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Study Protocol

Efficacy and safety of herbal medicine (Dangguijagyag-san) for primary dysmenorrhea: study protocol for a randomized, double-blind, placebo-controlled, parallel-group, multi-center trial

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ABSTRACT

Background: Dangguijagyag-san, also known as Dangguishao-yao-san in Chinese and Toki-shakuyakui-san in Japanese, has been frequently used to treat symptoms associated with dysmenorrhea. The purpose of this trial is to evaluate the efficacy and safety of the herbal medicine, Dangguijagyag-san, relative to those of active control, Gamisoyo-san, and a placebo control for primary dysmenorrhea.

Methods: This protocol details a randomized, double-blind, parallel-group, multi-center, investigator-initiated, controlled trial evaluating treatment of primary dysmenorrhea. Two hundred and forty participants will be randomly divided into one of three groups: 1) the Dangguijagyag-san experimental group (EG) (n = 105), 2) the Gamisoyo-san active control group (ACG) (n = 30), and 3) the placebo control group (PCG) (n = 105). The interventions will be administered for two menstrual cycles, and the follow-up will be carried out for the following six menstrual cycles. The primary outcomes are difference in response rates between the EG and the ACG (non-inferiority comparison) and difference in changes from baseline in average pain intensity measured by the visual analogue scale between the EG and PCG (superiority comparison). The secondary outcomes are pain scores derived from pain assessment tools (verbal multidimensional scoring system, retrospective symptom scale, and short form McGill pain questionnaire), dosage of analgesics, pattern diagnosis questionnaires, and short form 36 health survey. Adverse events and vital signs will be checked at every visit, and laboratory tests will be performed for safety evaluation.

Discussion: The results of this clinical trial will offer evidence for the efficacy and safety of Dangguijagyag-san for primary dysmenorrhea.

Trial registration: Clinical Research Information Service of Korea: KCT0003005

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Introduction

Primary dysmenorrhea is defined as painful menstrual cramps without any identifiable pelvic pathology, such as uterine fibroids, adenomyosis, endometriosis, or pelvic inflammatory diseases.¹ Many studies have reported that the prevalence of primary

dysmenorrhea varied from approximately 45–80% among general population,^{2–7} and 17–60% of dysmenorrheic women missed school or work regularly.^{3–5} According to the consensus guidelines for primary dysmenorrhea,⁸ nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line treatment. However, a systematic review⁹ reported that NSAIDs caused adverse events, including mild neurological symptoms (headache, dizziness, or drowsiness) and gastrointestinal intolerance (nausea or indigestion). Oral contraceptives may be recommended for some women,⁸ but oral contraceptives may not be suitable for patients attempting to become pregnant and might cause adverse effects, such as nausea, headaches, weight gain, or vaginal bleeding.^{8,10}

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Dangguijagyag-san (DJS), also known as *Danguishaoyao-san* in Chinese and *Toki-shakuyakui-san* in Japanese, has been frequently used to treat general symptoms associated with dysmenorrhea in Korean and Taiwanese practical fields.^{11,12} It was first mentioned in *«Jin Gui Yao Lue»* by *Zhong-Jing Jang* and has been used for menstruation-associated symptoms, nourishing blood, harmonizing nutrients, relieving stasis, reducing pain, fortifying the spleen, and draining dampness. DJS consists of six herbal medicines: *Angelicae Gigantis Radix*, *Cnidii Rhizoma*, *Paeoniae Radix*, *Poria Sclerotium*, *Atractylodis Rhizoma Alba*, and *Alismatis Rhizoma*. Previous studies reported that DJS could influence the function of corticotropin-releasing hormone, inhibit hyperactivity of the adrenal axis,¹³ improve luteal insufficiency,¹⁴ have estrogenic effects,¹⁵ and exert neuroprotective effects on postmenopausal neurodegenerative diseases.¹⁶

A previous systematic review¹⁷ showed that DJS was significantly more effective than analgesics in terms of risk ratio (RR) (1.31, 95% confidence interval (CI) 1.06–1.63), and was superior to the placebo. However, the number of studies included in this review was small, and the overall risk of bias was high, so a large, well-designed study with rigorous guidelines is needed. Despite frequent use of DJS, no clinical trials conducted in Korea have evaluated the efficacy of DJS for primary dysmenorrhea. Thus, this trial is to evaluate the efficacy and safety of DJS compared to active control and a placebo control for primary dysmenorrhea. This trial aimed to verify the two hypotheses that administration of DJS for two menstrual cycles will improve primary dysmenorrhea equivalently or better than Gamisoyo-san (GSS) administration and reduce menstrual pain more effectively than placebo administration.

