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Original Article

Beneficial effect of Gyejibokryeong-hwan on climacteric syndrome with blood stasis pattern: A randomized, double-blinded, placebo-controlled clinical pilot trial

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ABSTRACT

Background: Gyejibokryeong-hwan (GBH), a herbal mixture that is widely used for climacteric syndrome, is studied for its efficacy; however, no study evaluated the GBH indication, which is a blood-stasis pattern based on traditional Chinese medicine theory.
Methods: This is a randomized, double-blinded, placebo-controlled clinical pilot trial. Fifty subjects with climacteric syndrome were recruited and randomly assigned to GBH group or placebo group. Subjects were administered GBH or placebo granules for 4 weeks followed by 4 weeks of observation period. For the primary outcome, the Menopause Rating Scale (MRS) was evaluated. For the secondary outcomes, quality of life, degrees of abdominal resistance and tenderness, blood-stasis pattern questionnaire and degree of upward movement of *Qi* were evaluated.
Results: After 4-week intervention, the mean change of total MRS score significantly decreased in the GBH group compared to the placebo group ($p = 0.037$). The quality of life related to physical health ($p = 0.008$) and blood-stasis pattern ($p = 0.018$) significantly improved in the GBH group but not in the placebo group.
Conclusion: Our findings provide evidence of the feasibility of recruiting subjects with GBH indications and show that GBH may have clinical efficacy for the treatment of menopausal symptoms, especially urogenital symptoms, without any significant adverse events.
Trial registration: Clinical Research Information Service (CRIS identifier: KCT0002170).

1. Introduction

The climacteric syndrome comprises a series of physical and psychological conditions experienced by perimenopausal or postmenopausal women secondary to the physiological gradual decline in ovarian function and the oestrogen level. Menopausal symptoms include hot flashes, night sweats, palpations, sleep disturbances, fatigue, anxiety, mood swings, weight gain, vaginal dryness, and urinary incontinence which negatively affect quality of life.[1,2] Hormone replacement therapy is a relatively safe and effective option for treating menopausal symptoms, especially in vasomotor symptoms,[3] but confers an increased risk of breast cancer, dementia, deep vein thrombosis, and stroke.[4–7] Therefore, many women who are concerned about potential risks, have a history of breast cancer, or are dissatisfied with their earlier treatment avail comple-

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mentary and alternative medicine (CAM) treatments. According to a prospective cohort study of 3302 women from 5 ethnic groups at 7 sites in the United States, 80% of menopausal women reported using CAM treatments.[8]

Gyejibokryeong-hwan (GBH; *Gui-zhi-fu-ling-wan* in Chinese, *keishibukuryogan* in Japanese) is a traditional herbal medicine that is widely used in East Asia for various gynaecological diseases. Despite attempts to evaluate the efficacy of GBH in the treatment of various menopausal symptoms,[9–12] rigorously designed randomized controlled trials (RCT) are still lacking. A placebo-controlled RCT showed that GBH did not significantly improve hot flashes[9] and highlighted the importance of inclusion criteria that include traditional symptom patterns as approximately 20% of patients experience adverse effects, such as diarrhoea, due to formula mismatch and this may affect the drop-out rate of the treatment group.[11]

In Korean medicine (KM), GBH is specifically used for patients with a blood-stasis pattern that is characterized by pathological stagnation due to poor blood circulation that manifests as menstrual disorder, palpitations, hot flashes with cold, clammy extremities, and fixed pain with resistance of pressing.[13] Although pattern identification is a key element for individually tailored herbal prescription, assessing the efficacy of CAM treatments proves challenging due to the complexity of RCT designs that reflect each symptom pattern and the associated treatments. A retrospective comparative study of the effects of three major Kampo formulae for menopausal symptoms and sleep disturbances found that women who took GBH – patients with blood-stasis pattern – had a relatively higher body weight, resting energy expenditure, blood pressure and pulse rate than patients with other symptom patterns.[10] One of the hurdles that make it difficult to include symptom patterns in the inclusion criteria is that pattern identification relies on the practitioner's empirical, subjective diagnosis. Thus, despite efforts to differentiate between symptom patterns in climacteric syndrome, no study has included blood-stasis pattern as an inclusion criterion.

