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Original Article

Clinical Efficacy and Safety of Gyebutang Granules Combined with Acupuncture for the Treatment of Knee Osteoarthritis: Protocol for a Multicenter, Randomized, Assessor-blinded, 2-armed Parallel, Controlled Trial

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ABSTRACT

Background: Due to the aging population in Korea, knee osteoarthritis (KOA) has become an increasingly common condition. Many patients with KOA prefer analgesics, herbal medicines, acupuncture, or exercise, rather than arthroscopic surgery or a knee replacement. Gyebutang (GB) granules are a herbal extract widely used to treat KOA in traditional Korean medicine, but there is insufficient evidence of its efficacy and safety.
Methods: A multicenter, randomized, assessor-blinded, 2-armed parallel, controlled clinical trial has been designed to investigate the efficacy and safety of GB combined with acupuncture for the treatment of KOA. There will be 100 patients with KOA enrolled in the study from 3 traditional Korean medicine hospitals. The participants will be randomly allocated to an experimental group (GB and acupuncture) or a control group (celecoxib and acupuncture) in a 1:1 ratio. Both groups will receive acupuncture treatment once a week for 6 weeks; one group will receive GB and the other will receive celecoxib for the same duration.
Results: The primary outcome will be the change of knee osteoarthritic pain, based on scores on a 100 mm visual analog scale. The secondary outcomes will be scores on a numeric rating scale, the Western Ontario and McMaster Universities osteoarthritis index, patient global assessment, European quality of life 5-dimension 5-level scale, and adverse events.
Conclusion: The results of this study will provide evidence of efficacy and safety of GB as a treatment for patients with KOA.

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Introduction

Knee osteoarthritis (KOA) has a high prevalence among the elderly and is a major cause of disability [1]. KOA is characterized by pathological degeneration of the knee joint, including loss of articular cartilage, thickening of the subchondral bone, formation of spurs, and secondary joint inflammation [2]. Patients with KOA typically complain of pain, stiffness, crepitus, swelling, bone tenderness, and reduction in the range of motion as structural damage of the knee joint progresses [3]. These symptoms and functional disability can reduce a patient's quality of life and increase the risk of morbidity and mortality [4].

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KOA in the general adult population has an estimated prevalence of about 24%, however, prevalence increases with age, and the number of patients with KOA is expected to rise as society ages. KOA may affect up to 80% of people aged 65 years or more in some countries [5,6]. Thus, KOA has become a significant public health issue, and is associated with significant medical costs and increasing global economic burden. Currently, in Korea, KOA is the third leading cause of increasing care expenses for inpatients and the 6th leading cause of increasing care expenses for outpatients [7].

In the absence of effective conventional therapies for KOA, patients adopt complementary and alternative medicine (CAM) therapies to help with their chronic pain and reduced function. The National Health Interview Survey 2005 of the United States reported that 41.1% of people with arthritis used CAM [8], and in many European countries, the rate of use of CAM was reported in 1994 to be between 20% and 49% [9]. In Korea in 1999, 53.9% of patients complaining of musculoskeletal symptoms said they have used CAM [10], and the rate of use of CAM in chronic arthritis patients was reported to be 96.6% [11].

These CAM therapies are often used in conjunction with Western medical treatments. According to surveys conducted in 1999 in Canada, and in 1994 in Australia, 40% to 60% of outpatients being treated by rheumatologists used CAM treatments in combination with Western medicine [12,13]. In the United Kingdom in 1994, 28% of outpatients being treated by rheumatology and orthopedics departments, used CAM in addition to Western medical treatment [14]. In Korea, there is a dual medical system in which traditional Korean medicine and Western medicine coexist, so both are often used together to treat diseases [15]. In addition, many CAM therapies such as acupuncture, moxibustion, and herbal medicines are used at the same time to produce synergistic effects rather than being used individually [16]. Among them, acupuncture has been considered as the treatment with effective analgesia and low risk, and is recommended in the management guidelines for KOA [17]. Some studies have reported the efficacy of acupuncture for pain relief and functional improvement in KOA patients [18,19], and meta-analysis reviews also suggested its positive effects [20,21]. Regarding combination treatment, Jia et al [22] reported that performing acupuncture in combination with Western medical treatment, is more effective in managing KOA compared to Western medical treatment alone.