Methods

This protocol was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)¹⁸ to improve the quality of reporting.

Trial registration

This trial has been registered at Clinical Research Information Service (<https://cris.nih.go.kr/cris/en/>) and the registration number is KCT0003005.

Study design

This is a multi-center, double-blind, three-arm, parallel-group, investigator-initiated, randomized, controlled trial consisting of an intervention phase for two menstrual cycles followed by short- and long-term follow-up phases for two and six menstrual cycles, respectively. After receiving an explanation of the trial and providing written informed consent, participants will be given screening numbers by visiting order. If a participant is suspected of suffering from secondary dysmenorrhea at a screening visit, an additional sonography will be conducted. Pain intensity of participants who completed the screening test will be assessed as baseline information during a run-in period. The run-in period will not exceed 40 days.¹⁹ Before the run-in period, the participants will be offered a diary and educated on how to record pain intensity using the visual analogue scale (VAS) from one day before menstruation starts until menstruation ends. The participants will be forbidden to

PHASE	INTERVENTION PHASE				FOLLOW-UP PHASE	
	V1	V2 ⁴⁾	V3 ⁴⁾	V4 ⁴⁾	V5 ⁴⁾	V6 ⁴⁾
	Screening	Baseline	1 st cycle	2 nd cycle	4 th cycle	8 th cycle
TIMEPOINT	-40 days	Day 0	Day 21-40	Day 42-80	Day 84-160	Day 168-320
Informed consent	X					
Participation of other studies or not	X	X	X	X	X	X
Demographics collection	X					
Physical examination	X					
Gynecological history taking	X					
Dysmenorrhea check	X					
Past history taking	X					
Drug or treatment history	X	X	X	X	X	X
Ultrasound ¹⁾	X					
Pregnancy or lactation check / Pregnancy test	X					
Eligibility screen	X					
Allocation		X				
EFFICACY ASSESSMENT						
VAS ²⁾	X	X	X	X	X	X
SF-36 v2		X		X		
VMSS		X	X	X	X	X
RSS		X	X	X	X	X
SF-MPQ		X	X	X	X	X
Dosage of analgesics ³⁾		X	X	X	X	X
Pattern diagnosis		X		X		
SAFETY ASSESSMENT						
Vital signs	X	X	X	X	X	X
Laboratory tests	X	X		X		
Adverse events			X	X	X	X
Diary distribution	X	X	X	X	X	
Diary withdrawal		X	X	X	X	X
Intervention supply		X	X			
Compliance test			X	X		

VAS: visual analogue scale; SF-36 v2: short form 36 health survey version 2; VMSS: verbal multidimensional scoring system; RSS: retrospective symptom scale; SF-MPQ: short form McGill pain questionnaire.

Fig. 1. Study schedule.

1) Sonography test will be conducted if necessary.

2) At the screening visit, the diary will be offered, and the participants will enter their VAS pain intensity in the diary during the run-in period. We will calculate the average VAS using the VAS measurement of the consecutive two days from the first day of menstruation, and round to the nearest hundredth. Final enrollment will be decided using the VAS calculated from the run-in period. The VAS in the run-in period will be used as the baseline value.

3) The dosage of analgesics will be reported in the diary.

4) Within three days from the last day of previous menstruation.

