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STUDY PROTOCOL

Modified Gwakjeongtang for Diarrhea-Predominant Irritable Bowel Syndrome: Study Protocol for a Randomized, Double-Blind, Placebo-Controlled, Pilot Clinical Trial

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Introduction: Irritable bowel syndrome (IBS) is a chronic condition characterized by recurrent abdominal pain associated with bowel movements. Modified Gwakjeongtang (MGT), an herbal prescription rooted in traditional East Asian medicine, consists of thirteen botanical drugs known for their potential to enhance intestinal barrier function, regulate gastrointestinal motility, and exhibit anti-inflammatory and antioxidant properties. Despite a few previous clinical trials highlighting MGT's potential for IBS symptom management, limited evidence exists with placebo control.

Methods and Analysis: In this pilot randomized clinical trial protocol, we aim to exploratively evaluate the efficacy and safety of MGT in patients with diarrhea-predominant IBS (IBS-D) by comparing it with a placebo. A total of 60 IBS-D patients will be enrolled, and eligible participants will be randomly allocated to either the MGT or placebo groups. Over a 4-week period, they will receive MGT or placebo granules three times a day. The primary endpoint will be the overall response rate post-treatment, determined through daily assessments of abdominal pain intensity and stool consistency.

Ethics and Dissemination: This clinical trial protocol has received approval from the Korean Ministry of Food and Drug Safety for an investigational new drug application and Institutional Review Board of the Kyung Hee University Korean Medicine Hospital. The research findings will be submitted and published in international peer-reviewed journal.

Trial Registration: Clinical research information service (registration number: KCT0008523).

Keywords: irritable bowel syndrome, herbal medicine, Gwakhyang-Jeonggi-San, Huoxiang-Zhengqi-San, Kkako-Shoki-San, clinical protocol

Introduction

Irritable bowel syndrome (IBS) is a chronic condition characterized by recurrent abdominal pain that persists for at least six months, along with specific symptoms such as pain relief with bowel movements, changes in bowel frequency, and alterations in stool consistency. Unlike functional constipation and diarrhea, IBS is characterized by abdominal pain.[1] IBS is categorized into three subtypes: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), and mixed-type IBS (IBS-M). Cases that do not fit into these subtypes are referred to as unclassified IBS (IBS-U). In the case of IBS-D, a diagnosis is made when > 25% of bowel movements correspond to type 6 or 7 on the Bristol Stool Form Scale (BSFS), and < 25% are classified as type 1 or 2.[2] The prevalence of IBS, as defined by the Rome IV criteria, was

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reported to be 4.6% among adults in the United States, Canada, and the United Kingdom.[3] Irritable bowel syndrome significantly impairs the patients' quality of life owing to recurrent symptoms and exerts a substantial impact on their work and social lives, leading to significant socioeconomic losses. Therefore, it is imperative to provide appropriate treatment for these patients to alleviate their symptoms and enhance their quality of life.[4]

To relieve IBS symptoms, dietary and lifestyle changes are recommended along with medication therapy, including antispasmodic agents. Specifically, various medications such as loperamide, ramosetron, and rifaximin are utilized to improve bowel habits and alleviate abdominal pain in patients with IBS-D.[5] However, owing to the limited effectiveness of current drug therapies in alleviating various IBS symptoms, there is a growing global demand for and interest in complementary and alternative medicines, including herbal medicines, to enhance the quality of life of patients with IBS.[6] Herbal medicines, in particular, hold promise for the treatment of disorders of gut-brain interactions,[7] as they comprise multiple active ingredients that can interact synergistically, potentially affecting various neurological, immune, and endocrine pathways mediated through the gut-brain axis.[8,9] According to systematic literature reviews, certain herbal medicines have shown potential effects in patients with IBS,[10–12] and when used alongside conventional therapy, they have been found to be safe while offering additional benefits. However, considering the low quality of the included studies, further trials are warranted.[13,14]