Herbal medicine, a CAM, has been also reported to be effective in treating KOA [23-25]. Gyebutang (GB) granules are a dried decoction of 7 crude herbs whose formula are derived from the Shang Han Lun [26]. GB is approved as an analgesic and antiphlogistic drug by the Ministry of Food and Drug Safety in Korea. Previous studies of GB reported that it provided pain relief and anti-inflammatory effects in response to cold stimuli-evoked or chemotherapy-induced neuropathy, and postherpetic neuralgia [27-30]. It was reported in a case study that GB reduced the volume of synovial fluid in a patient with pustuloticarthro-osteitis [31]. Thus, GB appears to have the potential for reducing the symptoms and functional limitations of patients with KOA. A clinical study is currently underway to validate the efficacy of GB versus placebo for patients with KOA [32]. However, more clinical trials are needed to verify the efficacy and safety of GB in patients with KOA.

In this report, a protocol for a randomized controlled trial was designed to evaluate whether there was an additional effect of treatment with GB granules compared with celecoxib (the active control) while receiving acupuncture as a basic treatment.

Materials and Methods

Objective

The primary aim of this study was to assess the efficacy and safety of GB relative to celecoxib in the treatment of KOA in patients receiving acupuncture as a basic treatment.

Design and setting

This trial will be a multicenter, randomized, assessor-blinded, 2-armed parallel, controlled clinical trial. At the screening visit, patients who want to participate will be given general information about the trial, including its purpose, eligibility criteria, procedures, potential risks and benefits, standards for withdrawal, freedom to withdraw consent, and protection of personal information. Each eligible patient will be asked to voluntarily sign the informed consent document.

Information on each individual, including demographic characteristics, past and present illnesses, and vital signs, will be recorded by a clinical research coordinator. The primary researcher will evaluate the eligibility of participants using the American College of Rheumatology classification criteria for KOA [33], laboratory tests, radiographical examinations, and physical examinations.

There will be 100 participants recruited who satisfy the eligibility criteria that will be randomly assigned to the experimental group (GB and acupuncture) or the control group (celecoxib and acupuncture) at a 1:1 ratio. There will be 7 visits over 6 weeks, during the treatment and assessment periods, and a final visit for follow-up at 12 weeks (Figs.1, 2).

Recruitment

All 100 participants will be recruited from 3 traditional Korean

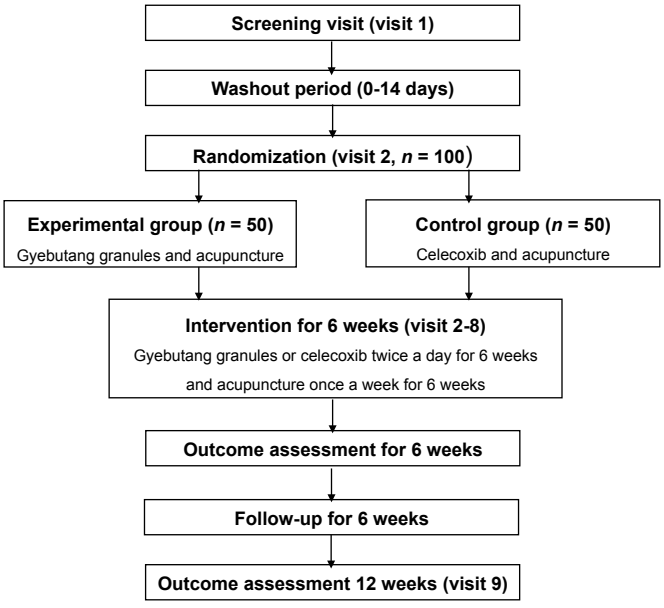

Fig. 1. Flowchart of study. Participants with diagnosis of knee osteoarthritis will be recruited from 3 centers. The experimental group and control group will receive medication (Gyebutang granules or celecoxib) and acupuncture treatment for 6 weeks, followed by a 6-week follow-up period. Outcome measures will be determined at every visit.