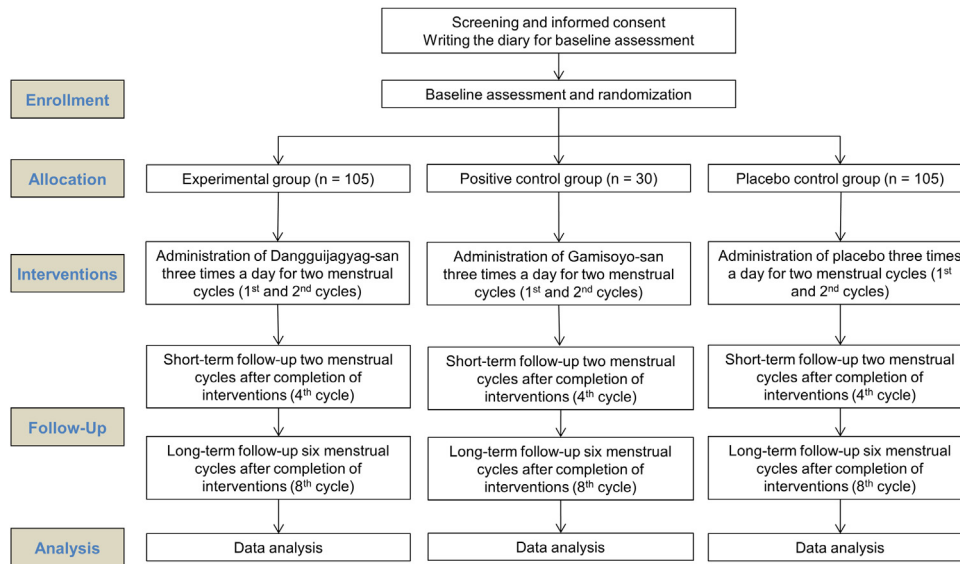


Fig. 2. Study flow.

self-administer the medications presented in the exclusion or drop-out criteria. Participants with average VAS pain scores greater than 50 mm on the first and second days of menstruation will be selected for enrollment in this trial, and the selected participants will receive randomly-generated enrollment numbers. Within three days from the end of the previous menstruation cycle, the participants will visit the clinic, return their diary, answer questionnaires regarding outcome measurements, and undergo laboratory tests. The intervention will be done during two menstrual cycles, and follow-up will be carried out during the next six menstrual cycles. One menstrual cycle may range from 21 to 40 days. The schedule of the trial is outlined in Fig. 1, and the study flow is shown in Fig. 2. We plan to conduct this trial for three years after institutional review board (IRB) approval.

Participants

Five university hospitals in the Republic of Korea will perform this trial; Kyung Hee University Hospital at Gangdong and Kyung Hee Medical Center in Seoul, Dongguk University Ilsan Korean Medicine Hospital in Gyeonggi-do, Semyung University Jecheon Korean Medicine Hospital in Chungchongbuk-do, and Daejeon University Dunsan Korean Medicine Hospital in Daejeon. Participants will be recruited through advertising posters in each hospital, and online advertisement will be used.

Inclusion criteria

The inclusion criteria are: (1) reproductive-age female aged ≥ 18 and ≤ 40 years; (2) suffering from primary dysmenorrhea; (3) suffering from menstrual pain within the recent three consecutive months with an maximum VAS ≥ 50 mm during the run-in period; and (4) being provided with the details of this trial, understanding the details completely, willingness to voluntarily participate, and willingness to provide informed written consent upon detailed description of the study.

Exclusion criteria

The exclusion criteria are: (1) diagnosis of secondary dysmenorrhea due to pelvic pathology, such as uterine fibroids, adenomyosis, endometriosis, or pelvic inflammatory diseases; (2) lactating, currently pregnant, intention to become pregnant, or the possibility of pregnancy (human chorionic gonadotropin test positive); (3) cur-

rent intrauterine device; (4) metrorrhagia with menstrual cycles less than 21 days or oligomenorrhea with cycles over 40 days; (5) oral contraceptives or other hormonal treatment use within the past three months; (6) elevated liver enzymes (alanine transaminase or aspartate transaminase) twice the study reference values; (7) elevated blood urea nitrogen or creatinine 1.5 times higher than the study reference values; (8) depressive or anxiety disorder, or use of psychiatric medications such as antidepressants; (9) participation in other clinical trials within the past month; (10) use of Chinese herbal medicines or other alternative therapies for primary dysmenorrhea within the past three months; and (11) judged inadequate by investigators according to rejection and withdrawal criteria.

