The efficacy and safety of Ojeok-san plus Saengmaek-san for gastro-esophageal reflux-induced chronic cough: a protocol for a pilot, randomized, double-blind, placebo-controlled trial

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Study protocol

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Abstract

Background Gastro-esophageal reflux disease (GERD) is a major cause of chronic cough. GERD-induced chronic cough is difficult to diagnose because some patients do not complain of any gastrointestinal (GI) reflux symptoms. Although chronic cough due to GERD is highly prevalent, no effective treatment is currently available, especially for GERD-related cough without GI symptoms. As the herbal medicines Ojeok-san and Saengmaek-san can effectively treat GERD and cough, we aim to evaluate the efficacy and safety of a combination of these components for relieving chronic cough due to GERD.

Methods This is a study protocol of a randomized, double-blind, placebo-controlled, single-center pilot trial. After one-week run-in period, a total of 30 patients with GERD-induced chronic cough will be randomly allocated to an intervention group (n=15) or placebo group (n=15). Participants will receive 5.76 g of Ojeok-san plus Saengmaek-san or a placebo three times per day for 6 weeks. The primary outcome measures, the frequency and severity of cough, will be recorded using a cough diary. The secondary outcome measures will include a cough visual analog scale, the Leicester Cough Questionnaire (Korean version), Gastrointestinal Symptom Rating Scale, Hull Airway Reflux (hypersensitivity) Questionnaire, Pattern Identification for Chronic Cough Questionnaire, Pattern Identification for Gastroesophageal Reflux Disease, and safety testing. Adverse events will also be reported.

Discussion This will be the first clinical trial to explore herbal medicines for the GERD-related chronic cough, including patients without GI reflux symptoms. This study will provide useful evidence regarding the efficacy and safety of Ojeok-san plus Saengmaek-san treatment. In addition, this trial will offer scientific basis for the combination of herbal medicines. This finding will also serve as an important data for conducting a larger-scale clinical trial on GERD-induced chronic cough.

Trial registration This trial has been registered with Clinical Research Information Service (CRIS) of South Korea (http://cris.nih.go.kr; registration number: KCT0003115). Registered August 28, 2018.

Background

Cough is the most common respiratory symptom encountered in an outpatient practice. This symptom can be classified by duration as follows: acute, <3 weeks; subacute, 3–8 weeks; and chronic, ≥8 weeks [1]. Of these, chronic cough is of interest to respiratory medicine clinicians, because it is associated with a poorer quality of life and complications such as nausea, chest pain, rib fractures, urinary incontinence, syncope, and depression [2].

The main causes of chronic cough include upper airway cough syndrome (UACS), cough variant asthma (CVA), and gastroesophageal reflux disease (GERD). GERD is second or third common cause of this condition [3, 4], although some reports present GERD as the most common cause, occurring in 30–40% of patients [5, 6]. The mechanism of GERD to induce cough involves vagal mediation of the esophageal-tracheal-bronchial reflex triggered by acid reflux into the lower esophagus and aspiration [7, 8]. The incidence of chronic cough due to GERD ranges from 5 to 41% among the adults [9, 10].

The prevalence is varied because of the differences in population. Moreover, GERD-related cough is often difficult to diagnose because it has no symptoms that are caused due to reflux. It has been reported that approximately 70% of reflux-related chronic cough patients are without gastrointestinal (GI) reflux symptoms such as heartburn [10, 11].

GERD related cough patients who do not complain of GI symptoms show no abnormality, even at 24-hour esophageal pH monitoring, so there is a possibility of misdiagnosis. Therefore, American college of chest physicians (ACCP) guideline suggested predicting reflux-cough syndrome by means of excluding other diseases that cause chronic cough [10], and the updated guidelines also support this suggestion [12]. In GERD-related chronic cough patients without the typical symptoms of GERD, the effect of proton-pump inhibitors (PPI) as a standard therapy for GERD might be sometimes ineffective [13]. Therefore, these patients were recommended against PPIs. The only option available for management of such patients is a few lifestyle changes, such as diet modification or elevating the head of their beds [12]. Therefore, a more effective treatment for GERD-induced chronic cough, with or without GI syndromes like heartburn or regurgitation, is required.

There are 56 types of insurance-covered Korean medicine (KM) granules used in Korea. Among them, *Ojeok-san* (OJS) and *Saengmaek-san* (SMS) have been used in this study. OJS are the most frequently prescribed insurance-covered KM granules and are used for digestive disorders. SMS is widely used for relieving cough. This method of prescribing a mixture of herbal medicines is a commonly applied prescription method in Korea.