	Study period								
	Screening	Treatment							Follow-up
Week	-2~0	0	1	2	3	4	5	6	12
Visit	1	2	3	4	5	6	7	8	9
ENROLMENT:									
Informed consent	X								
Participant education	X								
Demographic characteristics	X								
Physical examination	X							X	
Vital signs	X	X	X	X	X	X	X	X	X
Medical history	X								
Knee X-ray	X								
Laboratory tests	X							X	
Eligibility assessment	X								
Random allocation		X							
INTERVENTION:									
Medication prescription		X		X		X			
Acupuncture treatment		X	X	X	X	X	X	X	
ASSESSMENTS:									
Compliance check			X	X	X	X	X	X	
Pain on NRS	X	X	X	X	X	X	X	X	X
Pain on 100 mm VAS	X	X	X	X	X	X	X	X	X
WOMAC		X	X	X	X	X	X	X	X
PGA		X	X	X	X	X	X	X	X
EQ-5D-5L		X			X			X	
Adverse events		X	X	X	X	X	X	X	X
Concomitant medication and treatment check		X	X	X	X	X	X	X	X
Expectation and credibility questionnaire		X							

Fig. 2. Schedule of enrollment, intervention, and assessment.
EQ-5D-5L, European quality of life 5 dimension 5 level scale; NRS, numerical rating scale; PGA, patient global assessment; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

medicine hospitals: Semyung University Korean Medicine Hospital in Chungju (n = 34), Kyung Hee University Korean Medicine Hospital at Gangdong (n = 33), and Dongguk University Ilsan Oriental Hospital (n = 33). The clinical trial will be advertised on the bulletin boards of these hospitals, the internet, in local newspapers, posters in local communities, and banners in public spaces.

Eligibility criteria

A researcher who is a traditional Korean medicine doctor (TKMD) will obtain voluntary consent from each participant after explaining general information about the trial, and after assessment of the participants eligibility.

Inclusion criteria

1) Age 40 to 69 year-old.
2) Diagnosis of KOA according to the American College of Rheumatology criteria [33], and (a) and (b) below:
   (a) Presence, within the previous 6 months, of unilateral or bilateral knee arthritic pain during weight bearing activity.
   (b) Pain from KOA rated as more than 40 mm on a 100 mm visual analog scale (VAS).
3) Agreement to participate and signing an informed consent document.
4) Considered as trustworthy and willing to cooperate with the trial for the next 3 months.

Exclusion criteria

1) Traumatic knee injury within the last 6 months.
2) An operation of the knee within the last 6 months.
3) Intra-articular knee injections (including steroids and mucus supplements) within the last 3 months.
4) Suspicion of an inflammatory arthritis, such as rheumatoid

arthritis, an infectious disease, or an autoimmune disease, based on physical and diagnostic examinations.
5) In receipt of treatment for a mental disorder, such as depression and schizophrenia.
6) Liver disease (AST or ALT level more than 2-fold above the normal limit).
7) Renal disease (serum creatinine > 2.0 mg/dL).
8) Other diseases that may interfere with treatment, such as serious gastrointestinal disease, cardiovascular disease, hypertension, diabetes, kidney disease, liver disease, thyroid dysfunction, or hemorrhagic disease.
9) Contraindication or hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs).
10) Being pregnant or breast-feeding.
11) Judged by the researcher as unsuitable for treatment with herbal medicine.
12) Participation in other clinical trials, within the last 4 weeks or currently participating in other clinical trials.