Drop-out criteria

Participants may request to cease participation in the study at any point in time, or the investigators may withdraw participants if they meet the discontinuation criteria. Participants will be discontinued from the trial if: (1) inclusion or exclusion criteria are violated; (2) a patient requests to be removed from the trial; (3) adverse events which make participation difficult; (4) noncompliance with the interventions (compliance under 70%); (5) protocol violation which significantly affects the trial; (6) self-administration of medications which affect the trial; (7) efficacy test becomes impossible; and (8) other decisions made by the investigators.

Compliance (%)

$$= \frac{\text{Dosage administered} (= \text{dosage prescribed} - \text{dosage returned})}{\text{Dosage planned}} \times 100$$

Randomization and concealment

Participants will be randomly assigned to the experimental group (EG), the active control group (ACG), or the placebo control group (PCG) at a ratio of 7:2:7 stratified by recruitment site. Stratified block randomization will be used according to probability theory. An independent statistician will generate random sequences using R software version 3.4.2 (R Project for Statistical Computing, Vienna, Austria), and the computer-generated random

sequences will be transferred directly to the pharmaceutical company in order to avoid exposure to investigators. An independent statistician or a third party will manage the random sequences and allocate participants into each group according to the pre-generated random sequences.

Blinding

Trial participants, investigators, and outcome assessors will be blinded until the end of this study. Unblinding before completion of this trial will occur if serious adverse events transpire during the study period. After the investigators review and approve the reasons for unblinding, participants will be connected with a principal investigator and go through an unblinding procedure.

Intervention

Participants will receive oral DJS, GSS, or placebo three times per day for two menstrual cycles according to group allocation. The intervention period will be unique for each individual, ranging from 42 days to 80 days. Therefore, the participants will be provided with enough medication for 43 days of administration, considering a maximum of 40 days and window visit (three days), for each menstrual cycle. To improve participant adherence to the intervention protocols, the remainder of unused medicine will be returned. Alternative treatments that affect dysmenorrhea, such as acupuncture, moxibustion, infrared radiation, and low frequency therapy, will not be permitted. Drugs that participants self-administer and are not specified in the inclusion or exclusion criteria will be permitted, but oral contraceptives, psychotropic drugs, and any herbal medicines will be prohibited. The descriptions of interventions will follow the interventions item of the Consolidated Standards of Reporting Trials (CONSORT) Extension for Chinese Herbal Medicine Formulas.²⁰

Experimental group

Participants in the EG group will be provided light brown-colored DJS granules 3.0 g (Hanpoong Pharm & Foods Co., Ltd., Jeonju, Korea). DJS consists of DJS soft extracts (1.70 g), lactose hydrate (0.56 g), and cornstarch (1.32 g). DJS soft extracts will be prepared by extracting, filtering, decompressing, and concentrating the DJS herbs shown in Table 1. Each ingredient satisfies Korean Pharmacopoeia (KP) standards, and authentication and quality control methods are presented in the KP. In this trial, DJS will be orally administered three times per day, before or between meals, for two menstrual cycles.

Table 1
Composition of Dangguijagyag-san and Gamisoyo-san.

Prescription	Chinese name	Latin name	Dose (g)
Dangguijagyag-san	Danggui	<i>Angelicae Gigantis Radix</i>	1.00
	Chuanxiong	<i>Cnidii Rhizoma</i>	1.00
	Shaoyao	<i>Paeoniae Radix</i>	2.00
	Fuling	<i>Poria Sclerotium</i>	1.33
	Baizhu	<i>Atractylodis Rhizoma Alba</i>	1.33
	Zexie	<i>Alismatis Rhizoma</i>	1.67
	Total		8.33
	Danggui	<i>Angelicae Gigantis Radix</i>	0.46
	Shaoyao	<i>Paeoniae Radix</i>	0.34
	Fuling	<i>Poria Sclerotium</i>	0.03
Baizhu	<i>Atractylodis Rhizoma Alba</i>	0.46	
Gamisoyo-san	Chaihu	<i>Bupleuri Radix</i>	0.21
	Zhizi	<i>Gardeniae Fructus</i>	0.44
	Mudanpi	<i>Moutan Radicis Cortex</i>	0.45
	Gancao	<i>Glycyrrhizae Radix et Rhizoma</i>	0.34
	Bohe	<i>Menthae Herba</i>	0.13
	Total		2.86

Active control group

Participants in the ACG will be provided with 2.86 g of a brown-colored GSS powder (Hankook Shinyak Co., Nonsan, Korea). The composition of GSS is shown in Table 1. Each ingredient satisfies KP standards, and authentication and quality control methods are presented in the KP. In this study, GSS will be administered orally three times per day, before or between meals, for two menstrual cycles.