OJS is a traditional herbal formula comprising of 17 herbal medicines. It is known to treat the symptoms associated with common cold, acute, or chronic gastroenteritis, and stomach cramps [14]. OJS has been widely used to treat digestive disorders including GERD and is approved by the Ministry of Food and Drug Safety of Korea (MFDS) to treat GERD. According to a recent report, OJS acts on the lungs to improve the symptoms caused owing to airway inflammation and pulmonary fibrosis [15]. Therefore, we expect that OJS will effectively reduce upper respiratory tract inflammation caused by reflux.

SMS consists of Liriopis Tuber, Ginseng Radix, and Schisandrae Fructus. SMS moisturizes the respiratory mucosa and inhibits coughing, and has been used mainly for the treatment of dry cough [16]. SMS is also approved by MFDS to treat cough**.** SMS treats coughs that are either caused by pulmonary fibrosis or as a side effect of radiation [17, 18]. Additionally, recent studies have demonstrated that SMS regulates gastrointestinal motility by increasing the activity of Kajal cells in the gastrointestinal tract [19].

Although chronic cough due to GERD is highly prevalent, no effective treatment is currently available, especially for GERD-related cough without GI symptoms. In traditional Korean medicine, the combination treatment with drugs that are effective for each disease has been widely used for comorbidity such as GERD-induced cough. The effects are clear, but scientific evidence of their therapeutic benefits is lacking. OJS plus SMS, the combination treatment for the respiratory and digestive systems, has been used in clinics for a long time. In a previous study, we reported the cases of GERD-induced chronic cough treated

with OJS plus SMS [20]. Moreover, both the drugs are insurance-covered granules; hence, they are economical to the patients.

To diagnose patients with reflux-related cough with or without GI symptoms, this study recruited patients in accordance with the guidelines provided by the ACCP. Subsequently, we aim to explore the efficacy and safety of OJS plus SMS for chronic cough due to GERD. Additionally, the reflux symptoms will be evaluated to determine if there is a difference in the effectiveness of the drug between the group with or without the symptoms of reflux.

Methods/design

The present protocol was designed according to Standard Protocol Items: Recommendations for International Trials 2013 (SPIRIT 2013: see online supplementary file S1). This trial is a randomized, double-blind, placebo-controlled, single-center study, which has been authorized by the MFDS (approval number 31617) and registered with the Korean Clinical Trial Registry (KCT0003115). This trial will be conducted at Kyung Hee University Korean Medicine Hospital. A flowchart of the study is shown in Figure 1.

Figure 1. Study flowchart

This trial has been approved by the Institutional Review Board of the Kyung Hee University Korean Medicine Hospital (KOMCIRB 2018-05-017-001). The protocol complies with both the Declaration of Helsinki and Good Clinical Practice Guidelines. All eligible patients have to provide their signed informed consent prior to enrollment.

Recruitment

Thirty participants with reflux-induced chronic cough will be recruited through advertisements and referrals in Kyung Hee University Korean Medicine Hospital. The participants deemed eligible in screening of the inclusion and exclusion criteria will be recruited as study subjects and assigned to the experimental and control groups as per 1:1 ratio. Each group will be prescribed a drug for 6 weeks.

Participants

Inclusion criteria

We will include participants who 1) are between 19 and 70 years of age; 2) have a history of cough continuously for >8 weeks; 3) have been diagnosed with reflux esophagitis within the last 1 year; and 4) have provided written consent to the clinical trial agreement.

Exclusion criteria

Participants will be excluded from the study if they 1) present with abnormal findings as established by the chest x-rays, pulmonary function test (PFT) with bronchodilator test, fractional exhaled nitric oxide