Modified Gwakjeongtang (MGT) is a traditional herbal prescription used in the field of complementary and alternative medicine to alleviate diarrhea and abdominal pain symptoms in patients with IBS. It is based on the renowned herbal prescription, Gwakhyang-Jeonggi-San (known as Huoxiang-Zhengqi-San in Chinese and Kkako-Shoki-San in Japanese). There are various versions of MGT, each incorporating a different herbal ingredient to enhance its therapeutic effects.[15,16] In a clinical trial involving 105 patients with IBS-D, the group that received MGT for eight weeks exhibited a higher efficacy than the group that received smecta.[17] In another study involving 102 patients with IBS-D, the combination of MGT with pinaverium bromide and flupentixol-melitracen has been shown to be effective and safe for treatment.[18]

The safety and efficacy of MGT for the treatment of IBS have been supported by evidence from clinical practice and other studies. However, to date, no placebo-controlled double-blind clinical trials have been conducted. Therefore, in this pilot randomized clinical trial protocol, we aim to exploratively evaluate the efficacy and safety of MGT in patients with IBS-D by comparing it with a placebo based on established practices and previous research.

Materials and Methods

Trial Design and Setting

This trial is designed as a parallel-group exploratory clinical trial with an allocation ratio of 1:1. The primary objective of this trial is to assess the effect of MGT on IBS symptoms in comparison to the placebo. The overall response rate following administration will be compared between the MGT and placebo groups. The trial will be conducted at a university hospital in Seoul, Korea.

Eligibility Criteria

Inclusion Criteria

Participants aged 19–65 years will be included in the study. The inclusion criteria encapsulate three aspects: a diagnosis of IBS according to the Rome IV criteria, the presence of abdominal pain rated at 3.0 or higher on a scale of 0–10 over the preceding 10 d, and IBS-D. This subtype of IBS is characterized by presence of type 6 or 7 stools on at least one occasion for ≥ 3 d within the past 10 d, with these specific stool types constituting ≥ 25% of the total bowel movement.

Furthermore, the eligibility requirement mandates having undergone colonoscopy within the previous five years, yielding no clinically significant findings. Additionally, participants with no clinically significant findings based on medical examinations and clinical laboratory tests and who willingly provide written consent to participate in the clinical trial will be included.

Exclusion Criteria

Participants will be excluded from enrollment if they have a medical history of celiac diseases or organic colorectal diseases, such as Crohn's disease, ulcerative colitis, or gastrointestinal malignancy. Those who have undergone major abdominal surgeries, such as gastrectomy or cholecystectomy (excluding appendectomy and hemorrhoidectomy), will

also be excluded. Additionally, participants with underlying conditions that could potentially cause chronic diarrhea, such as hyperthyroidism, chronic pancreatitis, and lactase deficiency, will not meet the eligibility criteria. Participants with a history of major psychiatric disorders within the past two years and those who have experienced acute infectious diseases within the past two weeks will be excluded. Moreover, participants with impaired liver or kidney function, or with levels of aspartate aminotransferase, alanine transaminase, blood urea nitrogen, and creatinine exceeding two times the upper limit of normal at the screening visit will also not be eligible. Participants with uncontrolled hypertension, cardiovascular diseases, primary hyperaldosteronism, or electrolyte disorders, such as hypokalemia, will be excluded.

Furthermore, individuals who have taken certain medications within the past four weeks, including systemic steroids, antipsychotics, antidepressants, anti-anxiety medications, Z-drugs, and narcotic analgesics, will be excluded. Those who have taken specific medications within the past two weeks, such as antibiotics, gastrointestinal prokinetics, serotonin receptor agonists and antagonists, non-steroidal anti-inflammatory drugs, dietary fiber supplements, bulk-forming laxatives, probiotics, or herbal medicines containing the same ingredients as the investigational product, will not meet the criteria for enrollment. Other exclusion criteria for this study can be found on the following clinical registration webpage: https://cris.nih.go.kr/cris/search/detailSearch.do?seq=24920

Intervention

MGT and Placebo Granules

Participants assigned to the experimental group will receive orally administered MGT granules at a dose of 10 g (one sachet) three times daily for four weeks. Concurrently, participants allocated to the placebo group will be administered placebo granules orally, totaling 10 g, three times daily over the same four-week timeframe. It is recommended that both the investigational products be taken 30 min after meals.

