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Original Article

Effects of herbal medicine (*Danggwijagyaksan)* for treating climacteric syndrome with a blood-deficiency-dominant pattern: A randomized, double-blind, placebo-controlled pilot trial ☆

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ABSTRACT

Background: *Danggwijagyaksan (DJS)* has been one of the most widely used herbal medicines for gynecological disorders in traditional East Asian medicine. Several clinical studies about *DJS* have shown improvement in menopausal symptoms. This pilot study aimed to evaluate the efficacy, safety and feasibility of *DJS* for treating climacteric syndrome with a blood-deficiency-dominant pattern.

Methods: This was a randomized, double-blind, placebo-controlled pilot trial. A group of 45-to 60-year-old women with climacteric syndrome were registered for the trial. The participants received treatment over a 4-week period and were then followed for 4 weeks. The primary outcome measure was the mean change in the Menopause Rating Scale (MRS). Secondary outcome measures included the World Health Organization Quality of Life-BREF (WHOQOL-BREF), the Blood-Deficiency Scoring System (BDSS), lean body mass, and serum hormone levels, including follicle-stimulating hormone (FSH) and estradiol (E_2) levels.

Results: The MRS and BDSS scores decreased significantly in both groups, but the differences between two groups were not significant. The WHOQOL-BREF scores increased in the control group. No statistically meaningful differences in serum hormone levels or lean body mass were observed in both groups. There were no serious adverse events, and the laboratory tests were within the normal range. The recruitment rate, completion rate and medication adherence rate were over 90% in both groups, indicating high feasibility.

Conclusions: *DJS* showed clinical effectiveness in the treatment of climacteric syndrome with a blood-deficiency-dominant pattern. Additionally, *DJS* was shown to be safe and feasible for a large-scale study to confirm the efficacy of the treatment.
Trial registration: Clinical Research Information Service (CRIS, https://cris.nih.go.kr): KCT0002387.

1. Introduction

Climacteric syndrome is a group of many symptoms that are caused by ovarian aging and hormone changes during the menopausal period. Women who experience climacteric syndrome may experience vasomotor symptoms such as hot flashes, sweating, and palpitation and physical symptoms such as sleep disturbances, mood changes, depression, memory loss, sleeping dis-

☆ Trial registration: Clinical Research Information Service (CRIS) of Korea (https://cris.nih.go.kr): KCT0002387.

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orders, and urinary symptoms.[1,2] Hormone replacement therapy (HRT) has been used as a conventional therapy for climacteric syndrome. But because of its side effects,[3,4] alternative therapies has been frequently considered to managing menopause-related problems.[5] In East Asian countries, traditional herbal medicines have been widely used, and reported to be effective in relieving menopausal symptoms.[6-8]

Pattern identification is a diagnostic system in East Asian traditional medicine that is used to identify types of pathologic conditions. Climacteric syndrome can be divided into various pattern types such as liver-qi stagnation, kidney-yin deficiency, kidney-yang deficiency, non-interaction between the heart and kidney, and dual deficiency of the heart-spleen in Korean medicine, and blood-deficiency pattern is one of the common types of menopausal disorders.[6,9] Blood-deficiency refers to a pathologic condition by insufficient blood production and inability to nourish organs, resulting in general weakness, headache, dizziness, fatigue and coldness of lower limbs, etc.[8]

Danggwijagyaksan (*DJS, Dang-Gui-Shao-Yao-San* in Chinese; *Toki-Shakuyaku-San* in Japanese), a prescription in the *Jin gui yao lue* (the *Jingui Collection of Prescriptions,* written in Chinese *Han Dynasty*), was reported to be effective for abdominal pain during pregnancy.[10] *DJS* has been one of the most widely used medicines for gynecological disorders in traditional East Asian medicine, and it has been especially effective for disorders such as dysmenorrhea and menstrual irregularities induced by blood deficiency.[11,12] Several experimental studies have suggested the possibility of using *DJS* for the treatment of postmenopausal cardiovascular disease[13] and osteoporosis.[14] Clinical studies have shown an improvement in hot flashes and the general quality of life of menopausal women,[15] as well as improvement in menopausal symptoms including decreased blood pressure and increased lean body mass.[16] However, large-scale studies have not been conducted on the effects of *DJS* on menopausal disorders. Furthermore, no study has been conducted on the pattern of blood-deficiency in women with menopausal disorders.

