-byung* symptoms; STAXI-S, State trait anger expression inventory-state anger.

3.3. Secondary outcomes

At the 1-month follow-up assessment, reduction of PHQ-15 score from the baseline was −9.05 (95% CI: −11.80, −6.29) in HJD group versus −4.06 (95% CI: −7.33, −0.77) in placebo group (LS mean difference −3.12 [95% CI: −6.97 to 0.55], $p = 0.0939$ at follow-up). Reduction of ISI score at the follow-up was −6.91 (95% CI: −8.42, −5.40) in HJD group, and −6.00 (95% CI: −8.08, −3.92) in placebo group (LS mean difference −1.92 [95% CI: −4.09 to 0.25], $p = 0.0830$ at follow-up). Changes of SRI, VAS-HS, and STAXI-S score throughout the study is also presented in Table 2. Stress response, Hwa-byung symptoms, and state anger were alleviated in both groups after the administration, but the differences between groups were not statistically significant. Reduction of VAS-HS score at post-treatment was −19.76 (95% CI: −26.31, −13.01) in HJD group versus −11.61 (95% CI: −17.12, −6.10) in placebo group (LS mean difference −5.61 [95% CI: −13.73 to 2.52], $p = 0.1760$ at post-treatment). Results of subscale analysis of SRI and VAS-HS are presented in Supplementary Table 1 and 2 respectively. Among various Hwa-byung symptoms, heat sensation and dry mouth seems to be improved better in HJD group compared to placebo group (Supplementary Table 2).

Success of blinding was assessed at the post-treatment, and 18 (81.8%) participants in HJD group versus 15 (75%) participants in placebo group answered that they thought to have received HJD granules, not placebo granules. There was no significant difference between two groups based on fisher's exact test ($p = 0.7139$).

3.4. Safety outcomes

Adverse events reported throughout the study are presented in Table 3. The proportion of patients experiencing an adverse event seems to be higher in the HJD group (31.82%) than in the placebo group (9.09%), which difference was not statistically significant ($p = 0.1324$). Six of 22 (27.27%) patients in HJD group reported mild

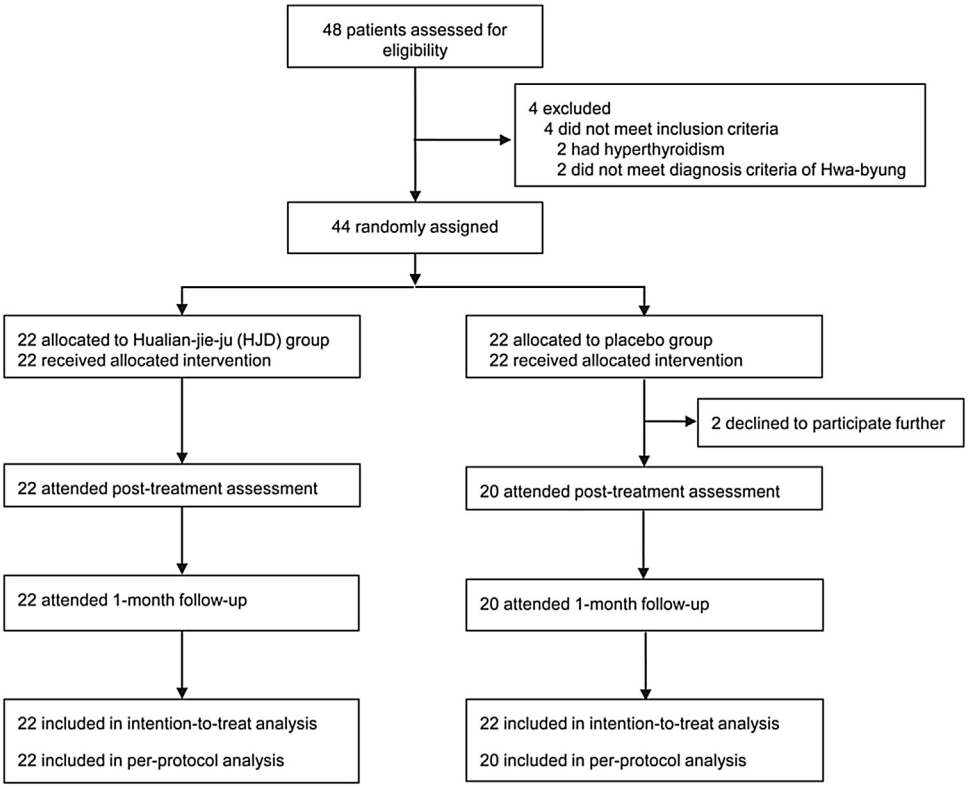

Fig. 1. Flow chart outlining study design.

indigestion during treatment, whereas, one of 22 (4.55%) patients in placebo group reported mild indigestion. All adverse events were recovered naturally, without treatment cessation. No severe adverse event was observed in both groups.