Placebo control group

Participants in the PCG will be provided light brown-colored granules (3.0 g) (Hanpoong Pharm & Foods Co., Ltd., Jeonju, Korea). Placebo granules consist of lactose hydrate (1.476 g) and cornstarch (1.500 g) (excipients), and caramel pigment 0.014 g and ginseng-scent powders 0.010 g (coloring agents). The placebo and DJS granules will be produced by the same company so they are identical in appearance, taste, smell, color, and packaging. Each excipient satisfies KP standards, and quality control methods are presented in the KP. The placebo will be orally administered three times a day, before or between meals, for two menstrual cycles.

Rescue medication

If participants do not tolerate pain and want to take analgesics, NSAIDs will be permitted. Participants will indicate the frequency, dosage, components, and brand names of the self-administered NSAIDs in their diaries.

Primary outcomes

The primary outcomes of this trial are as follows: (1) response rates of EG and ACG at the end of the interventions (V4) for non-inferiority comparison; and (2) changes in the VAS average at the end of the interventions (V4) from baseline of EG and PCG for superiority comparison.

The intervention will be considered effective if the change in the average VAS measured at the end of the interventions (V4) compared to that at baseline (V2) is more than 15 mm. The minimal clinically important difference (MCID) of endometriosis, a representative disease causing secondary dysmenorrhea, is 10 mm using VAS,²¹ and the degree of improvement in primary dysmenorrhea is somewhat higher than that in secondary dysmenorrhea.²² Using previous studies and opinions of clinical specialists in the gynecological fields, we chose a change in VAS of 15 mm as the MCID. We will calculate the average of the VAS measurements from the first and second days, using the records on the given diary, and we will round to the nearest hundredth. The diary form is attached in appendix 1.

Secondary outcomes

The secondary outcomes of this trial are as follows: (1) differences in scores on the verbal multidimensional scoring system (VMSS), short form McGill pain questionnaire (SF-MPQ), and retrospective symptom scale (RSS) after the second menstrual cycle (V4) between EG and ACG for non-inferiority comparison; and (2) differences in VMSS, RSS, and SF-MPQ at every visit (V2-6), SF-36v2 and pattern diagnosis at baseline (V2) and after the second menstrual cycle (V4), and dosage of NSAIDs administered at every visit (V2-6) between EG and PCG for superiority comparison.

Pain will be assessed using ancillary pain assessment tools, such as VMSS, SF-MPQ, and RSS, and measurements will be obtained at baseline (V2), during every visit, after two menstrual cycles of interventions (V3, V4), and after the second and sixth menstrual cycles following the end of administration of study interventions (V5, V6). Quality of life will be measured using SF-36v2. Pattern diagnosis of qi stagnation pattern and blood stasis pattern will be assessed at

baseline (V2) and after the second menstrual cycle (V4). The differences over time of VMSS, RSS, SF-MPQ, and NSAID dosage will be compared between EG and PCG. The detailed outcome measurement schedule is shown in Fig. 1.

Visual analogue scale (VAS)

Menstrual pain intensity will be assessed using VAS (0–100 mm). A diary for recording VAS will be given to the participants at every visit (V1–5), and the participants will be taught to check their pain intensity every day during each menstrual cycle. The participants will be instructed to return the diary at the next visit (V2–6).

Verbal multidimensional scoring system (VMSS)

VMSS is a scale that assesses impaired working ability, systemic symptom appearance, and requirement of analgesics due to dysmenorrhea with grades 0–3.²³ We will use the Korean version of VMSS.²⁴ VMSS for each participant's previous menstrual cycle will be assessed by a clinical research coordinator at V2–6.

Retrospective symptom scale (RSS)

RSS measures physical or psychological symptoms, restricted hours due to dysmenorrhea, and dosage of analgesics.²⁵ The total scores of 18 physical or mental symptoms, time, and the number of analgesics administered will be used. The participants will self-complete the RSS for the preceding menstrual cycle at V2–6.