Therefore, a preliminary clinical trial was conducted to evaluate the efficacy, safety and feasibility of *DJS* for the treatment of peri- and postmenopausal women with a blood-deficiency-dominant pattern.

2. Methods

2.1. Study registration

The research information was registered with the Clinical Research Information Service (CRIS) (Registration number: KCT0002387). The research protocol was published in advance.[17]

2.2. Study design

This study was a randomized, double-blind, placebo-controlled, parallel-group pilot clinical trial. The subjects who voluntarily signed the consent forms were evaluated according to the inclusion/exclusion criteria. The selected subjects were randomly assigned to the *DJS* group or the placebo group and received treatment and evaluation in each group. Both groups took the drug (or placebo) for 4 weeks, and the study had a follow-up period of 4 weeks.

2.3. Participants

2.3.1. Inclusion criteria

(1) 45–60 years old
(2) Presence of peri- or postmenopausal climacteric syndrome (including natural or induced menopause)
(3) MRS score of 9 or higher
(4) Blood-Deficiency Scoring System (BDSS) score of 30 or higher
(5) Willingness to participate in the clinical trial and provide written consent

2.3.2. Exclusion criteria

(1) Having undergone postmenopausal hormonal therapy within 3 months of the screening visit
(2) Having received traditional Korean medicine to improve symptoms of climacteric syndrome within 4 weeks of the screening visit
(3) Having taken any medication or functional food to mitigate symptoms of climacteric syndrome within 4 weeks of the screening visit
(4) Having received a diagnosis of serious mental diseases such as depression or anxiety disorders and/or currently taking psychotropic drugs
(5) Having uncontrolled thyroid diseases
(6) Having aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or gamma-glutamyl transpeptidase (γ-GTP) values $>$ 1.5-times the upper normal level
(7) Having blood urea nitrogen (BUN) or creatinine value $>$ 1.5-times the upper normal level
(8) Currently undergoing transfusion or erythropoietin therapy for severe anemia
(9) Experiencing vaginal bleeding of an unknown cause after menopause
(10) Having lactose intolerance
(11) Currently participating in other clinical trials
(12) Meeting other criteria considered inappropriate for this trial by the investigator

2.4. Randomization and blinding

Randomization was performed using block randomization, and each group was represented by a code (A or B). The subjects, research doctor, coordinator, management pharmacist, monitoring staff, and statisticians were provided with only the group code (A or B) and did not know which group was the *DJS* group and which group was the placebo group. The person responsible for blinding gave the random assignment and group information to the pharmaceutical company.

A blinding test was performed at the 3rd visit to verify whether participant blinding had been successfully achieved. Bang's blinding index was calculated by asking the subjects to choose which group (*DJS* group, placebo group, or do not know) they thought they were assigned to. This blinding index has a value from -1 to 1. A score of 1 point indicates the correct alignment of the subject's guess and group assignment, and a score of -1 point indicates a completely opposite prediction, both of which indicate unsuccessful blinding. A score of 0 indicates the most successful blinding.[18]

2.5. Intervention

The treatment drug, *Danggwijagyaksan* (Hanpung Pharmaceutical, Wanju, Republic of Korea), was given in the form of a light brown granule. The 3 g dose included the main ingredient, *DJS* soft extract (1.70 g), together with lactose hydrate (0.56 g) and corn starch (1.32 g). *DJS* soft extract is composed of six herbs: *Angelica gigas Nakai, Cnidium officinalen Makino, Paeonia lactiflora Pallas, Poria cocos Wolf, Atractylodes japonica Koidzumi*, and *Alisma orientale Juzepzuk*. The placebo was a light brown granule with the same properties as the test drug. The placebo included corn starch (1.887 g), lactose hydrate (1.00 g), citric acid hydrate (0.09 g), caramel color (0.02 g), and ginseng incense powder (0.003 g). Both

were light brown granules packaged in silver, opaque wrappers. All participants in both groups took 3 g of medication in granular form, three times a day before or between meals during the 4-week treatment period.

2.6. Outcome measures

2.6.1. Primary outcome

(1) MRS

The MRS is a standard measure developed to assess various menopausal symptoms and health-related quality of life.[19] The MRS was assessed at baseline, week 5, and week 9.