(FeNO), and nasal endoscopy, that might lead to cough; 2) were diagnosed with acute respiratory diseases (including upper respiratory tract disorders) within the last 1 month; 3) were diagnosed with chronic respiratory diseases (e.g., chronic obstructive pulmonary disease, bronchial asthma, bronchiectasis, interstitial lung disease, and other chronic respiratory diseases) within the last 2 years; 4) were diagnosed with LA grade C or higher GERD within the last 1 year; 5) exhibit symptoms indicative of malignant disease within the gastrointestinal tract (e.g., severe dysphagia, bleeding, weight loss, anemia, bloody stools); 6) history of surgical or endoscopic anti-reflux treatment; 7) Currently, are suffering from a disorder, such as postnasal drip syndrome, active infection requiring systemic antibiotic therapy, or a blood-clotting disorder; 8) have a lifetime smoking history of ≥20 packs (400 cigarettes); 9) have used an angiotensin-converting-enzyme inhibitor during the previous 4 months; 10) have used cough medicines, glucocorticoids, leukotriene receptor antagonists, anticholinergic drugs, long-acting β2 agonists, antihistamines, proton pump inhibitors, histamine receptor antagonists, mucosal protective agents, gastrointestinal motility promoters, antacids, antidepressants, anxiolytics, lower esophageal sphincter agonists, or any herbal medication within the previous 2 weeks; 11) have allergies or sensitivities to the experimental medicine/placebo; 12) have a body mass index (BMI) <18.5; 13) have an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level at least two-fold higher than the upper normal limit or a serum creatinine level at least 1.2-fold the upper normal limit; 14) have a mean cough diary score of <2 during the 1-week run-in period; 15) record <10 entries in the cough diary during the 1-week run-in period; 16) have a history of malignant tumors (e.g., lung or esophageal cancer) within the last 5 years; 17) are excessive drinkers; 18) are pregnant or breastfeeding; 19) do not consent to use birth control during the trial; 20) participated in clinical trials for the same disease within the past 3 months; or 21) are deemed unsuitable by the investigators.

Rejection and withdrawal criteria

The rejection and withdrawal criteria will be as follows: 1) treatment that could affect the clinical trial results without any instruction by the investigator; 2) failure to adhere to the protocol or compliance rate <80%; 3) a serious adverse event (SAE) during the trial; 4) voluntary withdrawal from the trial; 5) use of drugs such as steroids, persistent bronchodilators, and anti-leukotriene, anticholinergics, proton pump inhibitors, histamine receptor antagonists, mucosal protective agents, gastrointestinal motility promoters, antacids, antidepressants, anxiolytics, and lower esophageal sphincteric agonist preparations during clinical trials; 6) use of any herbal medications; 7) any other reasons deemed inappropriate by the investigators.

Intervention

OJS plus SMS

Subjects in the intervention group will be administered a total 5.76 g of OJS (4.35 g/each) plus SMS (1.41 g/each) granules. The participants will be instructed to consume these granules three times per day for 6 weeks. The dosage is based on the requirements of the MFDS. The OJS and SMS granules are manufactured by Han Kook Shin Yak Pharm Co. Ltd. (Nonsan, Chungnam, Republic of Korea), a company

that has obtained authorization from the Korea Good Manufacturing Practice. Both the OJS and SMS granules and their ingredients have been approved by the MFDS. These ingredients are presented in Table 1. Voucher specimens will be reserved at the research library of Han Kook Shin Yak Pharm Co. Ltd.

Table 1. Composition of *Ojeok-san* and *Saengmaek-san*

Placebo

The control group will receive a total of 5.76 g of OJS and SMS placebo granules. The participants will be instructed to consume these granules three times per day for 6 weeks. The placebo is manufactured by the Han Kook Shin Yak Pharm Co. Ltd. in accordance with the placebo guidelines of the MFDS. Although granules do not contain active ingredients, their appearance, taste, and aroma are similar to the experimental intervention granules. The OJS and SMS placebos comprise of starch, lactose, citric acid, caramel color, and ginseng flavor powder.

All products were packaged by Han Kook Shin Yak Pharm Co. OJS and SMS are packaged in 4.35 and 1.41 g, respectively, and each placebo is packaged in the same amount. OJS and SMS or OJS placebo and SMS placebo will be provided to each randomized participant at visits 1 (week 0 ± 3 days), 2 (week 2 ± 3 days), and 3 (week 4 ± 3 days). The clinical trial drugs and placebo will be stored at the Korean medical clinical trial center (K-CTC) clinical research pharmacy in Kyung Hee University Korean Medicine Hospital. An independent and a well-trained pharmacist will be responsible for all the procedures related to drugs. The study process is outlined in the Figure 2.

Figure 2. Study process

Randomization and allocation concealment

Participants will be assigned randomly in 1:1 ratio to the intervention group (OJS plus SMS group) and control group (placebo group). An independent statistician will conduct participant randomization using a randomization table created with SAS version 9.1.3 for Microsoft Windows (SAS Institute Inc., NC, Cary, USA). After receiving an explanation of the study and providing a consent form to participate in the clinical trial, each subject will be given a screening number (S□□-□□□) in order. Subjects who are finally selected to participate in the clinical trial following the screening test and 1-week window period will be given a registration number (R□□ - □□□). A third party will allocate each subject to a group according to the registration number and the random assignment table.