4. Discussion

In this randomized controlled trial of HJD granule for somatic symptoms and insomnia in patients with *Hwa-byung*, HJD granules showed potential effect for insomnia in *Hwa-byung* patients after seven days of administration. Meanwhile, effect of HJD granules for general somatic symptoms was not significant in this study. Mild indigestion was occurred in 27.3% of participants who administrated HJD granules.

Insomnia is one of the *Hwa-byung* symptoms listed in diagnostic criteria of *Hwa-byung*, and representative somatic symptom in early stages of *Hwa-byung*.[13] Also, insomnia is one of the general symptoms after stressful events,[25]and identified as a predictor of mental disorders including depression.[26] Baseline mean ISI score of included participants were 15.98, and ISI score over 7 is considered as mild insomnia, and that over 15 is considered as moderate insomnia. All included *Hwa-byung* patients except two had mild to severe insomnia. In this trial, seven days of HJD administration relieved insomnia better compared with placebo at post-treatment. Root of *Scutellaria baicalensis*, one of the component of HJD granule and having active ingredients of *Baicalin*, reported to have sedative-hypnotic effect by inhibition of release of glutamate.[27] From the systematic review of herbal medicine for insomnia based on pattern of Traditional Chinese Medicine (TCM), root of *Scutellaria baicalensis* and Fruit of *Gardenia jasminoides* were frequently used herbs for insomnia patients with 'Liver-qi stagnation transforming into fire'; and Bark of *Phellodendrom amurense* and Rhizome of *Coptis chinensis* were used for insomnia patients with 'Hyperactivity of fire due to yin deficiency'.[28] Crude herbs included in HJD granules were frequency used for insomnia related to fire/heat pattern in previous researches. Also, there have been reports that individuals with insomnia are more likely to seek complementary and alternative medicine including herbal medicine.[29–31] Among various herbal medicine formula, HJD may be an attractive option in the case of *Hwa-byung* patient or patients with fire/heat pattern, for relieving sleep problems. There has been a randomized clinical trial of acupuncture for insomnia of *Hwa-byung* patient, which showed better effect compared to sham acupuncture.[32] Further researches about the combination treatment of acupuncture and HJD granule for insomnia of patients with Hwa-byung are suggested.

Hwa-byung is a type of somatization disorder resulting from suppressed anger.[33] Considering the indication of HJD granule, effect on somatic symptoms were targeted to be measured, but there was no validated tool for measuring the somatic symptoms of *Hwa-byung*. Instead, general somatic symptoms were measured by PHQ-15. The severity of somatic symptoms measured by PHQ-15 range from minimal, mild, moderate, to severe (score 0–4, 5–9, 10–14, or 15–30).[17] Baseline mean PHQ-15 score of included participants was 20.00 and reduced after the administration in both HJD and placebo groups. Effect of HJD granule for general somatic symptoms of *Hwa-byung* patients was not superior to placebo in our result. Additionally, specific symptoms of Hwa-byung were measured by VAS-HS. Among fifteen *Hwa-byung* symptoms, heat sensation and dry mouth seems to be improved better in HJD group compared to placebo group. As *Hwa-byung* means 'fire disease' in Korean, the symptoms of *Hwa-byung* can be summarized by the features of 'fire'. When considering HJD is composed of representative 'heat-clearing' herbs in oriental traditional medicine, the result is interesting that HJD was effective on heat sensation and dry mouth, which are the reflective symptoms of the disease. In previous research, *Bunsimgi-eum* (BSGE), another herbal medicine, was tested for *Hwa-byung* patients. VAS for chest discomfort and Likert scale for major symptoms of *Hwa-byung* measured. After treated

Table 2
Changes in primary and secondary outcomes in the Huanglian-jie-du (HJD) group and the placebo group from the baseline until 7-day and 1-month follow-up.