The detailed names and dosages of the constituent herbs of the MGT granules are listed in Table 1. Individual herbs were placed in extraction vessels. Subsequently, purified water was added at a proportion of 8–10 times the weight of the

Table 1 Names and Dosages of Constituent Herbs in 10 g of Modified Gwakjeongtang (MGT) Granules*

Herbal Name	Scientific Name	Part Used	Dosage
Taraxaci Herba	*Taraxacum platycarpum* [Asteraceae]	Whole plant	3.32 g
Geranii Herba	*Geranium thunbergii* [Geraniaceae]	Aerial part	3.32 g
Dolichoris Semen	*Lablab purpureus* subsp. *purpureus* [Fabaceae]	Seed	3.32 g
Plantaginis Semen	*Plantago asiatica* [Plantaginaceae]	Seed	2.49 g
Agastachis Herba	*Agastache rugosa* [Lamiaceae]	Aerial part	2.49 g
Perillae Folium	*Perilla frutescens* var. *crispa* [Lamiaceae]	Leaf and twig	1.66 g
Angelicae Dahuricae Radix	*Angelica dahurica* [Apiaceae]	Root	1.66 g
Citri Unshius Pericarpium	*Citrus* × *aurantium f. deliciosa* [Rutaceae]	Ripe pericarp	1.66 g
Poria Sclerotium	*Wolfiporia extensa* [Polyporaceae]	Sclerotium	1.66 g
Poria Sclertum Cum Pini Radix	*Wolfiporia extensa* [Polyporaceae]	Sclerotium attached to the roots of pine trees	1.66 g
Zizyphi Semen	*Ziziphus jujuba* [Rhamnaceae]	Seed	1.66 g
Magnoliae Cortex	*Magnolia obovata* [Magnoliaceae]	Bark	1.45 g
Pinelliae Tuber	*Pinellia ternata* [Araceae]	Tuber	1.45 g
Arecae Pericarpium	*Areca catechu* [Arecaceae]	Pericarp	1.04 g

(*Continued*)

Table 1 (Continued).

Herbal Name	Scientific Name	Part Used	Dosage
Syzygii Flos	*Syzygium aromaticum* [Myrtaceae]	Flower bud	1.04 g
Amomi Fructus	*Wurfbainia villosa* [Zingiberaceae]	Ripe fruit or seed mass	1.04 g
Alpiniae Officinari Rhizoma	*Alpinia officinarum* [Zingiberaceae]	Rhizome	1.04 g
Glycyrrhizae Radix et Rhizoma	*Glycyrrhiza uralensis* [Fabaceae]	Root and rhizome	0.83 g
Zingiberis Rhizoma Recens	*Zingiber officinale* [Zingiberaceae]	Rhizome	1.24 g

Notes: *10g of MGT granules contain 4.34g of dried extract, which is obtained through water extraction of the combined herbs listed in the table.

herbs. The mixture underwent extraction at a temperature of 95–105 °C for a duration of 3 h, followed by filtration. The resulting filtrate was then concentrated under reduced pressure, maintaining the temperature below 60 °C, to yield a soft extract. This concentrated extract was subsequently vacuum-dried at a temperature range of 65–75 °C, resulting in the production of a dried extract with an approximate yield of 12.8%. The dried extract was blended with excipients, specifically cornstarch and lactose monohydrate, to create the MGT granules. A single dose of the MGT granules, amounting to 10 g (one sachet), incorporates 4.34 g of the dried extract. To ensure quality control, it is required to contain a minimum of 16.1 mg of hesperidin in each single dose.

In contrast, the placebo granules consist of corn starch, lactose monohydrate, cocoa extract, caramel color, gardenia yellow color, and ginseng flavor powder. These placebo granules have been intentionally formulated without any active ingredients and designed to resemble the brown color, odor, and taste of the MGT granules. The manufacturing process of the investigational products (the MGT and placebo granules) adhered to quality standards and was conducted at the Herbal Medicine Production Center, National Institute for Korean Medicine Development, following the Good Manufacturing Practice guidelines.