Blinding

The drug and placebo will be administered by code and by double-blind methods in which the investigator and the participants will not know whether the drug is a test drug or a reference drug. Additionally, the clinical trial pharmacist will be blinded to the treatment allocation. For this purpose, placebo will be made similar to the experimental medicine with respect to the characteristics, taste, and flavor. The medicine manufacturers directly label the code assigned to the experimental medicine and

placebo, and the third party matches the generated random number and code. When a third party registers each study subject, it sends the test number or the control number of the matching test drug to the researcher by telephone, text message, mobile communication application, etc., according to the random number assigned. When a severe or medically significant event occurs, the statistician will uncover the blinding,

Strategies to improve adherence

To improve the participant retention, financial reimbursement will be given to the participants. Scheduling appointment will be made for screening and each visiting date. The mobile text messages will be sent prior to the visit to remind for the day, which is to enhance compliance.

Outcome measures

Primary outcome measurement

The primary outcome will be the cough diary score at week 6. The mean cough symptom score in the cough diary during 1-week run-in period will be set as the baseline score of each participant enrolled in and randomized for the trial. We plan to compare between groups in the mean scores of the cough diary at week 6.

The cough diary is an evaluation scale that divides the severity and frequency of cough into five stages [21]. The subjects will conduct self-evaluations twice daily, and the cough diary will be prepared at 20:00 (daytime, 08:00–20:00) and at 8:00 (nighttime, 20:00–8:00). Patients will be required to evaluate their symptoms twice per day (daytime and nighttime). Cough frequency will be graded on a five-point scale as follows: 0, no cough; 1, infrequent/occasional; 2, several times; 3, many times; and 4, all the time. Cough severity will be graded on a five-point scale as follows: 0, Symptom is not present.; 1, Symptom is present; is not a problem; does not interfere/hinder activity/ interactions/sleep in any way; 2, Symptom is present; is somewhat of a problem; may interfere/hinder certain activities/interactions/sleep; 3, Symptom is present; is a problem; frequently interferes/hinders many activities/interactions/sleep; and 4, Symptom is present; is a major concern; very frequently interferes/hinders most activities/interactions/sleep. The total cough score (range: 0–8) is the sum of the daytime and nighttime cough symptom scores.

Secondary outcome measurement

Cough visual analog scale (VAS): The cough VAS is a rating scale that rates the degree and frequency of coughing on a scale of 0–10 points, with 0 indicating "no cough" and 10 indicating "unbearable cough". After study registration, the investigator will provide each subject with a 2-week self-recording diary at baseline and weeks 2, 4, and 6. The participants will record daily entries and return the data to the investigators on weeks 2, 4, 6, and 8, respectively. We plan to compare between groups for the results of means of cough VAS evaluated at week 2,4, and 6.

Leicester Cough Questionnaire (LCQ-K): The LCQ is a 19-item questionnaire that is used to measure the quality of life according to the cough [22]. These 19 items are divided into three parts: physical, mental, and social. Each item score ranges from 1 to 7 points, and a higher score indicates better health. We will use the validated LCQ-Korean version [23]. The means of LCQ-K score between the groups evaluated at week2, 4, and 6 will be compared.

Gastrointestinal Symptom Rating Scale (GSRS): The GSRS is a widely used and validated self-reported GI symptom scale. It includes 15 symptom items grouped into five symptom areas that can be scored on a seven-point scale [24]. The mean scores of GSRS between the groups evaluated at week 2, 4, and 6 will be compared.

Hull Airway Reflux (hypersensitivity) Questionnaire (HARQ): The HARQ is a self-reported tool that is used to measure airway hyper-responsiveness due to laryngopharyngeal reflux. Symptoms of airway hypersensitivity caused by laryngeal reflux are grouped into 14 items. Each item is scored on a range of 0–5 points, with a maximum total score of 70 points [25]. We plan to compare between groups for the results of means of HARQ evaluated at week 2, 4, and 6.

Pattern Identification for Chronic Cough Questionnaire (PICCQ): The PICCQ is a tool used to identify patterns of chronic cough. Chronic cough is, thus, classified into four patterns: wind-cold, phlegm-turbidity, fire-heat, and deficiency (lung deficiency and kidney yang deficiency) [26]. Using descriptive analysis, the distribution of participants according to each pattern differentiation is depicted as frequency and ratio.

Pattern Identification for GERD: This tool is used to analyze the distribution of pattern in patients with GERD, who complain of cough as the main symptom. Four GERD patterns have been identified: pattern/syndrome of liver qi invading the stomach, spleen-stomach weakness, spleen-stomach dampness-heat, and stomach yin deficiency [27]. The distribution of participants according to each pattern differentiation for GERD is described as frequency and ratio using descriptive analysis.