2.6.2. Secondary outcomes

(1) World Health Organization QOL-BREF (WHOQOL-BREF)

The WHOQOL-BREF is a questionnaire developed to evaluate quality of life. The WHOQOL-BREF is an abbreviated version of the WHOQOL, and it has been reorganized in accordance with the culture and situation of Korea.[20] A higher score on WHOQOL-BREF indicates a better quality of life. The WHOQOL-BREF was assessed at baseline, week 5, and week 9.

(2) Blood deficiency pattern scoring system (BDSS)

The *Blood deficiency scoring system* (BDSS) is a questionnaire to diagnose and evaluate the blood-deficiency pattern of Korean traditional medicine.[21] The BDSS was assessed at baseline, week 5, and week 9.

(3) Lean body mass

Lean body mass is calculated by subtracting the body fat mass (kg) from the body weight (kg) and was measured by a body composition analyzer (InBody 770, InBody CO., LTD., Seoul, Korea).

(4) Serum hormone levels

The serum female hormones assessed included follicle-stimulating hormone (FSH) and estradiol (E_2). The hormone test was performed at baseline, week 5, and week 9. The blood specimens were analyzed using the electrochemiluminescence immunoassay (ECLIA) method.

(5) Safety and feasibility assessment

To assess the safety of *DJS*, the adverse events and vital signs of the patients were examined, and laboratory tests were performed. In addition, to evaluate the feasibility of this trial, the recruitment rate, completion rate, and medication adherence were calculated.

2.7. Statistical analysis

Statistical analysis was performed using Strategic Applications Software (SAS®) version 9.4 (SAS Institute Inc., Cary, NC, USA). For the baseline characteristics, continuous data are presented as the mean and confidence interval and were analyzed using Student's *t*-test (or Wilcoxon rank sum test). Categorical data were analyzed using the chi-square test after the frequency and percentage were presented. Analysis of covariance (ANCOVA) was conducted to analyze the between-group differences in the primary and second outcome measures. A paired *t*-test was also followed to evaluate the significance of pre- and post-treatment differences within each group.

The full analysis set (FAS) was used for the main analysis to achieve the ideal intention-to-treat (ITT) principles. The subjects who did not meet the eligibility criteria, who did not take the test drug or who were not evaluated after randomization were excluded from the analysis.

2.8. Sample size calculation

In order to calculate sample size, this study followed the previous research that was grounded on the change of the MRS score.[15] After 30 days of *DJS* administration, the change in the MRS score was 10.8 on average. We anticipated approximately 20% changes in the MRS score in the *DJS* group, which generates 2.16 of the MRS score. The standard deviation was 8.012 according to the data acquired from this study. The sample size in each group was determined based on the formula as described in equation. According to the equation, 14 participants were needed in each group. Considering dropout rate of 15%, 17 participants per group were required for this study.

$$n = \frac{2\left(z_{\alpha/2} + z_{\beta}\right)^2 \sigma^2}{\delta^2} = \frac{2(1.96 + 0.84)^2 (8.012)^2}{(-8.64)^2} = 14$$

$$n' = \frac{n}{1 - \omega} = \frac{14}{1 - 0.15} = 17$$

2.9. Ethical approval

This clinical trial was approved by the Institutional Review Board (IRB) of Daejeon University Dunsan Korean Medicine Hospital (Approval number: DJDSKH-17-DR-10).

3. Results

3.1. Participant flow

Screening was conducted to determine the suitability of the 37 subjects who agreed to participate in the study. Two participants withdrew consent, and one failed to meet the inclusion criteria. We randomly assigned the 34 remaining subjects. The recruitment rate was 91.8%.

All subjects in the *DJS* group completed the clinical trial without dropping out. One of the subjects in the *DJS* group did not complete the follow-up because she refused the blood test at the last visit. However, because all subjects completed the medication protocol, despite one subject who failed to follow-up, the results of all 17 subjects were analyzed.

One of the subjects in the placebo group was excluded due to a violation of the inclusion/exclusion criteria and an adverse reaction. A total of 16 subjects were analyzed; therefore, the completion rate was 97% (Fig. 1).

3.2. Baseline characteristics

There were no statistically significant differences in the demographic data of the two randomly assigned groups, except for the duration of climacteric syndrome (Table 1).