Criteria for Discontinuing Allocated Interventions

In the events of serious adverse events occurring in participants, and upon the investigator's assessment that further administration is inappropriate, adverse events reaching a severity level that renders continuous administration unsuitable, or symptoms deteriorating to the extent that alternative treatment becomes necessary, the allocated interventions will be discontinued. There are no plans to modify the allocated interventions.

Procedure for Monitoring Adherence

The investigational products will be dispensed every two weeks, along with an additional provision worth 3 d of medication incorporated into the two-week supply to account for potential delays arising from window visits (equivalent to a total of 17 d worth of medication). During subsequent visits, participants will be requested to bring both the remaining medication and empty sachets of the investigational product they have consumed. Adherence will be calculated by assessing the ratio of the actual amount of the investigational product consumed by the participant to the prescribed amount (%) during the given period. The participants will be strongly encouraged to maintain a compliance rate of 70% or higher.

Permitted and Prohibited Concomitant Interventions

Permitted concomitant medications: participants who have been using medications not considered as contraindications for a minimum of four weeks before engaging in the clinical trial will be allowed to continue their usage, which is subject to the investigator's discretion. Additionally, medications intended for the short-term treatment of other conditions can be used after consultation with the investigator. All concomitant medications used throughout the study period will be monitored during each visit and documented.

Prohibited concomitant medications: throughout the course of the clinical trial, the use of specific medications that might impact participant symptoms or influence trial outcomes will be restricted. The prohibited medications are consistent with those listed in the exclusion criteria.

Outcomes

Primary Clinical Outcome

The primary outcome of this study will be assessed using the overall response rate. An overall responder among individuals with IBS-D is defined as a participant who showed a daily response rate exceeding 50% during the four-week treatment period. A daily responder, in turn, is defined as a participant who experienced a minimum of 30% reduction in abdominal pain intensity in comparison to their baseline (referred to as an abdominal pain intensity responder). Additionally, the participant should have a BSFS score of < 5 for all bowel movements on that particular day or in the absence of any bowel movements (referred to as a stool consistency responder).[19,20] Participants will be instructed to record their daily abdominal pain severity (worst abdominal pain score in the past 24 h) and stool consistency using the BSFS[21] throughout the entire study duration.

Secondary Clinical Outcomes

Secondary outcomes will encompass response rates to abdominal pain intensity and stool consistency, each measured separately. The definitions of daily responders for abdominal pain intensity and stool consistency have been provided above. An individual will be deemed a responder if their daily response rate exceeds 50% during the evaluation period for each outcome.

To assess participant perceptions of change anchors, a global symptom assessment for the following three key aspects will be conducted: "How would you rate your abdominal pain overall over the past 7 days?" "How would you rate your diarrhea overall over the past 7 days?" and "How would you rate your IBS symptoms over the past 7 days?" This assessment will be conducted at weeks 2, 4, and 8.

Furthermore, numeric appraisal of abdominal pain (average daily abdominal pain) and assessment of the number of pain-free days (defined as days with abdominal pain rated < 3 on a 0–10 scale) will be employed. Similarly, the numeric evaluation of stool consistency (average daily frequency of BSFS type 6 or 7 and the number of days experiencing BSFS type 6 or 7) will serve as a secondary outcome.[22]

In addition, the IBS Symptom Severity Scale (IBS-SSS)[23] and IBS Quality of Life (IBS-QOL)[24,25] will be used to assess symptom severity and quality of life related to IBS. To evaluate overall quality of life, the EuroQol-5 Dimension-5 Levels (EQ-5D-5L)[26] and WHO Quality of Life Assessment Instrument Abbreviated Version (WHOQOL-BREF)[27] will be employed. The IBS-SSS will be assessed at weeks 0, 2, 4, and 8, whereas the IBS-QOL, EQ-5D-5L, and WHOQOL-BREF will be assessed at weeks 0, 4, and 8.

Safety Outcomes

Adverse events will be meticulously recorded during each visit. The severity of the observed adverse events and their potential relationship with the investigational product will be evaluated. Additionally, any clinically significant alterations in vital signs or laboratory test results will be monitored. Vital signs will be assessed at each visit, and laboratory tests will be conducted at weeks 0, 2, and 4.