This study was conducted to characterize the indication for GBH (blood-stasis pattern), in terms of inclusion criteria and outcome assessments, and aimed to assess the feasibility of the study design as well as the efficacy and safety of GBH in the treatment of climacteric syndrome in women with the blood-stasis pattern.

2. Methods

2.1. Study design

This double-blind, placebo-controlled randomized trial was conducted at two traditional KM hospitals in Daejeon, Republic of Korea, from October 26, 2016 to May 13, 2019. Following the initial screening visit, subjects were randomly allocated to either the GBH or placebo arm for the first 4 weeks during the 8-week study duration, and then followed up period for 4 weeks, as described in the trial protocol that was published previously.[14] The study protocol was approved from the institutional review boards of Daejeon KM Hospital of Daejeon University (approval no. DJOMC-141–1) and Dunsan KM Hospital of Daejeon University (approval no. DJDSKH-17-DR-07). The trial was pre-registered in the Clinical Research Information Service (CRIS identifier: KCT0002170).

2.2. Sample-size calculation

An adequate sample size was estimated based on a previous study.[12] Assuming approximately 20% of the value would be observed with the treatment group, the mean changes in the Menopause Rating Scale (MRS) score after 4 weeks were estimated as −7.27 and −1.45 in the treatment and control groups, respectively, with an estimated intergroup common standard deviation of 6.73. Thus, 25 participants in each group were required to achieve 80% power at a 5% level of significance (two-sided) and an anticipated drop-out rate of 15%.

2.3. Participants

Participants were recruited through advertisements on the subway, local newspapers, and hospital bulletin boards and underwent eligibility screening after voluntarily providing written informed consent for study participation. The inclusion criteria for women in this study were: (1) age, 45–60 years; (2) menopausal (natural/induced menopause) status, with pre- or post-climacteric symptoms; (3) MRS score ≥9 points; (4) moderate or high physical strength according to the subjective judgement of the physician based on KM theory; (5) moderate or high degree of upward movement of *Qi*; (6) moderate or high degree of lower abdominal resistance and tenderness; and (7) willingness to provide written informed consent for participation in the trial.

Women with the following exclusion criteria were excluded: (1) seriously unstable medical condition; (2) severe mental disease; (3) aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyl transpeptidase (γ-GTP) levels ≥1.5 times the normal upper limit; (4) blood urea nitrogen (BUN) and creatinine levels ≥1.5 times the normal upper limit; (5) thyroid-stimulating hormone level <1.5 times the normal lower limit; (6) body mass index <18.5 kg/m^2; (7) haemoglobin level <11 g/dL; (8) received oestrogen therapy in the preceding year; (9) received herbal medicine therapy related to climacteric syndrome in the preceding 4 weeks; (10) postmenopausal idiopathic vaginal bleeding; (11) lactose intolerance; (12) current participation in other clinical studies; (13) residents of care facilities or nursing homes; (14) refusal to provide written informed consent; and (15) other conditions conferring unsuitability for participating in the clinical trial.

2.4. Randomization and blinding strategies

Subjects were randomly assigned to either the GBH group or the placebo group with a 1:1 ratio, using random numbers generated with a computerized block-randomization method by an independent statistician and sent to the pharmaceutical company for allocation-concealment packaging to ensure blinding of all investigators, participants, coordinators, pharmacists, and clinical research associates. To assess whether the blinding process was successfully achieved, a post-study blinding questionnaire was obtained from all participants.

2.5. Interventions

Participants in both groups were administered either GBH or the placebo (3 g granules per packet) thrice daily for 4 weeks. Both GBH and the placebo drugs were manufactured by Hanpoong Pharmaceutical (Wanju, Republic of Korea) in accordance with the good manufacturing practices guideline. GBH was prepared according to the granulation method using 1.33 g GBH soft extract, obtained from an aqueous extract of five herbs in the same ratio: *Cinnamomi Ramulus, Poria Sclerotium, Moutan Radicis Cortex, Paeoniae Radix*, and *Persicae Semen*. The placebo comprised brown granules, made of corn starch, citric acid hydrate, lactose hydrate, caramel colour, and ginseng flavour, that tasted, smelled, and appeared similar to GBH. Compliance was assessed based on the number of used and unused drug packets returned by the participants.

During the study, participants in both groups were prohibited from concomitant use of any treatments, including menopause-

related hormone therapy, non-prescription medicines, herbal medicines, or functional health foods, that were likely to affect the study outcomes.

