Original Article

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

Yujin Choi, Yunna Kim, Ojin Kwon, Sun-Yong Chung, Seung-Hun Cho

* Corresponding author at: Kyung Hee University Medical Center, Kyung Hee University, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea. E-mail address: choshi@khmc.or.kr (S.-H. Cho).

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.

© 2020 Korea Institute of Oriental Medicine. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Hwa-byung is one of the cultural concepts of distress in Korea, which is believed to result from accumulation of suppressed anger. 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. This syndrome is comprehensible in the Confucian cultural context, which discourages people from expressing anger or negative emotions socially to maintain stable relationships. 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. 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. The prevalence of Hwa-byung based on these criteria has been reported to be 5.4% in the local Korean population.

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. HJD has been reported to have potential pharmacological effects on hyperlipidemia, tumor, arthritis, liver injury, Alzheimer’s disease, and depression. There are a few previous studies about HJD...
for the Hwa-byung patients. A case report about the effect of HJD pharmacopuncture on heat sensation around chest has been reported. 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 heart sensation and insomnia, 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. In the early stage of Hwa-byung, expression of anger and acute stress reaction including chest discomfort, flushing, and insomnia are predominant. 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. Using a protocol approved by the Kyung Hee University Korean Medicine Hospital Institutional Review Board (Approval Number KOMCRIB-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. The validity and reliability of the diagnostic criteria for Hwa-byung have been reported to be high in Korean populations. The diagnostic criteria of Hwa-byung is available at previously published protocol of this study, and clinical guideline for Hwa-byung. 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 Cryptis chinensis 2.0 g, Bark of Phellodendron 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 (KGPCP). 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) and Insomnia Severity Index (ISI) 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. ISI measure the severity of insomnia, which score range from 0 to 28, higher score means severe insomnia.

The secondary outcomes include the Stress Response Inventory (SRI), Visual Analogue Scale for Hwa-byung Symptoms (VAS-HS), State Trait Anger Expression Inventory-State Anger (STAXI-S). Subscales of SRI includes stress response symptoms of tension, aggression, somatization, anger, depression, fatigue, and frustration. VAS-HS were based on fifteen Hwa-byung symptoms listed in diagnostic criteria of Hwa-byung. 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 to 2.02], 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.

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

---

**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 (77.84, 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.
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 administered 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. Also, insomnia is one of the general symptoms after stressful events, and identified as a predictor of mental disorders including depression. 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. 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-qì stagnation transforming into fire’; and Bark of Phellodendron amurense and Rhizome of Coptis chinensis were used for insomnia patients with ‘Hyperactivity of fire due to yin deficiency’. Crude herbs included in HJD granules were frequently 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. 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. 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. 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). 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
with BSGE for 4 weeks, Hwa-byung symptoms were relieved, but there was no difference compared to placebo.\textsuperscript{34} Likert scale for major symptoms of Hwa-byung was also measured in another clinical trial of Sihogayonggolmyeoreo-tang, which also showed no difference with placebo.\textsuperscript{24} Likert scale for major symptoms of Hwa-byung measures four somatic symptoms and two psychological symptoms.\textsuperscript{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,\textsuperscript{29} 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.\textsuperscript{2} In an epidemiological study, Hwa-byung was distinguished from depressive disorder or anxiety disorder.\textsuperscript{30} 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.\textsuperscript{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                | 0                    |
| 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.

Acknowledgements

We would like to thank all the participants. Also, we thank Eun-Ji Choi and Hye-Weon Seo from Kyung Hee University for their contributions in planning and managing this clinical trial.

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.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HB16C0068).

Ethical statement

This research has been approved by the Kyung Hee University Korea Medicine Hospital Institutional Review Board (Approval Number KOMCRIB-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.