Outcomes	HJD group	Placebo group	Mean difference†	p-value†	Mean difference††	p-value††
PHQ-15						
Baseline	21.23 (19.14, 23.32)	18.77 (16.31, 21.23)				
Post-treatment	13.95 (11.64, 16.27)	13.00 (10.08, 15.92)	0.50 (−3.02, 4.02)	0.7812	0.93 (−2.46, 4.32)	0.5834
Difference‡	−7.27 (−10.12, −4.42)	−5.60 (−9.27, −1.93)				
p-value‡	<.0001*	0.0048*				
week 5	12.18 (9.49, 14.87)	14.55 (11.69, 17.41)	−3.12 (−6.97, 0.55)	0.0939	−2.42 (−5.92, 1.08)	0.1693
Difference‡	−9.05 (−11.80, −6.29)	−4.05 (−7.33, −0.77)				
p-value‡	<.0001*	0.0183*				
ISI						
Baseline	14.91 (12.93, 16.89)	17.05 (14.83, 19.26)				
Post-treatment	9.05 (7.32, 10.77)	13.10 (10.32, 15.88)	−2.56 (−4.72, −0.39)	0.0208*	−4.05 (−7.03, −1.07)	0.0089*
Difference‡	−5.86 (−7.44, −4.28)	−3.95 (−5.68, −2.22)				
p-value‡	<.0001*	0.0001*				
week 5	8.00 (6.12, 9.88)	11.05 (8.63, 13.47)	−1.92 (−4.09, 0.25)	0.0830	−3.05 (−5.95, −0.14)	0.0404*
Difference‡	−6.91 (−8.42, −5.40)	−6.00 (−8.08, −3.92)				
p-value‡	<.0001	<.0001*				
SRI						
Baseline	86.77 (77.94, 95.61)	79.27 (67.22, 91.32)				
Post-treatment	56.05 (44.11, 67.98)	53.55 (43.90, 63.20)	−1.49 (−13.09, 10.12)	0.8017	3.10 (−11.71, 17.91)	0.6748
Difference‡	−30.73 (−40.96, −20.49)	−26.70 (−35.33, −18.07)				
p-value‡	<.0001*	<.0001*				
week 5	39.09 (21.14, 49.04)	42.30 (34.46, 50.14)	−5.34 (−17.41, 6.73)	0.3848	−2.87 (−16.57, 10.84)	0.6748
Difference‡	−47.68 (−57.56, −37.80)	−37.95 (−51.01, −24.89)				
p-value‡	<.0001	<.0001				
VAS-HS						
Baseline	63.51 (57.54, 69.49)	58.01 (51.58, 64.45)				
Post-treatment	43.75 (36.88, 50.63)	46.36 (38.58, 54.14)	−5.61 (−13.73, 2.52)	0.1760	−2.63 (−11.91, 6.65)	0.5700
Difference‡	−19.76 (−26.51, −13.01)	−11.61 (−17.12, −6.10)				
p-value‡	<.0001*	0.0003*				
week 5	31.91 (22.12, 41.71)	35.85 (30.34, 41.35)	−5.81 (−16.28, 4.68)	0.2778	−3.94 (−13.94, 6.05)	0.4299
Difference‡	−31.60 (−40.58, −22.62)	−22.13 (−30.79, −13.46)				
p-value‡	<.0001*	<.0001*				
STAXI-S						
Baseline	22.59 (19.93, 25.25)	21.73 (18.38, 25.08)				
Post-treatment	17.68 (15.06, 20.30)	18.10 (15.84, 20.36)	−1.06 (−3.84, 1.73)	0.4576	−0.46 (−4.28, 3.37)	0.8094
Difference‡	−4.91 (−7.98, −1.83)	−3.55 (−5.68, −1.42)				
p-value‡	0.0033*	0.0025*				
week 5	14.59 (12.60, 16.58)	15.75 (13.58, 17.92)	−1.46 (−4.22, 1.29)	0.2971	−1.17 (−4.81, 2.47)	0.5187
Difference‡	−8.00 (−11.17, −4.83)	−5.90 (−9.62, −2.18)				
p-value‡	<.0001*	0.0036*				

Values are mean (95% CI). † Least squares mean difference and p-value by Analysis of covariance (ANCOVA) with baseline as the covariate; †† Least squares mean difference and p-value by Mixed-effect model repeated measure (MMRM) with baseline as the covariate; ‡ Mean difference and p-value by paired *t*-test; * p-value<0.05.
PHQ-15, Patient health questionnaire-physical symptoms; ISI, Insomnia severity index; SRI, Stress response inventory; VAS-HS, Visual analogue scale for *Hwa-byung* symptoms; STAXI-S, State trait anger expression inventory-state anger.

with BSGE for 4 weeks, *Hwa-byung* symptoms were relieved, but there was no difference compared to placebo.[34] Likert scale for major symptoms of *Hwa-byung* was also measured in another clinical trial of *Sihogayonggolmoryeo-tang*, which also showed no difference with placebo.[24] Likert scale for major symptoms of *Hwa-byung* measures four somatic symptoms and two psychological symptoms.[13,24,34] *Hwa-byung* scale developed and validated by Kwon in 2008 is composed of personality and symptoms scale of *Hwa-byung*, which mainly focused on screening of *Hwa-byung* patients from the healthy control and depressive patients. VAS-HS measuring all listed fifteen symptoms in diagnostic criteria of *Hwa-byung* was adopted in this trial and another recent clinical trial of Hwa-byung,[35] to explore the changes in various *Hwa-byung* symptoms. Validated and reliable measurement for scoring specific symptoms of *Hwa-byung*, which is suitable to detect the treatment response is strongly required.