Exploratory Outcomes

The exploratory outcomes will encompass psychological scales such as the Beck Depression Inventory,[28,29] Beck Anxiety Inventory,[30,31] and Pain Catastrophizing Scale.[32,33] Additionally, gastrointestinal symptoms will be assessed using the Gastrointestinal Symptom Rating Scale[34] and the Gut Quotient.[35] Recognizing the significance of pattern identification in herbal medicine prescriptions, the participants' Cold, Heat,[36] Deficiency and Excess[37] pattern scores will be evaluated using a pattern identification questionnaire. To measure participants' trait characteristics, exploratory assessment will involve the Empathy Quotient,[38] Autism-Spectrum Quotient,[39] Obsessive-Compulsive Inventory-Revised,[40] and a Social Network Questionnaire. Furthermore, emotional stimulus tasks will be conducted, encompassing participants' self-reported emotional ratings and capturing their facial movement response under emotional stimuli.[41] Additionally, the superficial body temperature of the abdominal region will be assessed, recording the temperature of five acupoints, including CV4, CV12, CV17, and bilateral ST25.[42,43] Blood samples will be collected from the participants for genetic and methylation analyses, assessment of inflammatory cytokines (Tumor necrosis factor-α, Interferon-γ, Interleukin-1β, Interleukin-6, Interleukin-8, Interleukin-10),[44] and analysis of exosomes. Evaluation of exploratory outcomes is scheduled for weeks 0 and 4.

Participant Timeline

During the screening phase, participants will be guided to maintain a record of their abdominal pain and stool patterns in a diary for a span of two weeks, ensuring a minimum of 10 d. Following this screening period, participants who meet the inclusion and exclusion criteria will be eligible for enrollment in the clinical trial. The enrolled participants will then be randomly assigned to either the MGT or placebo groups. Participants will be instructed to take the MGT or placebo granules three times a day for a period of four weeks. Over the course of the four-week treatment phase and the subsequent four-week period following the completion of medication, the participants will continue the practice of recording their abdominal pain and stool patterns in the diary. IBS symptoms will be assessed at three distinct junctures: prior to commencing medication (week 0), upon concluding medication (week 4), and four weeks post medication completion (week 8). A schematic diagram of this trial is shown in Figures 1 and 2.

Sample Size and Recruitment

This clinical trial serves as a preliminary investigation aimed at assessing the efficacy and safety of MGT in comparison with a placebo for individuals with IBS-D. Based on the minimum recommended sample size for exploratory studies,[45]

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	-14~10 days	Week 0	Week 2 ± 3d	Week 4 ± 3d	Week 8 ± 5d
ENROLMENT:					
Informed consent	X				
Eligibility screen	X				
Allocation		X			
INTERVENTIONS:					
MGT granules			●	●	
Placebo granules			●	●	
ASSESSMENTS:					
Abdominal pain, Stool pattern diary	X	X	X	X	X
Global symptom assessment			X	X	X
IBS-SSS		X	X	X	X
IBS-QOL, EQ-5D-5L, WHOQOL-BREF		X		X	X
BDI-II, BAI, PCS		X		X	
GSRS, GQ		X		X	
KM pattern questionnaire		X		X	
EQ, AQ, OCI-R		X		X	
Emotional task		X		X	

Figure 1 Schedule of enrollment, interventions, and assessment.

