

BMJ Open Gyejibongneyong-hwan, a herbal medicine for the treatment of dysmenorrhoea with uterine fibroids: a protocol for a randomised controlled trial

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ABSTRACT

Introduction: Gyejibongneyong-hwan (GBH), or the Guizhi Fuling Formula in Chinese, is widely used to treat uterine fibroids in East Asian countries including Korea, China and Japan. This study will assess the efficacy and safety of the GBH formula for the treatment of dysmenorrhoea.

Methods and analysis: This study will be a randomised double-blind controlled trial with two parallel arms: the GBH group and the placebo group. This trial will recruit 38 women between 18 and 45 years of age with secondary dysmenorrhoea with uterine fibroids. The investigational drugs, either GBH or placebo, will be administered to the participants three times per day for two menstrual periods (8 weeks). The participants will be followed up for three menstrual cycles after administration of the drugs. The primary outcome will be the Numeric Rating Scale score of average menstrual pain. All analyses will be performed with SAS (V.9.1.3; SAS Institute, Cary, North Carolina, USA) by a statistician blinded to the allocation of the groups. Statistical analysis will be undertaken on the intent-to-treat (ITT) basis with a 95% CI using the last observation carried forward for missing values. The ITT analysis will include all randomised patients.

Ethics and dissemination: This research protocol has been reviewed and approved by the institutional review boards of the trial centre (number WSOH IRB 1606-03). Written informed consent will be obtained from all study participants prior to enrolment in the study. The results will be published in a peer-reviewed journal and will be disseminated electronically and in print.

Trial registration number: KCT0001967.

INTRODUCTION

Uterine fibroids (UFs) are also known as leiomyoma. They are the most common benign uterine growths in women of

Strengths and limitations of this study

- The strength of this study is the unbiased randomised controlled trial for effectiveness of Gyejibongneyong-hwan (GBH) formula.
- GBH formula is most widely used for dysmenorrhoea with uterine fibroids.
- However, since this is only a pilot study for the effectiveness of the GBH formula, the sample size is not big.

childbearing age.¹ They are also called uterine leiomyomata, myoma, fibromyoma and fibroids.² The main symptoms may include heavy, painful or prolonged menstrual periods; bleeding between periods; pelvic or low back pain; fullness in the lower abdomen, with or without urinary or rectal symptoms, due to compression; and reproductive problems, such as infertility, multiple miscarriages or early onset of labour.² Although several surgical approaches have been recommended for the management of UFs, these methods are invasive and cause tissue injury and other adverse events.³ There are also pharmacological therapies, such as gonadotrophin-releasing hormone agonists, but rapid recurrence, wide-ranging adverse side effects and reduced bone mineral density have limited their usage.³

East Asian countries, including Korea and China, have used alternative therapies for treating UFs.^{1 4-6} These treatments include acupuncture and various herbal medicines. Studies have reported on the effectiveness of these treatments, but most were pilot trials with small sample sizes. Large-scale clinical trials are needed to determine the efficacy of these treatments.¹

In Korean medicine, the main contributor to menstrual abdominal pain is blood stagnation. If the flow of blood or qi is interrupted, it may cause pain. The signs of blood stasis include easy bruising, tender abdominal pain and clots in menstrual blood. Gyejibongneyong-hwan (GBH) is one of the most popular Korean medicine formulas for periodical pain caused by dysmenorrhoea. GBH makes blood more fluid to induce smooth blood flow and reduce pain.¹ In this study, we aimed to investigate the effectiveness of GBH on UFs.

METHODS/DESIGN

Study design

This clinical trial will be conducted as a randomised double-blind placebo-controlled comparison study. Individuals, who must agree to participate in the study and provide written informed consent, will be eligible to take part in the study. These participants will be randomly assigned either to an experimental group or a control group and will receive either GBH or a placebo during their menstrual cycle (~8 weeks) after attending an education session related to the clinical trial.

In this study, data on two menstruation periods will be collected: the initial menstrual period (~5 days; ~4 weeks) and the second menstrual period (~5 days; ~8 weeks) after the administration of the medications. Participants will be evaluated to determine the safety, compliance and efficacy of the medications following oral administration during the first and second

menstrual periods. In the first and second menstrual periods after completing the administration of the medications, participants will be followed up and evaluated for the reoccurrence of dysmenorrhoea and the safety of the medication (table 1).