Safety and adverse event outcomes

Safety

Safety will be assessed using adverse reaction reports and clinical laboratory tests. Liver function tests include AST, ALT, alkaline phosphatase, total bilirubin, and γ-glutamyl transpeptidase levels, and renal function tests include blood urea nitrogen and creatinine levels. Women of childbearing age will be tested for pregnancy. This study will not be collecting additional biological samples. Genetic or molecular analyses are not performed.

Adverse events

An adverse event (AE) is an undesirable and unintended sign, symptom, or disease that does not necessarily have a cause-and-effect relationship with the intervention evaluated in a clinical trial. We will

continuously monitor subjects for AEs and make all related decisions based on both objective and subjective signs, as well as blood test results. All AE will be collected which occur throughout the clinical trial. The decision criteria for AE is as follows; 1) Grade 1 (Mild): It does not decrease the participants' ability to perform normal activities of daily living (function), and only minimally brings discomfort to the participants, which is easy to bear.; 2) Grade 2 (Moderate): It causes discomfort which significantly decreases the participants' ability to perform normal activities of daily living (function).; 3) Grade 3 (Severe or medically significant): It renders the participants of the clinical trial impossible to perform activities of daily living . 4) Grade 4 (Life-threatening consequences); 5) Grade 5 (Death related to AE). SAE referred to any of the following AEs occurring in a participant during the clinical trial: 1) death or danger to life; 2) hospitalization or extension of hospital stay due to an adverse event; 3) permanent or significant failure or degradation of function; 4) development of fetal malformations or abnormalities; 5) other medically important situations. The investigator rapidly reports all SAEs to the sponsor (usually within 24 hours), in order to: 1) ensure patient safety at clinical trial, and 2) meet the MFDS guideline for reporting. The investigator also reports to the Institutional Review Board.

Data collection, management, and monitoring

Data and instrumental measurements will be collected from all subjects at every visit using a paper-based case report form. Data entry and management will be completed by an independent data administrator to ensure data accuracy. Only the principal investigator and sub-investigators delegated by the principal investigator can access the data. The final dataset is only available to the principal investigator and the independent statistician. All procedures will comply with the confidentiality standards for medical data. All documents related to the conduct of clinical trials will be retained by the principal investigator or sub-investigator. The participants' information will be maintained in the storage for a period of 3 years after study completion. Important protocol modifications during this study will be communicated to the Institutional Review Board, trial registry, investigators, trial participants, and the journal of publication. An independent monitoring supervisor affiliated with the Kyung Hee University Korean Medicine clinical trial center would be assigned to contact and visit the researchers regularly and thus supervise the trial process.

The monitoring of this study is conducted by the individuals who are employed at the K-CTC of the Kyung Hee University Korean Medicine Hospital. The monitoring is performed in order to protect participants' rights and welfare, to prove whether reported data related to clinical trials are accurate, complete, and possible to be validated when contrasted against evidence documents, and to check whether a proposal for approved clinical trial and standard management and protocols of clinical trials are abiding regulations. The monitoring of meetings is performed 2-3 times annually. Besides, independent monitoring is conducted by the Korea Institute of Oriental Medicine, a sponsor of our study, in the first phase of patient recruitment and during the mid-phase of the study. This study is a preliminary research conducted by a single institution, wherein the steering committee as well as data management team has not been organized. Management and analysis of data will be performed solely by an independent expert statistician.

Sample size

This is a pilot study that examines the feasibility of conducting a large-scale randomized clinical trial of OJS plus SMS for treating chronic cough in patients with GERD. A pilot study for planning a larger study and estimating its effective size requires an adequate small sample size. We calculated the minimum number of recruiters required for a preliminary study according to the general rule [28]. Each group would require 12 participants with a power of 80% and α-value of 0.05. Assuming a total withdrawal and dropout rate of 20%, we estimated that a total sample size of 30 patients would be required.