References

1. Kohrt BA, Rasmussen A, Kaiser BN, et al. Cultural concepts of distress and psychiatric disorders: literature review and research recommendations for global mental health epidemiology. Int J Epidemiol 2014;43(2):365–406.
2. Min SK. Clinical correlates of hwa-byung and a proposal for a new anger disorder. Psychiatry Investig 2008;5(3):125–41.
3. Roberts ME, Han K, Weed NC. Development of a scale to assess Hwa-Byung, a Korean culture-bound syndrome, using the Korean MMPI-2. Transcult Psychiatry 2006;43(3):383–400.
4. Ninnemann K, Hwa-byung. In: Lour S, Sajatovic M, editors. Encyclopaedia of immigrant health. New York, NY: Springer New York; 2012:862–3.
5. Park YJ, Kim HS, Kang HC, Kim JW. A survey of Hwa-Byung in middle-age Korean women. J Transcult Nurs 2001;12(2):115–22.
6. Min SK, Suh SY, Song KJ. Symptoms to use for diagnostic criteria of hwa-byung, an anger syndrome. Psychiatry Investig 2009;6(1):7–12.
7. Kim J, Kwon J, Lee M, Park D. Development of hwa-byung diagnostic interview schedule (HBDIS) and its validity test. Korean J Health Psychol 2004;9(2):321–31.
8. Lee JC, Lee JH. Study on the prevalence of hwa-byung diagnosed by HBDIS in general population in kang-won province. J Orient Neuropsychiatry 2008;19(2):133–9.
9. Ye Y, Huang C, Jiang L, et al. Huanglian-jie-Du-Tang extract protects against chronic brain injury after focal cerebral ischemia via hypoxia-inducible-factor-1alpha-regulated vascular endothelial growth factor signaling in mice. Biol Pharm Bull 2012;35(3):355–61.
10. Qi Y, Zhang Q, Zhu H. Huang-Lian-Jie-Du decoction: A review on psychotherapy, pharmacological and pharmacokinetic investigations. Chin Med 2019;14(1):57.
11. Ye Y-L, Zhong K, Liu D-D, et al. Huanglian-jie-du-tang extract ameliorates depression-like behaviors through BDNF-TrkB-CREB pathway in rats with chronic unpredictable stress. Evid Based Complement Altern Med 2017;2017.
12. Kim J-U, Lee Y-J, Rhim E-K, et al. Two cases of chest heating sensation treated by Hwanggyunhaedang-herbal-acupuncture. J Pharmacopuncture 2003;6(2):127–35.
13. Kim J, Jung I, Kang H, Lee S, Jung S. Clinical guideline for hwa-byung, Korea: Clinical Research Center for Hwa-byung Seoul, 2013.
14. Cho H, Whang W, Kim J, Park H. Relationship between hwa-byung and emotional stress. Korean J Health Psychology 1997;2:170–80.
15. Choi YJ, Chung SY, Cho SH. The efficacy and safety of a Huanglian-jie-du decoction on Hwa-byung patients: A study protocol for a randomized controlled trial. J Pharmacopuncture 2018;21(1):7–13.
16. Han C, Pae CU, Patkar AA, et al. Psychometric properties of the Patient Health Questionnaire-15 (PHQ-15) for measuring the somatic symptoms of psychiatric outpatients. Psychosomatics 2009;50(6):580–5.
17. Kroenke K, Spitzer RL, Williams JB. The PHQ-15: Validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med 2002;64(2):258–66.
18. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2(4):297–307.
19. Cho YW, Song ML, Morin CM. Validation of a Korean version of the insomnia severity index. J Clin Neurol 2014;10(1):210–5.
20. Morin CM, Belleville G, Belanger L, Ivers H. The Insomnia Severity Index: Psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;34(5):601–8.
21. Koh KB, Park JK, Kim CH, Cho S. Development of the stress response inventory and its application in clinical sleep medicine. Psychosom Med 2001;63(4):668–78.
22. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the state-trait anxiety inventory; 1970.
23. Suh S. Stories to be told: Korean doctors between hwa-byung (fire-illness) and depression, 1970-2011. Cult Med Psychiatry 2013;37(1):81–104.
24. Choi WC, Park DM, Kang WC, Lee WC, Jung IC. Interim report about the effect of shoganyongolmoryeo-tang on the anxiety of hwa-byung. J Orient Neuropsychiatry 2012;23(4):133–52.
25. LeBlanc M, Beaulieu-Bonneau S, Merette C, Savard J, Ivers H, Morin CM. Psychological and health-related quality of life factors associated with insomnia in a population-based sample. J Psychosom Res 2007;63(2):157–66.
26. Hertenstein M, Feige B, Gmeiner T, et al. Insomnia as a predictor of mental disorders: A systematic review and meta-analysis. Sleep Med Rev 2019;43:96–105.
27. Shi M-M, Piao J-H, Xu X-L, et al. Chinese medicines with sedative-hypnotic effects and their active components. Sleep Med Rev 2016;29:108–18.
28. Yeung W-F, Chung K-F, Poon M-K, et al. Prescription of Chinese herbal medicine and selection of acupoints in pattern-based traditional Chinese medicine treatment for insomnia: A systematic review. Evid Based Complement Altern Med 2012;2012.
29. Sánchez-Ortuño MM, Bélanger L, Ivers H, LeBlanc M, Morin CM. The use of natural products for sleep: A common practice? Sleep Med 2009;10(9):982–7.
30. Pearson NJ, Johnson LL, Nahin RL. Insomnia, trouble sleeping, and complementary and alternative medicine: Analysis of the 2002 national health interview survey data. Arch Intern Med 2006;166(16):1775–82.
31. Meredith S, Frawley J, Adams J, Sibbritt D. The utilization of health services and self-care by older women with sleeping problems: Results from a nationally representative sample of 9,110 women. J Aging Health 2018;30(4):540–58.
32. Lee G-E, Kim N-K, Kim N-K-Y, Kang H-W-W. The effects of acupuncture treatment on Hwa-byung patient’s insomnia: Patient-assessor blind, randomized, placebo-controlled clinical trial. J Orient Neuropsychiatry 2012;23(1):31–48.
33. Kirmayer LJ, Sartorius N. Cultural models and somatic syndromes. Psychosom Med 2007;69(9):832–40.
34. Kim SH, Park YC, Hong KE, Kang W, Lee SK, Jung IC. The effect of Bunsings-eum on Hwa-byung: Randomized, double blind, placebo controlled trial. J Ethnopharmacol 2012;144(2):402–7.
35. Kwak H-Y, Choi E-J, Kim J-W, Suh H-W, Chung S-Y. Effect of the Emotional Freedom Techniques on anger symptoms in Hwabyung patients: A comparison with the progressive muscle relaxation technique in a pilot randomized controlled trial. EXPLORE 2019.
36. Min SK, Suh SY. The anger syndrome hwabyung and its comorbidity. J Affect Disord 2010;124(1-2):211–4.