The trial will be performed at the Wooseok Korean medicine hospital, which is a clinical centre in Korea, in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice. This protocol has been registered with the Clinical Research Information Service, Republic of Korea (KCT 0001967), which is a registry in the WHO Registry Network.

Eligible participants will be randomly allocated to one of the two groups (GBH group and placebo group) in a 2:1 allocation ratio (figure 1) due to ethical issue for placebo group. The evaluation of participants and the analysis of the results will be performed by professionals blinded to the group allocation.

Types of participants

Inclusion criteria

A total of 30 patients will be recruited through local advertising and from the outpatients of the one hospital. Patients must meet the following criteria:

1. Females between 18 and 45 years of age and diagnosed with Blood stasis syndrome.
2. Provide written informed consent to participate in the study.
3. Confirmation of uterine myomas by ultrasonography (over 2 cm).

Table 1 Schedule for treatment and outcome measurements

Items	Screening	Treatment period			Follow-up	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Participant agreement	•					
Blood sampling agreement	•					
Enrolment	•					
Demographic history	•					
Medical history	•					
Blood stasis screening	•					
Blood stasis questionnaire		•		•		•
Dysmenorrhoea		•	•	•	•	•
Numeric rating scale		•	•	•	•	•
A shortened version of the McGill pain questionnaire		•	•	•	•	•
Cox menstrual symptom scale		•	•	•	•	•
Physical examinations	•	•		•		
Clinical pathology examination	•	•		•		
Confirmation of inclusion and exclusion criteria	•	•				
Confirmation of medical history and history of changed treatments		•	•	•		
Randomisation		•				
Medication		•	•			
Adverse event			•	•	•	•
Ultrasonography	•			•		
Compliance check			•	•		

S, screening period; T, treatment period.

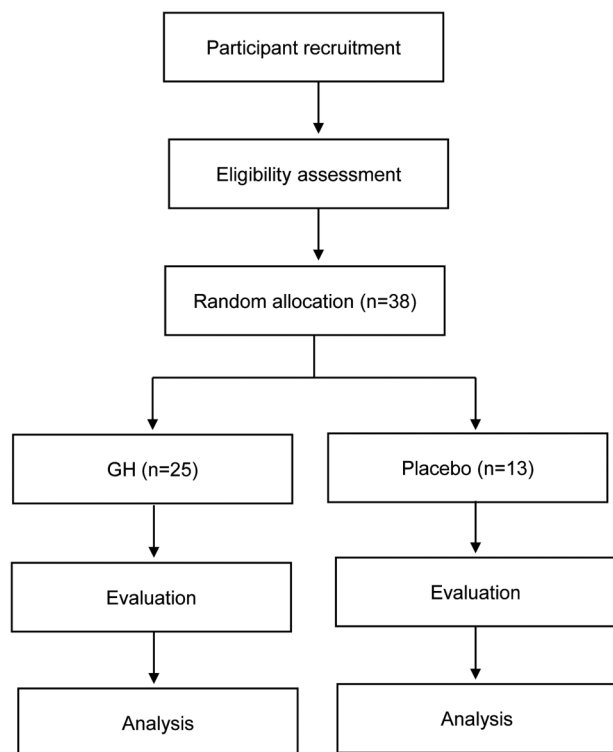


Figure 1 Flow chart of the study. GBH, Gyejibongneyong-hwan.

4. Agree to comply with the study regulations.

Exclusion criteria

1. Patients with heart disease, liver disease, kidney disease or any psychiatric condition.
2. Patients who are unable to communicate or are critically ill.
3. Pregnant women.
4. Patients with any condition that could influence the study assessment.
5. Patients who take regular medication, including serotonin, antidepressants or other antipsychiatric drugs.

Sample size

There are no previous studies on which to base the sample size calculation. The current study is designed as a pilot study to determine initial data for the primary outcome measure to perform a sample size calculation for a large-scale randomised controlled trial. A total sample size of 38 participants (treatment group: 25, control group: 13) will be included based on a possible 20% dropout rate.

Randomisation

Study participants who meet the eligibility criteria will be randomly assigned to one of two groups at their first visit through central randomisation in a 2:1 ratio. Randomisation will be conducted by a statistician using a computer-generated random allocation sequence through the predefined block randomisation list with random block sizes. Only the data manager has access to

this computer-generated randomisation list. Allocation concealment will be ensured because the randomisation code will be released after the participants are recruited into the trial and all baseline measures are obtained.