Randomization and allocation concealment

An independent statistician will generate a randomization list for group allocations using SAS Version 9.3 (SAS Institute Inc., Cary, NC, USA). Opaque envelopes, with randomized allocations sealed inside, will be sent to each institution, and kept in a double-locked cabinet. The manager of the randomization code will open a random envelope after a participant has met the eligibility criteria, and will allocate the participant accordingly. The manager will be the only allocation administrator to conceal random sequences until end of the study. An allocation log will be recorded in a separate file. The random sequences will be kept by the manager during the clinical trial period and concealed until the occurrence of the event predefined as a reason for code-breaking.

Blinding

This study cannot be double-blinded because the appearances (size and shape) of the medications (GB and celecoxib) are very different. Thus, only the assessor will be blinded in this open-label trial. To maintain blinding of the assessor, only the clinical research coordinator will handle random allocations, and will only provide the assessor with limited information about the participants. The assessor will perform written assessments in the case report form (CRF) without knowing a participant's allocation, and will have minimal conversation with participants when completing the documentation.

Interventions

Medication

The GB (3.75 g; TSUMURA, Ibaraki, Japan) which consists of Cinnamomi cortex, Paeoniae radix, Atractylodis lanceae rhizoma, Zizyphi fructus, Glycyrrhizae radix, Zingiberis rhizoma, and Aconite tuber (Table 1), will be given to participants in the experimental group twice a day for 6 weeks. Celecoxib (100 mg; brand name Celebrex, Pfizer Ltd., Seoul, Korea) will be given to participants in the control group twice a day for 6 weeks (Fig. 3).

Acupuncture treatment

Participants in both groups will receive acupuncture treatment once a week for 6 weeks. The following 8 acupoints, which are based on a text book, a consensus of TKMDs, and a previous study [34], will be used for each patient: Zusanli (ST36), Dubi (ST35), Liangqiu (ST34), Yinlingquan (SP9), Neixiyan (EX-LE4), Xuehai (SP10), Yanglingquan (GB34), and Ququan (LR8). If a participant has symptoms in both knees, acupuncture treatment will be provided bilaterally at the same time.

Table 1. Composition of Gyebutang Granules.

Medicinal herbs	Ratio (%)
Cinnamomi cortex	20.51
Paeoniae radix	20.51
Atractylodis lanceae rhizoma	20.51
Zizyphi fructus	20.51
Glycyrrhizae radix	10.25
Zingiberis rhizoma	5.12
Aconite tuber	2.56

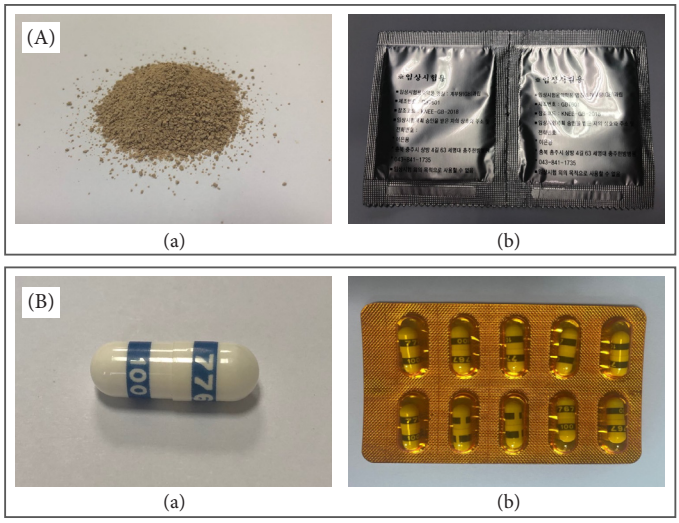

Fig. 3. Gyebutang granules and celecoxib. (A) Gyebutang granules (a) before packing, (b) after packing. (B) Celecoxib (brand name: Celebrex) (a) before packing, (b) after packing