3.3. Primary outcome

The total MRS scores were decreased in both the *DJS* group and placebo group at weeks 5 and 9, and these decreases were statistically significant. There was no significant difference in the MRS scores between the two groups (Table 2).

3.4. Secondary outcomes

The total WHOQOL-BREF score was increased at week 5 and decreased at week 9 in the treatment group; these changes were not statistically significant. In the control group, the score increased at both week 5 and week 9, and all changes were statistically significant. The WHOQOL-BREF score difference between the *DJS* and placebo groups was statistically significant at week 9; the scores in the control group were higher (Table 2).

The total BDSS scores were significantly decreased at weeks 5 and 9 in both groups. The difference of BDSS between two group was statistically significant at the 5th week of the test; the scores were higher in the *DJS* group (Table 2).

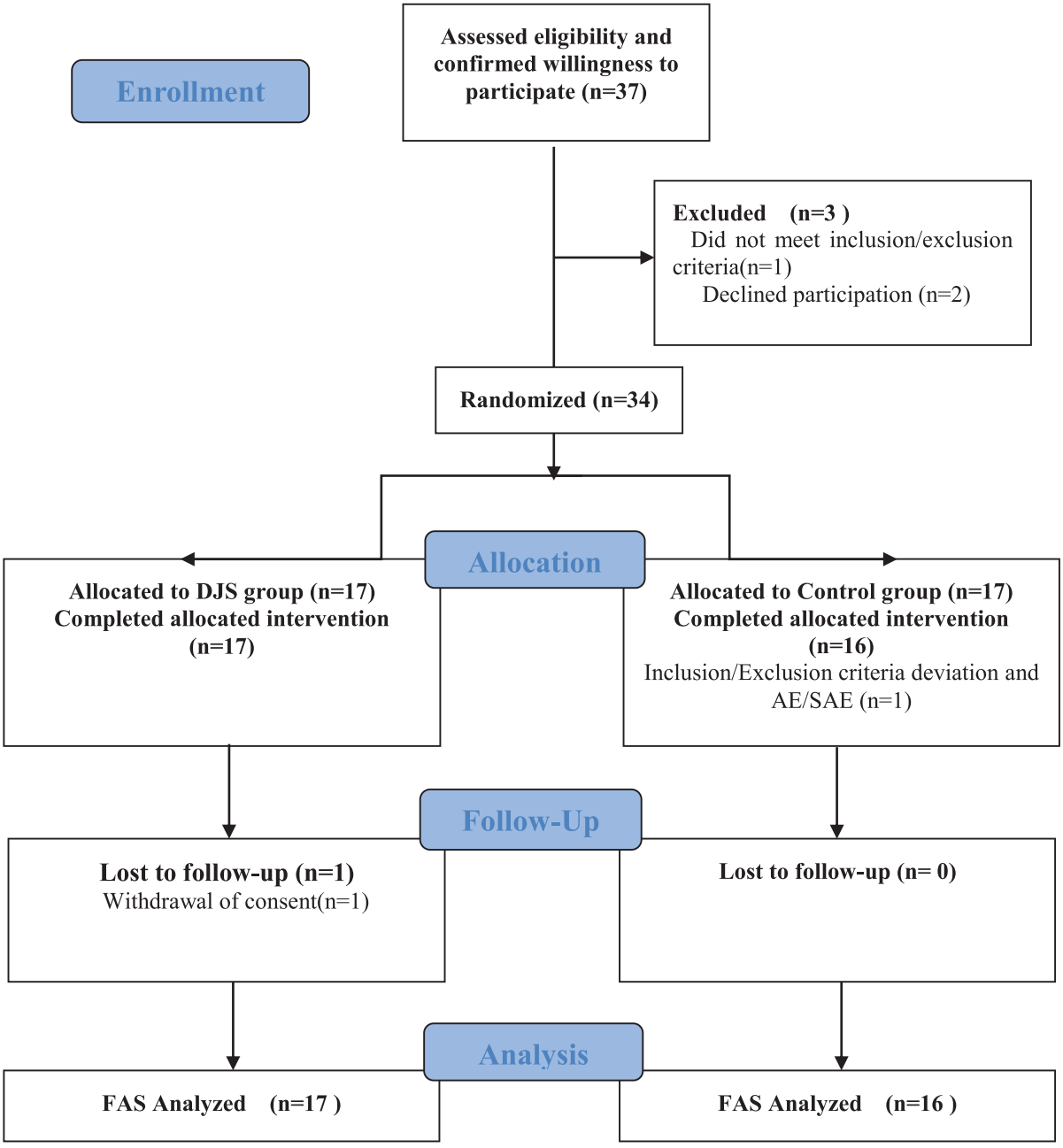

Fig. 1. CONSORT flow diagram.