Short form McGill pain questionnaire (SF-MPQ)

SF-MPQ is a shortened version of the long-form MPQ, and includes multidimensional scales, VAS, and descriptive scales. We will use the Korean version of SF-MPQ.²⁶ SF-MPQ includes 15 items of multidimensional scales (sensory and affective categories), VAS, and present pain intensity (PPI). We excluded the VAS portion of this questionnaire because we will assess the average VAS separately. The total score of the sensory categories, the total score of the affective categories, the total score of both, and PPI will be calculated. The participants will self-complete the SF-MPQ for the immediately preceding menstrual cycle at V2–6.

Short form 36 health survey (SF-36) v2.0

SF-36 is a tool for measurement of health-related quality of life, and consists of eight categories and 36 items. The participants will self-complete the SF-36 at V2 and V4.

Qi stagnation pattern diagnosis questionnaire

We will use the Korean version of this questionnaire, developed by Okitsu, to diagnose qi stagnation pattern.²⁷ We will use the total score of the degree of symptoms related to qi stagnation, on a scale of 0–2. The participants will self-complete the questionnaire at V2 and V4.

Blood stasis pattern diagnosis questionnaire

We will use this questionnaire, developed by Park et al., to diagnose blood stasis pattern.²⁴ The total score will be determined for symptoms related to blood stasis using Likert scoring 1–7. The participants will self-complete the questionnaire at V2 and V4.

Safety and adverse event outcomes

Blood pressure, pulse, and body temperature will be measured at every visit, and laboratory tests will be conducted at the screening visit (V1), baseline visit (V2), and after the second menstrual cycle of interventions (V4). Laboratory tests will include blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) in order to assess drug-induced injury to the kidney and liver. We will assess adverse

events at every visit from the start of administration of interventions to the final follow-up, based on the Common Terminology Criteria for Adverse Effect (CTCAE).²⁸ We will evaluate a causal relationship between the adverse events and the interventions with the following standards: certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable. Clinical research coordinators (CRCs) will record the symptoms, duration, degree, relationships, results, treatments, and severity of any adverse events.

Follow-up

Short-term and long-term follow-up will be conducted. Short-term follow-up will be for two menstrual cycles, and long-term follow-up will be for six menstrual cycles. The CRCs will regularly contact the participants by phone, and they will encourage the participants to fill out the given diaries and visit at the arranged dates. At the end of the last follow-up visit, participant involvement will be completed.

Sample size

A total of 240 women will be recruited for this trial; 105 participants will be allocated to the EG, 30 participants to the ACG, and 105 participants to the PCG. The total number of participants was calculated by applying an assumed drop-out rate of 15%.

Non-inferiority comparison

One of the primary outcomes of our study is to evaluate whether the response rate of EG is not inferior to that of ACG. To determine thresholds for response rate and limit of non-inferiority of GSS, we referred to the results of Deng (2010),²⁹ Qu (2015),³⁰ and Xie (2013).³¹ The response rates observed in those studies were 0.87, 0.96, and 0.90, respectively. Therefore, we assumed a GSS response rate of 0.91, the average of the three results. No studies have compared GSS with placebo medications, and we referred to the results of Qu (2015),³⁰ which implemented western medications if pain occurred in the control group. The response rates in the treatment group (n = 50) and control group (n = 50) were 0.96 and 0.54, respectively, in Qu's study. We established 0.27, calculated from the lowest limit of the 95% confidence interval of differences between the two groups, as the limit of non-inferiority. In addition, we assumed the response rate of DJS would be the same as that of GSS. Using PASS Software (version 14.0; NCSS Statistical Software, Kaysville, UT, USA), the sample size necessary to achieve a significance level of $\alpha = 0.025$ with 80% power is 25. Ultimately, we selected a sample size of 30 in each group to account for an assumed 15% drop-out rate.