2.6. Outcome measures

Outcome measures were assessed at baseline, Week 5, and Week 9. The primary outcome was the mean change in the MRS score after the intervention. The MRS is a validated tool for assessing quality of life (QoL) and menopausal symptoms amongst ageing women that adequately reflects complex physical and psychological factors.[15,16] The Korean version of the MRS, which comprises three subscales – psychological, somato-vegetative, and urogenital domains – was used to assess menopausal symptoms (the total score, sum score of all domains, ranges from 0 to 44). For secondary outcomes, the Korean version of the World Health Organization Quality of Life-BREF (WHOQOL-BREF),[17] blood-stasis pattern questionnaire,[18] degree of upward movement of *Qi*, and degree of lower abdominal resistance and tenderness were assessed, as described in the previously published trial protocol.[14] Levels of follicle-stimulating hormone and oestradiol was also conducted for understanding the climacteric condition. For safety outcomes, investigators checked for adverse events at every visit, and blood tests were conducted during screening and at Week 9.

2.7. Statistical analysis

Statistical analysis was performed as described in the trial protocol that was published previously.[14] All continuous values are presented as the mean and 95% confidence interval (95% CI), whereas categorical values are presented as frequency and percentage. Using SAS® Version 9.4 (SAS institute. Inc, Cary, NC), an independent statistician who was blinded to group allocation performed statistical analysis of the full analysis set (FAS); the multiple imputation method was adopted for incomplete data sets.[19] Analysis of covariance was performed for outcome values with the baseline values as covariates, each group as the fixed factor, and weeks 5 and 9 as dependant variables. The paired *t*-test was used for within-group comparisons and Fisher's exact test was performed for qualitative data analysis. *P*-values less than 0.05 in the two-sided test was considered statistically significant.

3. Results

3.1. Baseline characteristics

The study flow diagram (Fig. 1) shows that 50 of the 60 participants who provided written consent were eligible for the study, and 25 subjects were allocated to each group; one subject from the treatment group withdrew consent due to personal reasons during the treatment period. Thus, 24 and 25 subjects in the treatment and placebo groups, respectively, completed the allocated interventions. During the follow-up period, one patient in each group was lost to follow-up. There were no significant intergroup differences in baseline characteristics (Table 1). The post-intervention questionnaire administered to confirm successful blinding showed no significant intergroup differences ($p = 0.698$; Supplementary Table 1).

3.2. Feasibility outcomes

The study had an 83.33% recruitment rate and 94.00% completion rate. Medication adherence in the GBH and placebo groups was 92.52% (95% CI: 88.83, 97.86) and 96.04% (95% CI: 93.65, 98.43), respectively.

3.3. Climacteric symptoms

As shown in Fig. 2 and Supplementary Table 2, the mean total MRS score significantly decreased in the GBH group compared to the placebo group after the 4-week intervention (mean difference −3.83, $p = 0.037$), but was non-significant at Week 9 (mean difference −2.08, $p = 0.349$). Pre- and post-intervention comparisons within each group showed a significant decrease in the total MRS score in both groups at Week 5 (mean difference −9.25 and −6.56 in GBH and placebo groups, respectively; $p<0.001$) and Week 9 (mean difference −6.88 [$p = 0.001$] and −6.04 [$p<0.001$] in the GBH and placebo groups, respectively). Moreover, each subscale showed a significant decrease in both groups, and only the urogenital subscale showed a significant between-group difference (mean difference −1.51, $p = 0.019$).

The WHOQOL-BREF scores demonstrated no significant changes in all scores except for the physical subsection score (Supplementary Table 3). The GBH group showed a significant decrease in the physical subsection (mean difference 7.83, $p = 0.008$) at Week 5, although the intergroup difference was not statistically significant (mean difference 5.78, $p = 0.056$). To objectively determine the improvement of target symptoms, symptoms corresponding to the indication for GBH were assessed (Supplementary Table 4). The blood-stasis pattern score significantly decreased in the GBH, but not placebo group at Week 5 (mean difference −5.86, $p = 0.018$ and −1.32, $p = 0.480$, respectively). The degree of upward movement of *Qi* ($p = 0.019$ in week 5 and $p = 0.053$ in week 9) and degree of lower abdominal resistance and tenderness ($p<0.001$ in week 5 and 9) statistically decreased in both groups at weeks 5 and 9, and the improvement was significantly higher in the placebo group than in the GBH group.