Table 1
Baseline characteristics of subjects

	Herbal medicine (*DJS*)	**Placebo**	***p-value***
Age (year)	55.1 (53.3, 56.8)	54.6 (53.2, 56.1)	0.69
BMI (kg/m^2)	23.6 (22.0, 25.3)	22.46 (21.0, 23.9)	0.27
Type of menopause			0.63
Natural	14 (82.4%)	12 (70.6%)	
Induced	2 (11.8%)	2 (11.8%)	
None	1 (5.9%)	3 (17.7%)	
Duration of climacteric			
< 1 year	1 (5.9%)	2 (11.8%)	0.02*
1 ~ 5 year	8 (47.1%)	14 (82.4%)	
> 5 year	8 (47.1%)	1 (5.9%)	
Treatment (Yes/No)	7 (41.2%) / 10 (58.8%)	2 (12.5%) / 14 (87.5%)	0.12
Menopause Rating Scale (MRS)	26.9 (22.7, 31.0)	26.2 (22.6, 29.9)	0.81
Blood-deficiency Scoring System (BDSS)	72.8 (66.7, 78.8)	74.4 (70.6, 78.3)	0.63
Lean body mass	63.0 (57.0, 69.0)	63.8 (54.3, 73.2)	0.89
Follicle-stimulating hormone (FSH)	39.2 (36.9, 41.5)	38.4 (36.3, 40.4)	0.58
Estradiol (E_2)	65.6 (49.8, 81.4)	69.6 (52.6, 86.5)	0.72

* $p<0.05$

Table 2
Changes of outcome measures after intervention

	Herbal medicine *(DJS)* (n=17)		Placebo (n=16)		
	Mean (CI)	***P*[b]**	**Mean (CI)**	***P*[b]**	**LSMD [a]**
MRS score					
Baseline	26.8 (22.7, 31.0)		26.2 (22.6, 29.9)		
Week 5 (Endpoint)	14.5 (10.7, 18.5)	< 0.01**	14.5 (10.7, 18.5)	< 0.01**	0.18 (-5.25, 4.88)
Week 9 (Follow-up)	14.3 (10.0, 18.7)	< 0.01**	14.5 (11.0, 18.0)	< 0.01**	-0.39 (-4.73 3.95)
WHOQOL-BREF					
Baseline	72.7 (66.7, 78.8)		74.4 (70.6, 78.3)		
Week 5 (Endpoint)	74.2 (67.0, 81.6)	0.38	78.5 (73.5, 83.6)	< 0.01**	2.46 (-6.84, 1.91)
Week 9 (Follow-up)	71.5 (64.4, 78.7)	0.46	79.3 (74.6, 84.2)	< 0.01**	-6.89 (-11.65, -2.12) †
BDSS Score					
Baseline	63.0 (57.0, 69.0)		63.7 (54.3, 73.2)		
Week 5 (Endpoint)	36.4 (27.8, 45.1)	< 0.01**	50.5 (40.1, 61.0)	< 0.01**	-13.68 (-25.84, -1.51) †
Week 9 (Follow-up)	40.0 (27.5, 52.5)	< 0.01**	48.1 (34.9, 61.4)	< 0.01**	-7.08 (-20.85, 6.69)
Lean Body Mass					
Baseline	39.1 (36.9, 41.5)		38.3 (36.3, 40.4)		
Week 5 (Endpoint)	38.7 (36.6, 40.8)	0.09	38.0 (36.2, 39.8)	0.16	-0.02(-0.67, 0.62)
Week 9 (Follow-up)	39.4 (37.2, 41.6)	0.68	38.0 (36.1, 40.0)	0.32	0.29(-0.64, 1.22)
FSH					
Baseline	65.5 (49.8, 81.4)		69.5 (52.6, 86.5)		
Week 5 (Endpoint)	66.7 (51.0, 82.4)	0.75	68.1 (52.4, 84.0)	0.33	2.10 (-5.43, 9.64)
Week 9 (Follow-up)	68.9 (53.0, 84.9)	0.21	69.6 (53.2, 86.1)	0.79	5.18 (-4.52, 14.88)
Estradiol(E_2)					
Baseline	13.7 (3.2, 24.3)		12.8 (0, 25.7)		
Week 5 (Endpoint)	13.2 (0.8, 25.7)	0.87	8.7 (3.2, 14.4)	0.27	3.88 (-4.25, 12.01)
Week 9 (Follow-up)	30.3 (-13.8, 74.6)	0.34	11.7 (-1.2, 24.8)	0.86	16.48 (-18.73, 51.70)