Superiority comparison

The other primary outcome is to evaluate whether change in VAS resulting from EG is superior to that of PCG. No advanced studies of DJS have been performed, so we referred to the result of Park (2013),³² who evaluated the efficacy of an herbal medicine formula (Gyejibongnyeong-hwan) for primary dysmenorrhea. The change in average VAS in the treatment group was 1.75 ± 2.06 , and the change in PCG was 0.88 ± 1.64 . Using PASS ver 14.0, we calculated a sample size of 89 in each group to achieve a power of 80% with a significance level of $\alpha = 0.025$ using a two-tailed test. We revised the sample size to 105 in each group to account for an assumed 15% drop-out rate.

Overall, the valid sample size for the non-inferiority test and the superiority test were 89 in EG, 25 in ACG, and 89 in placebo PCG. The final sample sizes, considering a 15% drop-out rate, were 105 in EG, 30 in ACG, 105 in PCG, and 240 in total.

Data collection, management, and monitoring

Data from the participants and measurement instruments will be collected at every visit. A description of the study instruments is provided above. The paper-based case report form (CRF) will be used for data collection, and each participant and the investigators will sign and write the date. The CRFs will be kept in a secure location, and the investigators, agent of monitoring, and members who audit data from the IRB will access the data. Upon completion of the trial, the data will be stored for three years.

An agent of the Korean Medicine Clinical Trial Center (KCTC) of Kyung Hee University, independent from competing interests, will regularly monitor the original participant information documents, pharmacy log, storage of data, blinding maintenance, and process of the trial. Interim analysis will not be performed.

Statistical analysis

We will conduct intention-to-treat (ITT) analysis and per-protocol (PP) analysis. For ITT analysis, we will include the outcomes of all participants who receive at least one intervention, write in the diary for at least one day, and return the diary. If there are any missing data or any participant drops out of the study before completion of this trial, we will analyze the last data collected for each subsequent time point (last observation carried forward analysis). In PP analysis, we will include data from participants who completed the trial as planned. The response rates will be analyzed in both ITT and PP analysis groups. We will compare the analyzed results if the results of ITT and PP analysis are different. For the non-inferiority test, we will compare the results of PP analysis with those of ITT analysis, using PP analysis as the main analytical method and ITT analysis as an ancillary method. For the superiority test, we will compare the results of ITT analysis with those of PP analysis, considering ITT analysis as the main analytical method and PP analysis as an ancillary method. The safety test will be conducted for all participants who receive at least one intervention and results will be analyzed using raw data without any adjustment. We will perform a two-tailed test with α -level of 0.05 for all outcomes except for primary outcomes.

The two primary outcomes will be analyzed separately. For the non-inferiority comparison between EG and PCG, we will calculate the response rates of each group, measured at the end of the second menstrual cycles (V4), and 97.5% confidence intervals of the differences between the two groups. We will conclude non-inferiority if the lower confidence limit of the group difference is higher than -0.27, the margin of non-inferiority. For the superiority comparison between EG and PCG, we will present change in VAS as mean with SD, median, minimum, and maximum values at the end of the second menstrual cycle compared to baseline. We will implement analysis of covariance (ANCOVA) in which each group and trial sites (stratified variables) are factors with VAS at baseline considered as a covariate. The significance level is 0.025, and two-tailed tests will be conducted.

For continuous variables of secondary outcomes, we will also present change in VAS using mean with SD, median, minimum, and maximum values at the end of the second menstrual cycle compared to baseline. We will conduct ANCOVA in which each group and trial sites (stratified variables) are factors, with VAS at baseline considered as a covariate. For categorical variables, we will present frequencies and percentages, and we will implement the Cochran-Mantel-Haenszel test with trial site as a stratified variable. To analyze group effect, time effect, and group \times time interaction of the repeated measured data, repeated-measures analysis of variance (or repeated-measures ANCOVA) will be performed, and the generalized estimating equation (GEE) model test will be chosen depending on the characteristics of the data.

To assess safety, we will present frequency and proportions of adverse events by CTAEC, and we will use a Chi-squared test (or Fisher's exact test) to analyze differences among the groups. We will implement paired t-tests using the results of the laboratory portions of the screening tests and end of intervention tests, and we will analyze differences among the groups.