Statistical analysis

Statistical analysis will be performed using the SPSS statistical package (ver. 18.0; IBM, Inc., Armonk, NY, USA), and the level of significance will be established at α = 0.05. An independent professional statistician who is blinded to allocation will carry out the data analysis. The intent-to-treat (ITT) analysis will be used as the main analysis, and subordinately we will present per-protocol (PP) analysis. The ITT population will include all participants who have been treated with at least one dose of the study drug and who record and keep a minimum of one day's cough diary. The PP population will include all the participants of the study who have taken more than 80% of the either allocated investigational drug or placebo drug, and returned their self-reported cough diary, which is the primary assessment variable, with a minimum of 34 days' worth of assessment (more than 80% of the total 42 days of data evaluation). The cough diary will be used to compare the cough symptom scores at 6 weeks (visit 4). If the normality test is satisfied, the independent t-test will be used; otherwise, Mann–Whitney U test will be used. However, an analysis of covariance (ANCOVA) will be performed if significant differences in the baseline cough diary values are found between the groups. Inter-group comparisons of cough VAS will be evaluated on weeks 2, 4, and 6. Mean differences in the LCQ-K, GSRS, and HARQ scores will be evaluated at baseline and week 6. Missing values will be replaced by the last observed value of each subject according to the "last observation carried forward (LOCF)" method. This study will not be performing interim analysis.

Post-trail care

This clinical trial will adopt clinical trials insurance, if serious harm has occurred following the clinical trial, the participant of the trial will receive appropriate cover.

Dissemination policy

We will disseminate the results of this clinical trial widely through the conference presentations and published in the relevant journal. The data of this study will not be shared.

Discussion

Approximately 10–59% of cases of chronic cough can be attributed to GERD [29]. To the best of our knowledge, this is the first clinical trial to explore the efficacy and safety of herbal medicines for reflux-

related chronic cough, including patients without GI symptoms. Combination treatment such as OJS plus SMS is common in the clinical field for chronic cough due to GERD, but scientific basis is not yet proven. Therefore, we aim to investigate the feasibility of OJS plus SMS for chronic cough patients due to GERD. This will be a randomized, placebo-controlled, double-blind, parallel arm single-center clinical trial. This clinical trial was designed according to the Consolidated Standards of Reporting Trials guidelines [30]. Validated evaluation tools will be used to assess the severity and frequency of cough and to assess the effects of GERD and chronic cough on the patients' quality of life. Pattern identification is used to reflect the clinical field. We will evaluate the symptoms (e.g., epigastric fullness) related to gastrointestinal diseases that cause gastro-esophageal reflux via abdominal diagnostic methods.

This study is a pilot study, which will provide information about feasibility, on the duration of patient recruitment, dosing period, and whether there are problems that were not considered when planning a protocol, and so on. In the result analysis, primarily, the outcome will be the effectiveness on the cough, and secondarily, identification of the reflux symptoms, and to determine the relationship between the presence of the symptoms and the effect of the drug. In addition, we will try to identify the responder group, which are particularly responsive to the effect of the drugs, using pattern identification tool and abdominal diagnostic method.

However, there are some limitations. First, there is no definitive way with good levels of sensitivity and specificity to diagnose GERD-induced cough [31]. Gastric endoscopy has a sensitivity of less than 20% among patients with reflux-associated chronic cough [32]. Twenty four-hour esophageal pH monitoring or impedance/pH-metry can detect abnormal reflux, but these procedures are invasive and limited with respect to providing clear causal evidence [33]. Therefore, we follow the ACCP guideline to diagnose chronic cough patients with GERD in accordance with this clinical profile [12]. It has been reported that 91% of the patients diagnosed with this clinical profile were patients who responded to the anti-reflux treatment, despite the absence of GI symptoms [12]. We diagnosed GERD-induced chronic cough by conducting tests to eliminate other lung diseases, UACS, CVA, and eosinophilic bronchitis as the main causes of chronic cough in patients diagnosed with GERD. Therefore, we excluded smokers, subjects on angiotensin-converting-enzyme inhibitor therapy, and those with abnormal findings on the thoracic radiography. Subsequently, we checked for the other causes of chronic cough based on the ACCP guidelines and the Korean guidelines for chronic cough [34]. UACS, CVA, and eosinophilic bronchitis were checked for and excluded by the paranasal sinus X-ray and nasal endoscopy, by the PFT with bronchodilator test or methacholine bronchial challenge test and by FeNO test, respectively. Second, the sample size was small and performed in a single center, which is a characteristic of the pilot study. This study is being conducted to determine the sample size for validating large-scale studies with a pilot study, and to assess the feasibility of the research. Based on the results of this study, large-scale studies will be planned with larger sample sizes.

We hope that this research will provide a scientific basis for the combination of herbal medicines, as well as identify the responder group that is responsive to the effectiveness of OJS plus SMS. In future, we expect to conduct a well-designed clinical trial that would clearly provide a scientific evidence, based on

the results of this pilot study, to confirm the efficacy and safety of OJS plus SMS for the treatment of GERD-induced chronic cough.