The FSH and oestradiol levels and hsCRP, which is a predictor for the risk of cardiovascular disease, did not change significantly after the interventions in both groups (Supplementary Table 4).

3.4. Safety and adverse events

No safety-related changes in blood markers were observed (Supplementary Table 5). Throughout the study no serious adverse events occurred. There were 10 and 13 adverse events in the GBH and placebo groups, respectively, which included 2 adverse effects of climacteric symptom exacerbation and dyspepsia in the GBH group and 2 adverse effects of abdominal distention and abnormal increase in ALP, gamma-GTP, and hsCRP levels in the placebo group. Other adverse events included sore throat, vaginitis, lumbar sprain, facial paraesthesia, fatigue and 3 cases of upper respiratory infection that were reported in the GBH group, whereas fall injury; 2 cases of low back pain, gastroenteritis, lower limb fracture, headache, and ankle sprain; and 4 cases of upper respiratory infection were reported in the placebo group. There was no drop-out related to the adverse events.

4. Discussion

To the best of our knowledge, this investigation is the first GBH study to include a symptom pattern or the subjects' constitutional state in the inclusion criteria. Fifty menopausal women with GBH indications were recruited to evaluate whether a 4-week GBH, compared to placebo, administration could effectively improve menopausal symptoms. Our result provides evidence of the feasibility of recruiting subjects with GBH indications and also demonstrated that GBH may have beneficial effects on menopausal symptoms without significant adverse events. Significantly decreased total MRS was observed in the GBH group compared to the placebo group. Given the fact that a reduction of 5 points or more compared to baseline can be considered effective,[20] this result is