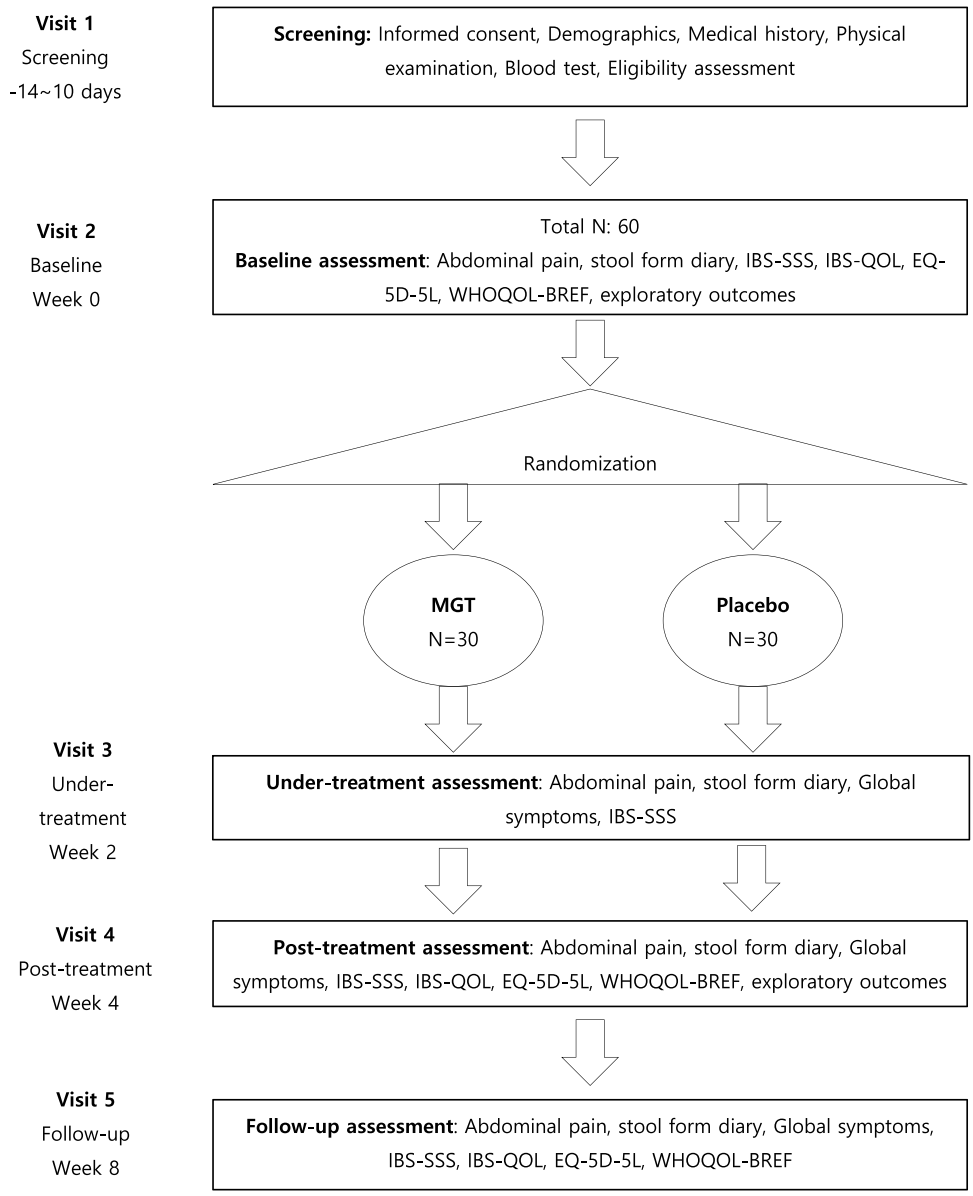

Figure 2 Schematic diagram of the planned trial.

we determined a sample size of 28 participants per group. Accounting for an anticipated dropout rate of 5%, the final target sample size was established at 30 participants per group, resulting in a total of 60 participants.

The participants will be recruited between August 2023 and October 2024. Authorized recruitment notifications endorsed by the Institutional Review Board (IRB) will be affixed to the bulletin boards of the clinical trial institution. Furthermore, these notifications will be available on the institution's official website. Online advertising platforms will also be engaged to facilitate recruitment. If any delays arise in participant enrollment, local advertising methods, such as subway and bus advertisements, will be employed as necessary.

Random Allocation and Blinding

Participants in this clinical trial will be allocated through block randomization using mixed block sizes of four and six. An independent biostatistician generated the random allocation sequence using SAS® software (Version 9.4 or higher, SAS Institute Inc., Cary, NC, USA). The biostatistician provided the generated random number table to the person responsible for packaging the investigational products. The investigational products were packaged and labelled using a random allocation sequence.

Allocation concealment will be maintained through sequentially-numbered, identically-packaged, and labelled investigational products, except for random numbers. The participants enrolled in the trial will be assigned random numbers sequentially. The allocation will remain blinded to both the participants and investigators.