Trial Status

The study is currently in the process of recruiting participants. Recruitment of participants commenced on January 4, 2019 and will be completed by August 2020. The protocol version number is KHMC-CCOS-P01, dated June 22, 2018.

List Of Abbreviations

ACCP: American college of chest physicians; AE: adverse event; ALT: alanine aminotransferase; ANCOVA: analysis of covariance; AST: aspartate aminotransferase; BMI: body mass index; CVA: cough variant asthma; FeNO: fractional exhaled nitric oxide; GERD: gastro-esophageal reflux; GI: gastrointestinal; GSRS: Gastrointestinal Symptom Rating Scale; HARQ: Hull Airway Reflux (hypersensitivity) Questionnaire; ITT: intention to treat; K-CTC: Korean Medicine Clinical Trial Center; KM: Koran medicine; LCQ: Leicester Cough Questionnaire; LCQ-K: Leicester Cough Questionnaire (Korean version); LOCF: last observation carried forward; MFDS: Ministry of Food and Drug Safety of Korea; OJS: Ojeok-san; PFT: pulmonary function test; PICCQ: Pattern Identification for Chronic Cough Questionnaire; PPI: proton pump inhibitor; SAE: serious adverse event; SMS: Saengmaek-san; UACS: upper airway cough syndrome; VAS: visual analog scale

Declarations

Ethics approval and consent to participate

This trial has been authorized by the Institutional Review Board of the Kyung Hee University Korean Medicine Hospital (KOMCIRB 2018-05-017-001).

Written informed consent will be obtained from all the participants by the principal investigator or sub-investigators. Informed consent form is presented as an additional file 1.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Y.H.B. and K.I.K. contributed equally to the design and development of the study protocol and are listed as co-first authors. Y.H.B. and K.I.K. wrote the draft of the manuscript; B.J.L and J.H.L contributed to the securing of funding for the project and to the study design; J.K., J.A., H.S.J. and C.Y. participated in the revision of the manuscript. S.J.K., Y.B., J.W.P., K.S.P. and H.J.J checked the methodology. All authors read and approved the final manuscript.

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Tables

Table 1. Composition of *Ojeok-san* and *Saengmaek-san*

jeok-san

Ingredients (Latin name)	Amount (g)
Atractylodis Rhizoma	0.95
Ephedrae Herba	0.2
Citri Unshius Pericarpium	0.4
Magnoliae Cortex	0.08
Platycodonis Radix	0.43
Aurantii Fructus Immaturus	0.31
Angelicae Gigantis Radix	0.37
Zingiberis Rhizoma	0.22
Paeoniae Radix	0.27
Poria Sclerotium	0.02
Cnidii Rhizoma	0.3
Angelica dahurica Bentham et Hooker f., Angelica d	0.31
Pinelliae Tuber	0.22
Cinnamomi Cortex	0.04
Glycyrrhizae Radix et Rhizoma	0.2
Zingiberis Rhizoma Crudus	0.03
Total	4.35

Saengmaek-san

Ingredients (Latin name)	Amount (g)
Liriopis Tuber	0.75
Ginseng Radix	0.30
Schisandrae Fructus	0.36
Total	1.41