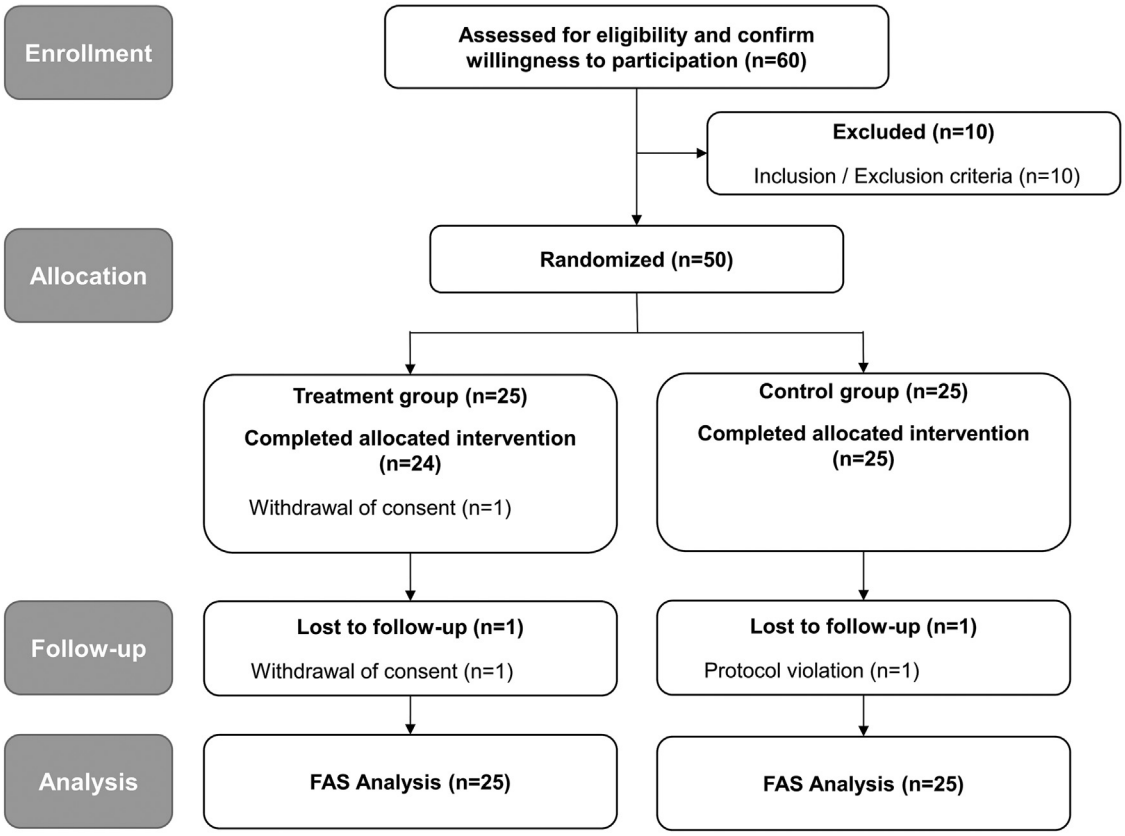

Fig. 1. Study flow chart.

Table 1
Baseline characteristics of the participants in the study subgroups.

Characteristics	GBH group (n = 25)	Placebo group (n = 25)	p
Age (years)‡	53.60 (52.31, 54.89)	52.04 (50.51, 53.57)	0.115
Job (Y / N)†	13 (52.00%) / 12 (48.00%)	11 (44.00%) / 14 (56.00%)	0.778
Education†			0.479
Elementary school	0 (0.00%)	2 (8.00%)	
Middle school	2 (8.00%)	2 (8.00%)	
High school	11 (44.00%)	13 (52.00%)	
University school	12 (48.00%)	8 (32.00%)	
Exercise (Y / N)†	18 (72.00%) / 7 (28.00%)	17 (68.00%) / 8 (32.00%)	0.999
Time (minutes/week)‡	221.10 (132.80, 309.40)	282.10 (183.10, 381.00)	0.337
Alcohol consumption (Y / N)†	8 (32.00%) / 17 (68.00%)	5 (20.00%) / 20 (80.00%)	0.520
Childbirths (live births)†			0.554
0	1 (4.00%)	2 (8.00%)	
1	2 (8.00%)	4 (16.00%)	
2	17 (68.00%)	17 (68.00%)	
3	5 (20.00%)	2 (8.00%)	
Menopause (Y / N)†	21 (84.00%) / 4 (16.00%)	17 (68.00%) / 8 (32.00%)	0.321

GBH, *Gyejibokryeong-hwan* (herbal medicine); Y: yes; N: no. Data are shown as mean (95% confidence intervals) or frequency (percentage).
† Fisher's exact test
‡ Analysis of variance.

meaningful because the mean difference of reduction was more than 9 points in GBH group whereas the placebo group showed a 6.56-point reduction in the total MRS score. Although there was no significant between-group difference, the GBH group, but not the placebo group, showed significant improvement in QoL related to physical condition as well as the degree of blood-stasis symptoms. Overall, the symptomatic improvement after the intervention reverted to some extent during the follow-up period, but did not fall to the baseline level.

The mechanism of action of GBH for the treatment of menopausal disorders has not been clearly identified. A study has found that GBH and their metabolites neither show oestrogenic activity nor contain common phyto-oestrogenic structures; the authors concluded that GBH might exert pharmacological effects on menopausal syndrome via other mechanisms.[21] This supports our results, which showed no significant pre–post changes in FSH or oestradiol levels. Previous studies on GBH have mostly focused on hot flashes as a target symptom, but the results obtained in our