Data Collection and Management

The collection of data on daily abdominal pain intensity and stool form constitutes a vital aspect in evaluating the primary outcomes of this study.[46] The participants will be provided with instructions to use a mobile application capable of recording daily stool forms and abdominal pain intensity. Throughout the screening phase, the participants will be educated on the application's functionality and given time to familiarize themselves with its features. The participants will have the flexibility to input information whenever required. Moreover, by leveraging the application's capabilities, a daily alarm will be set to prompt participants to record their most severe abdominal pain intensity within the past 24 h and daily stool condition once a day. Other patient-reported outcomes will be collected using paper-based questionnaires. We will employ the validated Korean versions of the questionnaires.

Data collected from various sources, including mobile application reports, written questionnaires, and laboratory test results documented in electronic medical records, will be entered into an electronic case report form (eCRF). During the development of the eCRF, data value ranges were established to mitigate errors. A clinical research associate will meticulously review and verify all data inputs in the eCRF to ensure their accuracy against the values in the source documents.

Statistical Methods

Statistical Methods for Analyzing Primary Clinical Outcome

The numbers and proportions of overall responders in each group at treatment completion (week 4) will be presented. Logistic regression analysis will be used to assess differences between the groups, yielding odds ratios (ORs) and their corresponding 95% confidence intervals (CIs).

This trial will serve as a pilot feasibility study aimed at exploring the effect size of MGT granules in comparison with placebo granules. The necessary sample size for subsequent definitive trials will be calculated based on the estimated effect size derived from the trial results.

Statistical Methods for Analyzing Secondary Clinical Outcomes

Binary variables: For response rates of abdominal pain intensity and stool consistency, we will present the count and proportion of overall responders within each group upon treatment completion. Using logistic regression analysis, we will compare the groups, furnishing ORs and the corresponding 95% CIs.

Continuous variables: An approach utilizing a mixed-effects model repeated measures (MMRM) will be adopted for each group and visit. This model will incorporate fixed factors representing the group and visit, with participants as random factors, accounting for the interaction between the group and visit. In cases where statistically significant variations are observed in demographic, sociological, or potentially influential IBS-related variables, additional fixed factors may be introduced. The results of the analysis will be presented as means and 95% CIs. If baseline values exhibit notable disparities between the groups, a supplementary analysis using analysis of covariance (ANCOVA) will be performed. This analysis will involve adjusting for baseline values as covariates.

For the clinical outcome analysis, a Full Analysis Set (FA) will be employed, and the per-protocol set (PP) will be used as a supplementary. The FA set will consist of participants who meet the selection and exclusion criteria, have received a random allocation, and underwent at least one assessment of the primary efficacy variables after taking the investigational product. The PP set will comprise of participants from the FA set who exhibit a medication compliance rate of at least 70% throughout the trial, have no missing data for primary efficacy variables, and have not used any concomitant prohibited medications that could affect trial outcomes.

Regarding the handling of missing data, no imputation will be performed for binary variables. Furthermore, for continuous variables analyzed using the MMRM approach, imputation is not necessary. However, in the event of auxiliary ANCOVA for continuous variables, multiple imputation methods will be employed.

Statistical Methods for Analyzing Secondary Clinical Outcomes

All reported adverse events will be presented according to the severity and causality of the investigational product. The occurrence rates of adverse events, adverse events leading to dropout, and occurrence rates of severe adverse events will be analyzed. The rates of clinical trial discontinuation due to treatment failure or adverse events will be presented for each group, along with their 95% CIs. The chi-square test or Fisher's exact test may be performed to compare the observed and expected frequencies among groups for comparing the frequency of adverse events.

Data Monitoring and Auditing

Oversight and auditing of the trial will be conducted by a Clinical Research Associate affiliated with the Korea Institute of Oriental Medicine. The associate will review and ensure the adherence of the trial to the study protocol, standard operating procedures, clinical trial management standards, and relevant regulations. This encompasses confirming the identification, collection, and reporting of serious adverse events; reviewing participant consent forms; assessing compliance with the clinical trial plan; examining eCRF and source documents; verifying the prescription and inventory records of the investigational product; and reviewing essential clinical trial documents, investigator files, and pharmacy records. Primary monitoring will occur within three weeks of enrollment of the first participant and will be conducted at regular intervals thereafter. Interim monitoring visits are planned to take place either after the enrollment of five participants or on a monthly basis, which is contingent on the pace of participant recruitment.