DJS: Danggwijagyaksan
[a] ANCOVA for comparison of mean difference between groups. Mean difference is the least square means difference (LMSD, 95% CI). The least square means difference were calculated by ANCOVA adjusted for baseline score († $p<0.05$).
[b] Paired *t*-test for comparison of mean change before and after treatment in each group. Difference is the mean change (95% CI) from baseline to week 5 and week 9 (** $p<0.05$).

Table 3
Blinding test index.

	Herbal medicine (*DJS*) (n=17)[b]	Placebo (n=16)[b]
Treatment group[a]	8 (47.1%)	5 (31.3%)
Control group[a]	4(23.5%)	4 (25.0%)
Not sure[a]	5 (29.4%)	7 (43.8%)
New Blind Index	0.24 (-0.14, 0.61)	-0.06 (-0.43, 0.30)

[a] represents the group that subjects think they belong.
[b] represents the actual group they belonged.

The changes of lean body mass, serum FSH level and serum estradiol (E_2) levels were not statistically significant in both groups. The difference between the *DJS* group and the placebo group was not significant at week 5 or 9 for lean body mass, serum FSH and E_2 levels (Table 2).

3.4.1. Assessment of blinding and medical adherence

The blinding index was 0.235 (-0.138, 0.608) in the *DJS* group and -0.063 (-0.429, 0.304) in the control group. There was no statistical difference between both groups (Table 3).

Medical adherence was 94.34% in the *DJS* group and 94.52% in the placebo group, which indicated a high compliance of over 90% in both groups (Supplement 1).

3.4.2. Adverse events

Five adverse events were reported: one in the *DJS* group and four in the placebo group.

The adverse event that occurred in the *DJS* group was abdominal discomfort; the event was thought to be related to the trial but resolved naturally without medication or treatment. In the placebo group, there were hypertension, constipation, cold, and shoulder pain events. The constipation was thought to be related to this trial but was resolved naturally. The hypertension, cold, and shoulder pain events were all considered unrelated adverse events. Although shoulder pain was not related to this trial, this event led to the admission of the subject, so she was excluded from the trial.

No significant abnormalities were observed in the blood tests performed for safety evaluation before and after the administration of the study drugs.

4. Discussion

In this study, we investigated the efficacy, safety and feasibility of *DJS* for treating climacteric syndrome with a blood-deficiency-dominant pattern. As a result of administering *DJS* or placebo to 34 subjects, the MRS and BDSS scores were significantly decreased in both the *DJS* and placebo groups, although the differences between two groups were not significant. The WHOQOL-BREF scores were significantly increased in the control group. No statistically meaningful differences in serum hormone levels or lean body mass were observed in both groups. There were no serious adverse effects related to the treatment, only minor mild digestive problems, and medication adherence was more than 90%.

To our knowledge, there has been no randomized controlled trial (RCT) for the effects of *DJS* on climacteric syndrome. Comparing our study with previous clinical trials administered with *DJS* for menopause, Park et al. reported that VAS scores of hot flush, sweating, and palpitation significantly decreased after taking *DJS* for 30 days, and MRS scores significantly increased, but this was a single-group study without a control group.[15] In the study of Terauchi et al., *DJS* reduced the frequency of sleep disturbance, diastolic blood pressure and increased lean body mass, but it was a retrospective study.[16] Pan et al. found to significantly improve climacteric syndrome when taking herbal medicine compared to the women taking HRT, but the effect of *DJS* alone was not known precisely because it was used with other herbal medicines.[22]

In recent studies, *DJS* has been identified with the clinical effects of improvement in menstruation-related headaches,[23] and headache and depression in middle-aged women.[24] As for the efficacy on blood-deficiency, Akase et al. revealed that the *DJS* has

ameliorative effect on iron-deficiency anemia rats in laboratory study,[25] and also reported it has improved signs of anemia in a women suffering from uterine myoma.[26] Considering these results, *DJS* could have attributed to regulating and adjusting the pathologic conditions of blood-deficiency in climacteric syndrome.