Blinding

To maintain blinding, only the sponsor and a staff member of the contract research organisation, who are not directly involved with this clinical trial, will be allowed to see the randomised treatment allocation table. The investigator of this study may use a separately arranged emergency code to break the blinded treatment code in the event of a medical emergency in which knowledge of the participant's treatment is essential for the immediate medical management or treatment decisions to manage the participant's medical condition. If the investigator wishes to unblind the study for any other reason, he or she should attempt to contact the sponsor in charge. The investigator should contact a medical monitor team immediately after unblinding the participant's treatment code. If for any reason a study participant is not kept blinded to the treatment code by an investigator or a clinical research coordinator in charge of performing assessments, the study will be discontinued for that participant. However, for ethical reasons, if the investigator judges that maintaining that individual's participation in the study is necessary to offer the treatments of the clinical trial to the participant, the investigator can allow this with special approval from the sponsor in charge.

Interventions

GBH formula and placebo

GBH is a Korean medicine formula for the treatment of dysmenorrhoea caused by blood stasis. The participants will take the investigational drug, either GBH or placebo, three times per day for two menstrual periods (8 weeks). The experimental group will take GBH orally with a two-per-day (Two times a day) regimen for two menstrual periods (~8 weeks). The control group will take a control medication orally with a Two times a day regimen for two menstrual periods (~8 weeks).

GBH comprises Cinnamomi Ramulus, Poria, Moutan cortex, Persicae semen and Paeoniae radix. The placebo comprises lactose, corn starch and food colouring and is similar in appearance, shape, weight, taste and colour to the GBH. As a rescue medication, 10 pain pills will be provided during each treatment cycle.

Patient recruitment

The IRB approved the advertisements of the study. We will use newspaper and poster for recruitment.

Data collection and management

Outcome measurements will be checked by an independent assessor for each patient. These data will be written on the case report form (CRF) by a certificated clinical research coordinator.

All privacy sensitive data will be removed. All identifying information of participants will be coded. Signed informed consent forms and returned coded/anonymised questionnaires will be stored in a locker separately from study records that link to participant identifying codes.

Types of outcome measures

Primary outcome measurement

The primary outcome will be the change in the Numeric Rating Scale (NRS) score of average menstrual pain at baseline (visit 1) and after treatment (visit 3).

Secondary outcomes measurement

The secondary outcome measures include the VAS score (maximum pain during the menstrual period) and the Short-Form McGill Pain Questionnaire (SF-MPQ) [14].

At visits 1 and 2, changes in dysmenorrhoea will be investigated using the following measurement tools: (1) the NRS, in which participants report their average pain intensity and the maximum pain score during 5 days prior to a visit to the investigational site; (2) the Cox Menstrual Symptom Scale (CMSS); and (3) a shortened version of the SF-MPQ. Dysmenorrhoea changes will be assessed using the NRS during the first and third menstrual periods (~5 days) after completing the administration of the medications.

Other observation items

A. Patient's consent, screening number assignment and demographic survey

Study participants will be recruited through open recruitment that is promoted by posters and online advertisements. Participants who are recruited will be given detailed information (ie, purpose and content of the study, risks and benefits of participating in the clinical trial) related to the study. Written consent and genetic testing consent will be obtained from all participants. A screening number will then be allocated to participants, and a demographic survey of each participant will be conducted and documented. Documentation requirements are as follows: (1) whether participants provide written informed consent and the date of that consent; (2) participant's initials; (3) gender; (4); date of birth on the participant's identification card; (5) age; and (6) address and contact information.

B. Investigation of medical history, including past obstetric/gynaecological history and medications

At the screening visit, an investigator will examine and record the participant's medical information (ie, history of diseases, surgeries and hospitalisations; hypersensitivity or allergy to specific drugs; age at menarche; birth history; menstrual history) in detail by taking a history and reviewing medical records. During the study period, concomitant medications that may influence the results of this study will not be permitted with the exception of study drugs and permitted analgesics. However, an investigator can

permit concomitant drugs and therapies at his or her discretion if necessary and the investigator should clearly document the rationale, with his or her signature, on the CRF. If any medications are taken or treatments are performed without the investigator's clinical judgement that may influence the results of this study, it may be necessary to eliminate the participant from the study.

C. Gynaecological blood stasis

Using a simple screening questionnaire comprising five items, participants who answer more than three items positively will be diagnosed with gynaecological blood stasis (table 2).