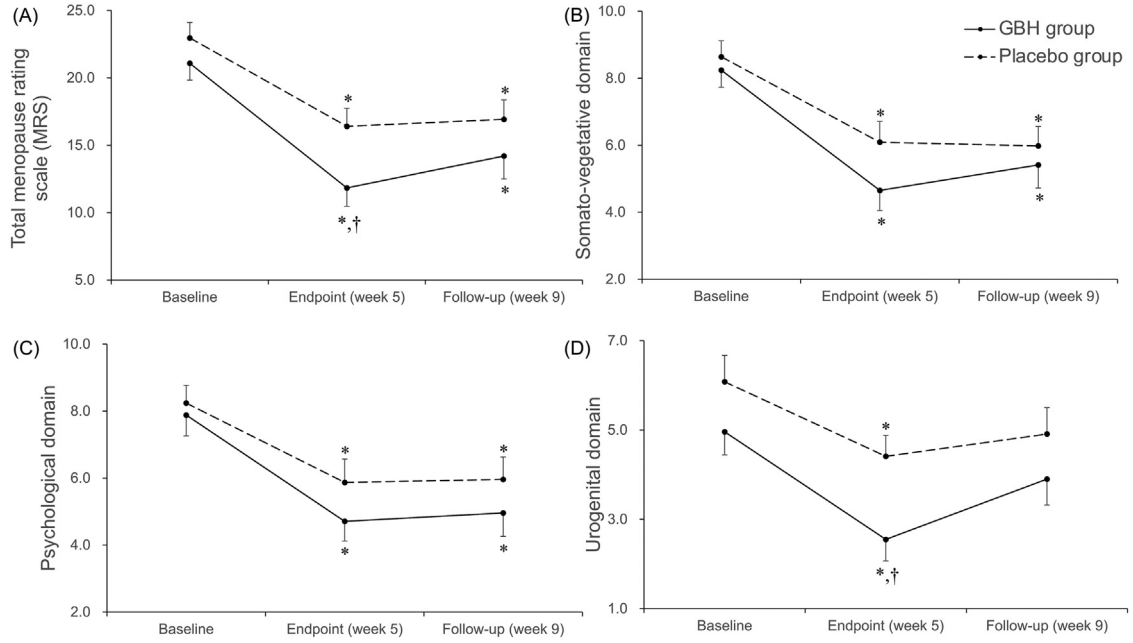

Fig. 2. Changes in the Menopause Rating Scale (MRS) scores. (A) Changes in the total MRS scores; (B) Changes in the somato-vegetative domain scores; (C) Changes in the psychological domain scores; (D) Changes in the urogenital domain scores. *: statistically significant difference ($p < 0.05$) compared to the baseline †: statistically significant difference ($p < 0.05$) between the *Gyejibokryeong-hwan* (GBH) and the placebo group.

study showed an overall improvement in all three subscales of the MRS. Interestingly, the urogenital subscale was the only category that showed a significant intergroup difference between the GBH and the placebo groups. To date, no studies have been conducted on the therapeutic effect of GBH on urogenital symptoms related to menopause, such as urinary frequency, urinary incontinence, vaginal dryness, and dyspareunia. Considering that *Poria sclerotium*, one of the major constituents of the GBH, has a diuretic effect, the administration of GBH may have contributed to the alleviation of micturition-related symptoms.[22,23] Moreover, GBH is traditionally known to regulate blood supply to the pelvic area by activation blood and removing blood stasis at the same time (in KM terminology '*circulate blood and eliminate stasis*').[24] It is supported by the fact that GBH inhibits uterine disorders, such as dysmenorrhoea, endometriosis, and adenomyosis, by preventing angiogenesis and regulating immune cells and immunoglobulin in endometrial tissues.[25] GBH may have improved urogenital symptoms with a similar mechanism, but little is known about the treatment effect of GBH on urogenital symptoms because usually these symptoms are not the primary complaints and often overlooked as treatment targets. Further research focusing on the treatment of urogenital symptoms will help understand the treatment mechanism of GBH and may also help improve the QoL of menopausal patients.

Our study is meaningful in that, unlike previous studies, we included the target symptoms of GBH as an inclusion criterion and used them as outcome measures. Despite the fact that blood stasis pattern diagnosis mostly depends on the practitioners' subjective evaluation, we have tried to quantify practitioners' evaluation. As there are many factors that can determine the indications for GBH, we decided to evaluate lower abdominal resistance and frequently asked questions to assess the degree of upward movement of *Qi* on a 5-point scale by blinded assessors. However, it was difficult to detect symptom changes sensitively with the 5-point scale, and from our results, it was not able to show consistent results with those of already validated questionnaires such as MRS and blood stasis pattern questionnaire. The concept of blood stasis ('*xueyu*' in Chinese, '*eohyeol*' in Korean, and '*oketsu*' in Japanese) has been widely used in East Asia, which broadly refers to disorders of blood circulation.[26] However, there have been some inter-country differences in the emphasis on blood-stasis symptoms. According to a study comparing representative instruments and literatures from Western and East Asian countries, the diagnosis of blood-stasis symptoms varies depending on regional clinical experiences and cultural backgrounds.[27] In order to overcome the coherence caused by differences in emphasis on blood stasis symptoms in each country, using recently developed and validated blood stasis syndrome questionnaire, which integrated Chinese, Korean and Japanese criteria of blood stasis criteria is recommended for the future studies.[28,29]