Ethical consideration and dissemination

The study has undergone external peer review during the funding process and has been approved by the IRB of Kyung Hee University Hospital at Gangdong (approval number: KHNMCOH 2017-09-005-001). Significant protocol modifications are not expected, but the principal investigators at each site will discuss and amend the protocol, and we will obtain approval from the IRB, if protocol amendments are deemed necessary. Investigators with a doctorate in Korean Medicine will obtain informed consent and will provide each participant with a copy of the consent forms. If the participant is a minor, both the participant and the legal representative should write informed consents. The privacy of the participants will be respected, and documents from the participants will be managed with enrollment numbers and initials. Participant personal information will be kept confidential (only accessible to the investigators or related monitoring agents), and all documents will be shredded after three years of storage.

If necessary, we will take adequate action for participants who complete or cease the trial. We acquired compensation insurance and will follow the agreement for compensation to victims if any participant experiences adverse events requiring treatment. The results of this trial will be published in a peer-reviewed journal, and any data revealing participant identification will be removed. Authorship will be assigned according to the criteria set forth by the International Committee of Medical Journal Editors (ICMJE) recommendations.

Discussion

The aim of our trial is to assess the efficacy and safety of DJS compared with GSS, positive control, and placebo control for primary dysmenorrhea. We will assess the superiority of DJS to placebo, and the non-inferiority of DJS to GSS to evaluate its efficacy.

GSS, which was chosen as a positive control in our study, is a description of an herbal combination in which Moutan Radicis Cortex and Gardeniae Fructus are added with *Shaoyao-san*, originating from «*Tai Ping Hui Min He Ji Ju Fang*». GSS is generally used for physical or psychological symptoms associated with menstruation or menopause, engendering blood, purging fire, and releasing stagnation. A recent pharmacologic study showed that GSS exerts anti-oxidant and anti-inflammatory effects.³³ The efficacy of GSS for dysmenorrhea has been acknowledged, and GSS is classified as "medicine for dysmenorrhea" by the Ministry of Food and Drug Safety (MFDS). GSS has been approved for coverage by the national health insurance in Korea, and is frequently used in Korean practical fields. As such, we adopted GSS as a positive control to strengthen the basis for DJS coverage.

The primary outcomes are response rates (determined by VAS) and pain intensity (VAS). We developed a diary for checking VAS and recording analgesic administration to allow for accurate pain intensity measurement. We will use the average VAS from the first and second days to determine menstrual pain intensity. The secondary outcomes of our trial include VMSS and RSS (scales for dysmenorrhea), SF-MPQ (multidimensional pain questionnaire), and SF-36v2 (health-related quality of life questionnaire). Additionally, we will identify the Korean Medicine patterns of the participants using *qi* stagnation pattern and blood stasis pattern

diagnosis questionnaires. DJS is effective for alleviating *qi* stagnation and blood stasis, so the total score of questionnaires will be used to evaluate these factors. Liver and kidney function tests will be performed to assess drug-induced injury, and any adverse event will be evaluated and treated as appropriate.

Primary dysmenorrhea is caused by an increase in menstrual fluid prostaglandin levels, and NSAIDs, the first-line treatment for primary dysmenorrhea, inhibit endometrial prostaglandin production and normalize uterine activity pattern.¹ Patients with primary dysmenorrhea typically require NSAIDs during every menstrual cycle to reduce pain because primary dysmenorrhea is a chronic and recurring condition resulting from increased prostaglandin levels.³⁴ According to Korean Medicine theory, therapeutic mechanisms improve symptoms by enhancing personal resistance to disease and prevent symptoms by improving the inner environment.³⁵ We hypothesize that DJS not only reduces menstrual pain and associated symptoms, but also maintains its efficacy during the next several months after administration. Therefore, we plan short- (two cycles) and long-term (six cycles) follow-up.

The limitation of our trial is that the interventions did not have the exact same appearance. DJS and GSS have to be produced according to the KP, so it was difficult to produce GSS accurately in the same dose and form as DJS and placebo. Despite this limitation, our clinical trial protocol adopted rigorous methods to minimize bias and was designed to provide information about the efficacy and safety of DJS. In contrast with previous studies that used modified DJS, We adopted original DJS for a large-scaled RCT. The 3-arm design that include both of superiority and non-inferiority test is also the strengths of our study.

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Supplementary material

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.imr.2020.02.002>.

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