D. Diagnosis of gynaecological blood stasis

For the diagnosis of gynaecological blood stasis, two gynaecologists specialising in Korean medicine will score the symptoms of blood stasis using a diagnostic table of blood stasis and make the diagnosis of blood stasis.

E. Physical examinations

Complete physical examinations will be performed at the screening visit and during the second menstrual period (~8 weeks later). The physical examination will include the cardiovascular system, lungs and respiratory system, gastrointestinal system, metabolism and endocrine system, renal and urinary system, reproductive system, musculoskeletal system, skin and connective tissue, neuropsychiatric system and other organs. At the screening visit, investigators will record the results of the physical examination on the CRF. In particular, if there are clinically significant abnormalities (as judged by the investigator) in the physical examination, those abnormalities will be recorded on the CRF.

F. Clinical pathology examination

Clinical pathology tests will be performed at the screening visit and at the second menstrual period (~8 weeks later) after the administration of the medications. The purpose of the clinical pathology tests is to assess the participants' overall medical condition and the safety of the study drug.

The following laboratory parameters will be included:

1. Complete blood count: White cell counts, red blood cells, haemoglobin, haematocrit and platelets.
2. Blood chemistry examination: Aspartate amino transferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen and creatinine.

Table 2 A simple screening questionnaire for gynaecological blood stasis

Symptoms	Yes/No (✓)	
Dark lumps in the menstrual blood	<input type="radio"/>	<input checked="" type="checkbox"/>
Menstrual pains	<input type="radio"/>	<input checked="" type="checkbox"/>
Dark menstrual blood	<input type="radio"/>	<input checked="" type="checkbox"/>
Dark red tongue	<input type="radio"/>	<input checked="" type="checkbox"/>
Sharp pains	<input type="radio"/>	<input checked="" type="checkbox"/>

3. Urinalysis: Protein, glucose, urobilinogen and ketones.

G. Ultrasonography

Ultrasonography will be performed to determine the progression of the UFs.

Confirmation of medical history and history of changed treatments

During visits 1, 2 and 3, investigators will evaluate any changes in the participants' medical history and treatment compared to those observed at the screening visit. If there are any changes, the investigators will record them on the CRF. If these changes meet the criteria for the exclusion, discontinuation or withdrawal of the participant, the investigators will inform the participant and discontinue the study.

Adverse events

Any expected or unexpected adverse events will be reported by the participants and practitioners at every visit and followed up to completion.

From the start of participation in the clinical study, investigators will ask the participants about adverse events. At every visit, investigators will also ask the participants to report any changes in health problems or any suspicion of adverse events since their past clinic visit, and they will investigate the occurrence of adverse events through an examination or interview. In the event of the presence or occurrence of adverse events, the following information should be recorded in detail: (1) the course of the event, including onset and duration; (2) severity; (3) any medical intervention or change in concomitant therapy; (4) known association of the event with the study drug or treatment; (5) presence of non-treatment-related factors known to be associated with the occurrence of the event; and (6) the results of a change in the study treatment or a medical intervention. Also, we will monitor the adverse events 6 months after the trial.

Treatment modification

Any severe adverse events of participants will be monitored. If participation would lead to, or worsen, related health problems, continuation of participation of the study or ancillary care will be discussed with the patient and medical expert.

Statistical analysis

All analyses will be performed with SAS (V.9.1.3; SAS Institute, Cary, North Carolina, USA) by a statistician blinded to the allocation of the groups. Statistical analysis will be undertaken on the intent-to-treat (ITT) basis with a 95% CI using the last observation carried forward for missing values. The ITT analysis will include all randomised patients.

A. Method of analysis of the primary validity evaluation variables

To evaluate changes in the average NRS scores of the experimental group taking GBH and the control group from before visit 1 to after visit 3 of the clinical trial after administering medications during the second menstrual period (~8 weeks), an independent two-sample t-test will be conducted. To compare each group before and after the clinical test, depending on normal distribution, a paired t-test or Wilcoxon signed rank test will be conducted. The NRS will evaluate pain in two ways and will be the object of the primary analysis based on average pain intensity during 5 days prior to a visit to the investigational site and maximum pain intensity prior to a visit to the investigational site.