This study has several contributions to clinical practices. This study has adopted a validated and reliable instrument, the BDSS, to minimize the potential bias that may occur due to the variances among doctors' perceptions.[27,28] The BDSS combines a self-administered questionnaire and a technical assessment by doctors. This tool allows the subjects to fill out the survey by themselves so that the questions can be completed without the intervention of others. The doctor's opinion is supplemented based on each subject's survey responses to enhance diagnostic accuracy.

DJS can be applied to wider range of menopausal women who could not receive conventional therapy due to its side effects. Hormone replacement therapy has been limited in its use due to the risk of developing embolism, breast cancer, and coronary heart disease.[4] *DJS* improved menopausal disorders without stimulating the secretion of sex hormones and affecting liver function in this trial. In addition, recent findings of *DJS* on improving blood flow by inhibiting thrombus formations supports its use to thromboembolism and cardiovascular disease in menopausal women.[13]

The current study has the following strengths. First of all, there has been a lack of studies that investigated the blood-deficiency type, and this study aimed to fill such void. Most of the pattern identification of climacteric syndrome considers the liver-qi stagnation and kidney-deficiency as major causes,[29] while blood-deficiency pattern has not been sufficiently explored. Additionally, only few studies described blood-deficiency on conditions of climacteric syndrome.

Second, despite the relatively short period of time of taking herbal medicines (i.e., 4 weeks), while other previous studies ranged from 2 to 6 months,[30-33] *DJS* was found to be effective to relieving symptoms of menopause with blood-deficiency. Specifically, the participants in the current study had approximately 12 points decrease in the MRS score, which far exceeds the minimal clinically important change for the MRS score of 5 points.[34] The effect persisted significantly in the follow-up period when not taking the drugs. Given that the most recommended period administering herbal medicine was 4 weeks, obtained from a survey by Korean medicine doctors,[29] it is appropriate period that can be applied in actual clinical practice. We expect that the perception of patients on the medication to be effective even within a short medication period, will help them persist the medication, resulting in successful completion of the treatment.

The limitations of this study are as follows. First, despite several attempts to overcome the placebo effect, a placebo effect occurred. In several RCTs performed before, placebo has often occurred and was a relatively common phenomenon.[30,35] This is usually explained by patients' expectations for improvement, and it has also reported to occur more frequently from patient-reported outcomes.[36] In subsequent study, we plan to consider several methods to minimize the contributing factors for placebo effect, e.g. setting other evaluation tools or analyzing the relationship between the outcome and psychological state.

Second, this study included menopausal women who were in the pre- or postmenopausal period, and there may be different conditions in these periods. The analysis by Fu et al.[33] was divided into premenopausal and postmenopausal groups. Subgroup analysis of more subjects would be required to provide a more accurate reflection of periodic conditions in a subsequent study.

In conclusion, *DJS* may have clinical effectiveness, safety, and feasibility for the treatment of climacteric syndrome with a blood-deficiency-dominant pattern. Therefore, it would be suitable to carry out a large-scale study to confirm the efficacy and safety of *DJS* treatment in the future.

Author contributions

Conceptualization: MKK, JHL and JEY. Methodology: MKK. Data curation: ARK and HJP. Software: OJK. Formal analysis: OJK. Investigation: EJP, SEB and JEY. Writing-original draft: EJP. Writing-review & editing: MKK, JHL and JEY. Supervision: JHL and JEY.

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Ethical statement

This clinical trial was approved by the Institutional Review Board (IRB) of Daejeon University Dunsan Korean Medicine Hospital (Approval number: DJDSKH-17-DR..-10).

Data availability

The data will be made available upon request.

Conflict of interest

The authors declare that they have no competing interests.

Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.imr.2021.100715.

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