Major emotion of *Hwa-byung* is suppressed anger, and *Hwa-byung* has been suggested as an anger disorder.[2] In an epidemiological study, *Hwa-byung* was distinguished from depressive disorder or anxiety disorder.[36] Improvement in state anger after treatment was expected, but reduction in state anger were similar in HJD and placebo groups. Effect on state anger superior to placebo was not observed in previous herbal medicine clinical trials for Hwa-byung.[24,34] There is a concern that state anger which is measured by STAXI-S has an limitation on reflecting the psychological symptoms of *Hwa-byung*. In this trial, HJD did not showed superior effect compared to placebo on psychological symptoms of *Hwa-byung*. However, reductions in 'flush of anger' 'sighing', and 'Hann', which referring to a mixed feeling of sorrow along with anger seems to be greater in HJD group than placebo, although it was not statistically significant (Supplementary Table 2). Further researches are needed to explore the potential effect of HJD on psychological symptoms of *Hwa-byung*. From our result of VAS-HS, it suggests that HJD mainly acts on somatic symptoms of *Hwa-byung* than psychological symptoms of *Hwa-byung*.

It is noteworthy that number of participants reporting adverse events of mild indigestion was greater in HJD group than placebo group. Practitioners should be careful to use HJD in *Hwa-byung* patients with digestive symptoms. When considering risk and benefit of HJD, it seems that HJD has more benefits than risk. All the adverse effects were mild, lasting no longer than 2 h, without need for treatment cessation.

The strengths of our study are summarized that this is the clinical trial of herbal medicine for mental health, which explored the effectiveness based on cultural concept of distress. Also, our study had several limitations. First, the sample size of this study was not sufficient to confirm the effect of HJD granules for primary and secondary outcomes. Large-scale randomized trial is needed. Secondly,

Table 3
Adverse events reported during the study.

	HJD group (N = 22)	Placebo group (N = 22)
Adverse events		
Indigestion	6 (27.27%)	1 (4.55%)
Pruritus	0	1 (4.55%)
Loose stool	1 (4.55%)	0
Severity of AE		
Mild	7 (31.82%)	1 (4.55%)
Moderate	0	1 (4.55%)
Severe	0	0
Causality of AE		
Definitely related	0	0
Probably related	0	0
Possibly related	7 (31.82%)	2 (9.09%)
Unlikely related	0	0
Definitely not related	0	0
Total	7 (31.82%)	2 (9.09%)

Data are n (%).

our study was conducted by a single center in Korea, and study population was all Korean. Considering *Hwa-byung* is a Korean culture-bound distress, the result leaves room for potential universal application of HJD on similar diseases. As suppressed anger is a common emotion, and insomnia after stressful events is also a prevalent symptom across culture, suggesting the need for further studies. Third, the clinical trial involved only patients with *Hwa-byung* in early stages, without any psychiatric drugs, and the effect of HJD granule in chronic *Hwa-byung* has yet to be demonstrated. Further investigation is needed to evaluate the long-term effect of administration of HJD granule. Fourth, there was no lower limit of ISI and PHQ-15 in our inclusion criteria. The symptoms of insomnia and somatic symptoms are partially included in the diagnostic criteria of *Hwa-byung*. If we had lower limit of PHQ-15 and ISI score in inclusion criteria, clearer outcome could have been expected. Fifth, ISI is a tool to evaluate the sleep quality in the recent two weeks, but we modified the period to one week because of our study design. The validation of modified period of ISI was not carried out, which should be taken into account when interpreting the result.

In summary, administration of HJD granule for 7 days showed the potential effect on insomnia in *Hwa-byung* patients. And effect of HJD granule was not superior to placebo on general somatic symptoms in this study. Based on the result of secondary outcomes, we suppose that HJD mainly worked on somatic symptoms including heat sensation and dry mouth, rather than psychological symptoms, which may need further researches. The administration of HJD granule increased the incidence of mild indigestion compared to placebo, which require further attention. Our study findings may provide helpful implications in use of HJD granule for *Hwa-byung* patients.

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Author contributions

Conceptualization: YC, SYJ, and SHC. Methodology: YC, SYJ, and SHC. Investigation: YC. Formal Analysis: OK. Writing - Original Draft: YC. Writing - Review & Editing: YK and SHC. Supervision: SHC.

Conflicts of interest

The authors declare no conflict of interest.

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Ethical statement

This research has been approved by the Kyung Hee University Korean Medicine Hospital Institutional Review Board (Approval Number KOMCIRB-170217-HR-004).

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.imr.2020.100453.

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