Protocol Amendments

The current version of the protocol is 1.3 (dated 12/04/2023). If an unavoidable protocol amendment is necessary during the course of the study, the revised protocol will be implemented only after approval by the IRB.

Confidentiality and Post-Trial Care

All records containing personal information that could identify the participants will be kept confidential. Participants' records will be managed based on unique identification numbers and initials assigned to them at the commencement of the study. Only authorized individuals will have direct access to the participants' cases and medical records. Any person or institution granted direct access to review clinical trial-related data is obligated to maintain the confidentiality of the participants' identities.

This clinical trial will be conducted in accordance with the principles of the Declaration of Helsinki. Continuous monitoring and observation will be performed in cases of adverse events that occur during the trial period until resolution or stabilization is achieved.

Dissemination Policy

The results of this clinical trial will be submitted to the Ministry of Food and Drug Safety of Korea within one year of the final observation date of the trial participants through the clinical trial information disclosure registration system. Additionally, the study's findings will be disseminated through presentations at conferences and publications in peer-reviewed journals.

Discussion

This protocol outlines a randomized, double-blind, placebo-controlled clinical trial aimed at assessing the efficacy and safety of MGT in patients with IBS-D compared to a placebo. MGT comprises 13 botanical drugs known for their protective effects on the intestinal barrier function,[47] regulation of gastrointestinal motility,[48] and anti-inflammatory and antioxidant properties.[49] Several clinical studies have reported its efficacy in managing IBS symptoms.[50,51] In a previous randomized controlled trial, patients with IBS-D who received Gwakhyang-Jeonggi-San in combination with probiotics for eight weeks experienced an increase in beneficial gut microbiota.[52] Systematic reviews of herbal medicines for IBS treatment have highlighted significant variations in prescription composition, even among those with the same name,

making it challenging to establish uniform efficacy.[13] Therefore, we designed a placebo-controlled clinical trial to assess the efficacy of a standardized prescription of MGT commonly used in South Korea.

Adhering to the guidelines for evaluating clinical trials of IBS treatments,[19] our primary efficacy assessment focuses on overall response rates concerning abdominal pain and stool consistency. While MGT is widely used in traditional Korean medicine for IBS-D treatment, a comprehensive evaluation of its effect on gastrointestinal symptoms has not yet been undertaken. Therefore, in this study, we aim to assess the efficacy using a range of secondary clinical outcomes, including specific assessments of abdominal pain intensity and frequency, stool form and frequency, pattern identification, superficial body temperature in the abdominal region, IBS-related quality of life, and other outcome variables. Moreover, recognizing the significance of psychosocial variables such as anxiety, depression, and stress in the progression of IBS,[53] we will investigate whether the symptoms of depression and anxiety improve before and after administration of the investigational product. Additionally, we will record and analyze the facial movement responses of patients with IBS-D under audio-visual stimuli to explore the various mechanisms through which MGT may regulate psychological symptoms in patients with IBS-D.

This clinical protocol is designed in accordance with established guidelines. The criteria for participant selection and the measured outcomes follow the Clinical Trial Evaluation Guidelines for Therapeutics of Irritable Bowel Syndrome published by the Ministry of Food and Drug Safety of Korea,[19] along with other relevant guidelines.[20,22] We have also followed the recommended protocol reporting guidelines[54] and its extension to traditional Chinese medicine.[55] Additionally, a placebo-controlled double-blind design, which is a reliable way to test the effectiveness of a new drug, will be used. The investigational products were prepared according to manufacturing standards, which adds credibility to our study. The results of this trial will provide objective evidence regarding the efficacy and safety of MGT granules in patients with IBS-D.

Ethics Statement

This study protocol was approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2022-09-005-004).

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Disclosure

The authors report no conflicts of interest in this work.

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