There are some limitations in this study. Although we have tried to remove conditions that can cause a placebo effect, it was impossible to completely rule out a placebo effect. As menopausal symptoms are closely related to autonomic dysfunctions, high placebo-response rate (34% in previous RCT study) is often shown in study with menopausal syndrome.[11] In subsequent studies, it is essential to include usual care group as another treatment arm or to include placebo lead-in period for all groups to rule out a placebo response. Another limitation is that while considering blood stasis pattern as inclusion criteria for this study, we cannot draw conclusion how GBH administration affects patients with different symptom pattern. In a pilot study of *Danggwijagyak-san* for the treatment of climacteric syndrome for those who have blood-deficiency pattern, which is an opposite pattern to blood stasis pattern, the MRS score decreased significantly after treatment.[30] Although a growing number of studies have evaluated the therapeutic effect for each symptom pattern, it has not yet been investigated what the objective difference is between the symptom patterns or whether the symptoms worsen when an opposing drug is administered. Further research is needed to determine whether the treatment effect will differ depending on the symptom patterns even for patients with same menopausal symptoms.

In summary, the results from the present study have shown that it is feasible to recruit subjects with GBH indications to receive either GBH or placebo for the treatment of climacteric syndrome. Our pilot data demonstrated that GBH may have clinical efficacy for the treatment of menopausal symptoms, especially on

urogenital symptoms without any significant adverse effects. Further full-scale trials are needed to determine the pharmacological effect of GBH on climacteric syndrome with blood stasis pattern.

Author contributions

Conceptualization: KH, JEY, JEK, and MK. Methodology: JEK, OK and MK. Software: OK. Validation: KH, JEY and OK. Formal analysis: KH and OK. Investigation: KH, JEY, JEK, ARK, HJP, SYJ, MK, CY, and JHC. Resources: JEY and JHC. Data curation: ARK, HJP and SYJ. Writing – Original Draft: KH. Writing – Review & Editing: KH, JEY, and JHL. Visualization: KH. Supervision: JHL. Project administration: MK and JHL. Funding acquisition: JHL.

Conflicts of interest

The authors report there are no competing interests to declare.

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Ethical statement

This research was reviewed and approved by the institutional review board of Daejeon Oriental Hospital of Daejeon University (approval no. DJOMC-141–1) and Dunsan Korean Medicine Hospital of Daejeon University (approval no. DJDSKH-17-DR-07). Informed consent was obtained from all participants.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.100951.