Figures

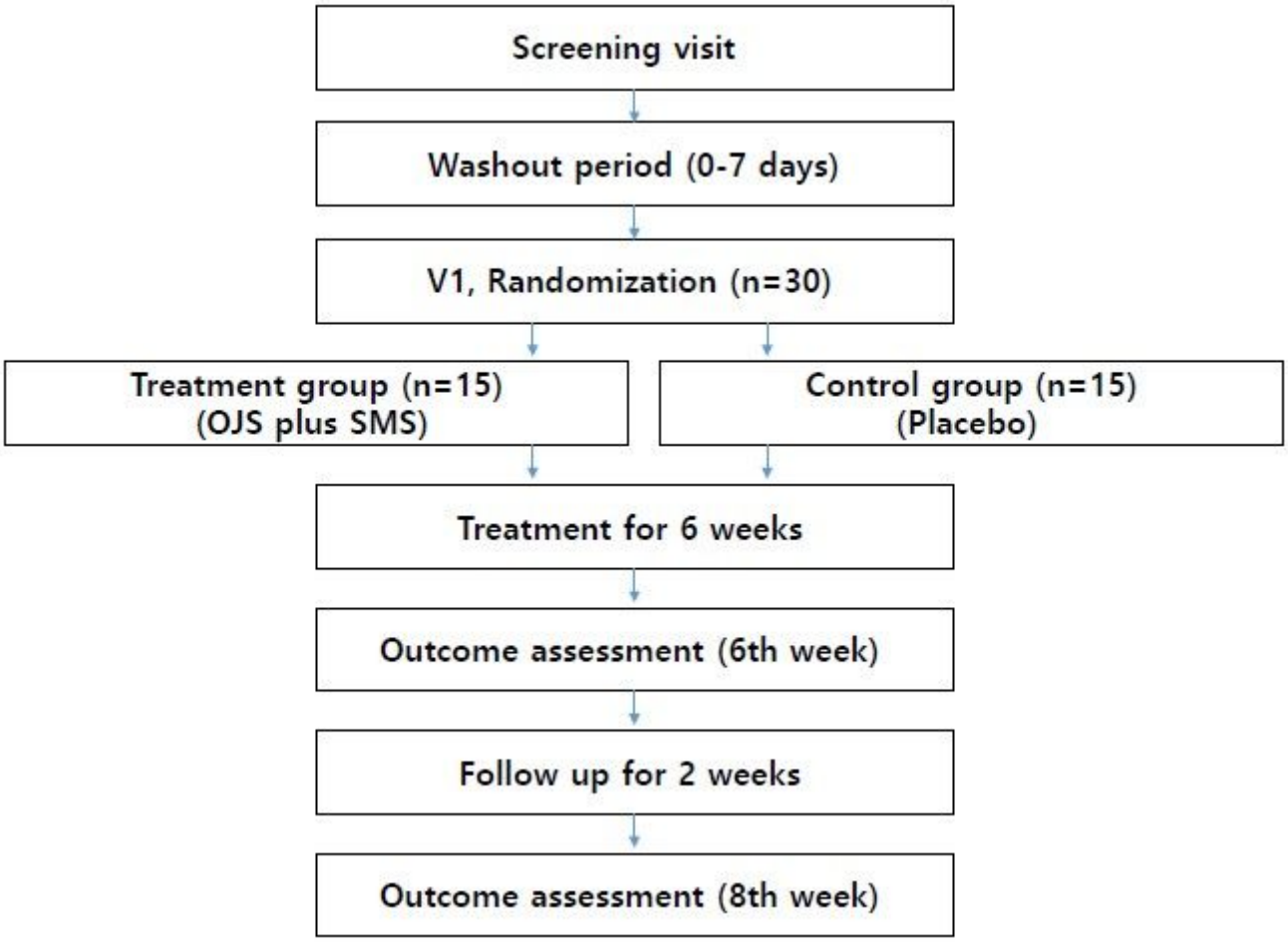

Figure 1

Study flowchart

	STUDY PERIOD						
	Enrollment	Allocation	Post-allocation				Close-out
Time point (Weeks)	-1	0	2	4	6	8	
Visit	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
ENROLLMENT:							
Informed consent	X						
Eligibility Screening:	X						
Demographics	X						
Symptom check	X						
Medical history	X						
Smoking history	X						
Medication history	X						
Height/weight/BMI	X						
Chest X-ray	X						
Nasal endoscopy	X						
Fractional exhaled nitric oxide	X						
Pulmonary function test with bronchodilator test	X						
Methacholine bronchial challenge test*	X						
Paranasal sinuses X-ray*	X						
Pregnancy test*	X						
Allocation		X					
INTERVENTIONS:							
OJS plus SMS		←	—	—	→		
Placebo		←	—	—	→		
ASSESSMENTS:							
Vital signs		←	—	—	—	→	
Cough symptom score**	←	—	—	—	—	→	
Cough VAS**		←	—	—	—	→	
LCQ-K		←	—	—	—	→	
Hull airway reflux questionnaire		←	—	—	—	→	
Gastrointestinal symptom rating questionnaire		←	—	—	—	→	
Korean medical diagnostic pattern questionnaire		←	—	—	—	→	
Abdominal examination		←	—	—	—	→	
Adverse event			←	—	—	→	
Safety	X	X				X	
Database completed and locked							X

* The test will be performed as needed, according to the judgment of the investigator.

**Cough diary: Two-week self-recording worksheets will be provided at baseline and weeks 2, 4, and 6 after registering the study subjects. The subjects will record data daily and return the worksheets to the investigators on weeks 2, 4, 6, and 8, respectively.

BMI, Body Mass Index; LCQ-K, Leicester Cough Questionnaire-Korean version; OJS, *Ojeok-san*; SMS, *Saengmaek-san*; VAS, Visual Analogue Scale.

Figure 2

Study process

Supplementary Files

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