An independent two-sample t-test will be used to assess changes in the average scores to verify size-related differences of uterine myoma in the experimental group taking GBH and the control group from before to after the clinical trial after administering medications during the second menstrual period (~8 weeks). To compare changes of the groups for before and after the clinical test, a paired t-test or Wilcoxon signed rank test will be conducted.

B. Additional analysis method of the secondary validity evaluation variables

1. SF-MPQ

An independent two-sample t-test will be used to assess changes in the average scores for each item and the total score of the SF-MPQ in each group from before to after the clinical trial. To compare changes of the groups before and after the clinical test, a paired t-test or Wilcoxon signed rank test will be conducted.

2. Degree of variation in blood stasis

In relation to the average variation in the diagnostic score of blood stasis in each group, an independent two-sample t-test will be used to assess changes in the average scores. To compare changes of the groups from before to after the clinical trial, a paired t-test or Wilcoxon signed rank test will be conducted. A correlation between the diagnostic score of blood stasis and other evaluation variables (ie, SF-MPQ, NRS) will also be analysed.

3. Observation of variation in dosage of analgesics

Regarding the average variation in the total number of patients taking analgesics in each group from before to after the clinical trial, an independent two-sample t-test will be used to assess changes in the average scores. To compare changes of the groups from before to after the clinical trial, a paired t-test or Wilcoxon signed rank test will be conducted.

4. Observation of changes in quality of life and symptoms of dysmenorrhoea

For the average variation in the scores of the CMSS in each group from before to after the clinical trial, an independent sample t-test will be used to assess changes in the average scores. To compare changes of the groups from before to after the clinical trial, a

paired t-test or Wilcoxon signed rank test will be conducted.

5. Observation of size-related differences in UFs

Regarding UFs related to valuables (average size of the largest UF, sum of all sizes of UFs and average size-related change in UFs) in each group from before to after the clinical trial, an independent two-sample t-test will be conducted to assess changes in the average scores. To compare changes of the groups from before to after the clinical trial, a paired t-test or Wilcoxon signed rank test will be conducted.

The comparison between groups will be conducted for the estimates from each item. For the continuous variables, an independent two-sample t-test will be conducted to assess the average change of the item and a non-parametric analysis will be applied if normal distribution is not satisfied.

Ethics

This research protocol has been reviewed and approved by the institutional review boards of the trial centre (number WSOH IRB 1606-03). Written informed consent will be obtained from all study participants prior to enrolment in the study.

DISCUSSION

UFs are very common in women. If a woman shows no serious symptoms, she does not require treatment.⁷ However, if a woman has serious pain or other symptoms, several therapy options can be used to treat the symptoms. Gonadotropin-releasing hormone agonists and synthetic steroids with antiprogesterone activity, such as mifepristone, slow or stop the growth of fibroids.⁸ Surgical therapy or uterine artery embolisation can also be considered.^{7,9} However, many women with UFs seek alternative, less invasive therapies.¹⁰ Therefore, several alternative therapies are considered for the treatment of UFs.¹¹ Among these, herbal medicines are treatment options.^{2,3,5,12} The GBH formula is widely used to treat UFs and dysmenorrhoea.¹³ We are aiming to assess the effectiveness of the GBH formula in the treatment of UF symptoms and whether it can improve blood stasis symptoms.

A recent systematic review for the GBH formula on dysmenorrhoea with UFs has been published.¹ Twenty-one trials were included in the review, but no conclusions were reached due to the limited number of trials and the low quality of the included studies. Although several trials have investigated the effectiveness of the GBH formula in the treatment of UF symptoms, most included trials did not follow the preferred reporting guidelines and few studies published the study protocols. We are aiming to publish the study protocol first, and we will then conduct a well-designed trial. It is better to do the power analysis for selection of the optimal number of participants. However, there are no previous studies on which to base the sample size calculation. Many studies were only focused on the either dysmenorrhoea or UFs.^{14–16} In

addition, the type of outcome measurements were different from our study. Thus, we designed this study as a pilot study to determine initial data for the primary outcome measure to perform a sample size calculation for a large-scale randomised controlled trial.

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Contributors JAL and JJ designed the study and wrote the draft. SY and EL developed the criteria and made the case report form. JC registered the study. BKM and MK decided on the statistical method and randomisation. MSL assisted in designing the study. The protocol was drafted by all authors.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval This research protocol has been reviewed and approved by the institutional review boards of the trial centre (number WSOH IRB 1606-03). Written informed consent will be obtained from all study participants prior to enrolment in the study.

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