References

1. McKinlay SM. The normal menopause transition: an overview. *Maturitas*. 1996;23(2):137–145.
2. Avis NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain V, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med*. 2001;52(3):345–356.
3. North American Menopause S. The 2017 hormone therapy position statement of the North American Menopause Society. *Menopause*. 2017;24(7):728–753.
4. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*. 2003;289(20):2651–2662.
5. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003;289(24):3243–3253.
6. Bath PMW, Gray LJ. Association between hormone replacement therapy and subsequent stroke: a meta-analysis. *J Neurol Neurosur Psychiatry*. 2005;76(6) 838-38.
7. Miller J, Chan BKS, Nelson HD. Postmenopausal estrogen replacement and risk for venous thromboembolism: a systematic review and meta-analysis for the US Preventive Services Task Force. *Ann Intern Med*. 2002;136(9):680–690.
8. Tetteh A. Use of complementary and alternative medicine during the menopause transition: longitudinal results from the Study of Women's Health Across the Nation. *Menopause*. 2008;15(5):1029.
9. Yasui T, Matsui S, Yamamoto S, Uemura H, Tsuchiya N, Noguchi M, et al. Effects of Japanese traditional medicines on circulating cytokine levels in women with hot flashes. *Menopause*. 2011;18(1).
10. Terauchi M, Hiramitsu S, Akiyoshi M, Owa Y, Kato K, Obayashi S, et al. Effects of three Kampo formulae: tokishakuyakusan (TJ-23), Kamishoyosan (TJ-24), and Keishibukuryogan (TJ-25) on Japanese peri-and postmenopausal women with sleep disturbances. *Arch Gynecol Obstet*. 2011;284(4):913–921.
11. Plotnikoff GA, Watanabe K, Torkelson C, La Valleur J, Radosevich DM. The tu-025 keishibukuryogan for hot flash management in postmenopausal women: results and lessons for future Research. *Menopause*. 2011;18(8):886.
12. Park JM, Yang JM, Kim DI. A clinical trial to verity the quality of life improvement efficacy of Dangguijakyak-san and Gyejibongnyeong-hwan granulation in postmenopausal women. *J Korean Obstet Gynecol*. 2007;20(3):213–228.
13. Li SM, Xu H, Chen KJ. The diagnostic criteria of blood-stasis syndrome: considerations for standardization of pattern identification. *Chin J Intergr Med*. 2014;20(7):483–489.
14. Kim JE, Cho J, Kwon O, Kim AR, Park HJ, Jung SY, et al. Effect of Guizhifulingwan (Keishibukuryogan) on climacteric syndrome: study protocol for a randomized controlled pilot trial. *Trials*. 2017;18(1):1–8.
15. Heinemann K, Ruebig A, Potthoff P, Schneider HPG, Strelow F, Heinemann LAJ, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Out*. 2004;2 45-45.
16. Schneider HPG, Heinemann LAJ, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): reliability of scores of menopausal complaints. *Climacteric*. 2000;3(1):59–64.
17. Kim WH, Hahn SJ, Im HJ, Yang KS. Reliability and validity of the korean world health organization quality of life (WHOQOL)-BREF in people with physical impairments. *Ann Rehabil Med*. 2013;37(4):488–497.
18. Yang DH, Park YJ, Lee SC, Park YB. Development of questionnaires for blood stasis pattern. *J Korea Instit Orient Med Diagn*. 2006;10(1):141–152.
19. Li P, Stuart EA, DB A. Multiple imputation: a flexible tool for handling missing data. *JAMA*. 2015;314(18):1966–1967.
20. Heinemann LAJ, DoMinh T, Strelow F, Gerbsch S, Schnitker J, Schneider HPG. The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study. *Health Qual Life Out*. 2004;2(1):67.
21. Wang Z, Kanda S, Shimono T, Enkh-Undraa D, Nishiyama T. The in vitro estrogenic activity of the crude drugs found in Japanese herbal medicines prescribed for menopausal syndrome was enhanced by combining them. *BMC Complem Altern M*. 2018;18(1):107.
22. Feng YL, Lei P, Tian T, Yin L, Chen DQ, Chen H, et al. Diuretic activity of some fractions of the epidermis of Poria cocos. *J Ethnopharmacol*. 2013;150(3):1114–1118.
23. Liu C, Fu YQ, Wang Y, Wang H, Liu WJ, Wang ZH, et al. Effects of Guizhi Fuling pill and be taken apart on warming yang and diuretic promoting blood circulation and removing blood stasis in model of mice with hysteromyoma. *J Liaoning Univ TCM*. 2009;11:11.
24. World Health Organization. *WHO International Standard Terminologies on Traditional Chinese Medicine*. Geneva: World Health Organization; 2022.
25. Kim JH, Shin HK. Literature review on biological effects of Gyejibokryeong-hwan against Gynaecological diseases. *JKM*. 2013;34(2):29–40.
26. Park B, You S, Jung J, Lee JA, Yun KJ, Lee MS. Korean studies on blood stasis: an overview. *Evid-Based Compl Alt*. 2015;2015:316872.
27. Birch S, Alraek T, Lee MS, Lee JA, Kim TH. Understanding blood stasis in traditional East Asian medicine: a comparison of Asian and Western sources. *Eur J Integr Med*. 2021:101341.
28. Kang BK, Park TY, Lee JA, Jung J, Lee MS. Development of a blood stasis syndrome questionnaire and its reliability and validity. *Eur J Integr Med*. 2016;8(6):942–946.
29. Kang BK, Park TY, Jung J, Ko M, Lee MS, Lee JA. The optimal cut-off value of blood stasis syndrome score in BSS diagnosis in Korea. *Evid-Based Compl Alt*. 2017;2017:8049481.
30. Park EJ, Baek SE, Kim M, Kim AR, Park HJ, Kwon O, et al. Effects of herbal medicine (Danggwijagyaksan) for treating climacteric syndrome with a blood--deficiency-dominant pattern: a randomized, double-blind, placebo-controlled pilot trial. *Integr Med Res*. 2021;10(3):100715.