Acupuncture treatment will be implemented by TKMDs who were formally educated in atraditional Korean medicine college for 6 years, licensed to perform acupuncture procedures, and have at least 1 year of clinical experience. Before treatment, the practitioner will place the participant in a supine position, with bent knees, and prior to sterilization of the skin. Sterile, stainless steel, disposable needles (0.30 × 40 mm; Dong Bang Acupuncture Inc., Boryeong, Korea) will be inserted to a depth of 10 to 30 mm, depending on the location of the acupoint. Then, the practitioner will induce De-Qi by rotating and maintaining needle position for 20 minutes. This protocol follows the Standards of Reporting Interventions in Controlled Trials of Acupuncture (Table 2).

Combined treatment

Medications that a participant has taken 4 weeks or more before participating in this clinical trial will be permitted, if the researcher considers that the medication will not affect the study outcome.

Table 2. Checklist for Items in STRICTA 2010*.

Item	Detail	Intervention
1. Acupuncture rationale	1a) Style of acupuncture	Manual acupuncture of traditional Korean medicine
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	1) Textbook 2) Study (Berman et al. 2004) 3) Consensus of traditional Korean medicine doctors
	1c) Extent to which treatment was varied	Standardized treatment
2. Details of needling	2a) Number of needle insertions per subject per session (mean and range where relevant)	8 needles (unilateral) / 16 needles (bilateral)
	2b) Names (or location if no standard name) of points used (uni/bilateral)	Zusanli (ST36), Dubi (ST35), Liangqiu (ST34), Yinlingquan (SP9), Neixiyan (EX-LE4), Xuehai (SP10), Yanglingquan (GB34), Ququan (LR8)
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	10-30 mm
	2d) Response sought	De-qi sensation
	2e) Needle stimulation	Acupuncture manipulation (rotating)
	2f) Needle retention time	20 min
	2g) Needle type (diameter, length, and manufacturer or material)	0.30 × 40 mm sterile, stainless steel and disposable needle (Dong Bang Acupuncture Inc., Boryeong, Korea)
3. Treatment regimen	3a) Number of treatment sessions	7 sessions
	3b) Frequency and duration of treatment sessions	Once a week for 6 weeks
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group	Taking medication (Gyebutang granules or celecoxib) based on random assignment
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	Practitioners and patients can talk about treatment and daily management
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Licensed traditional Korean medicine doctor with more than 1 year of acupuncture treatment experience
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	Not applicable
	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above	Not applicable

* This checklist, which should be read in conjunction with the explanations of the STRICTA items, is designed to replace CONSORT 2010's item 5 when reporting an acupuncture trial.

Information about these medications (purpose, product name, dose, and duration) will be recorded in detail in the CRF. NSAIDs, topical lidocaine, surgical interventions, steroid injections or oral steroids, psychotropic drugs, narcotic analgesics, or the other treatments (such as physical therapy and moxibustion) to relieve knee pain will not be allowed.

Outcome assessments

Primary outcome assessment

The primary outcome measure will be the mean change in the level of pain as rated on a VAS from week 0 (before treatment) to week 6. The VAS (a standard tool used in clinical studies of pain) is an unlabeled 100 mm line. If a patient score is 0 this will indicate no pain, if the patient indicates the maximum score of 100 mm, this will indicate unbearable pain [35]. The participant will indicate their subjective pain score on the line, and the researcher will record the values in mm at every visit.

Secondary outcome assessments

Pain on the numerical rating scale (NRS) is a widely used method in which a patient selects a number from 0 (no pain) to 100 (unbearable pain) that best describes the intensity of pain [36]. We will use this scale to evaluate participants at every visit.

The Western Ontario and McMaster Universities osteoarthritis index (WOMAC) is a self-reporting questionnaire (24 questions), with 3 subscales that assess pain (5 questions), stiffness (2 questions), and physical function (17 questions) related to KOA. Each question has a 5-points scale (none, mild, moderate, severe, extreme) [37]. Bae et al [38] designed a Korean version of the WOMAC (K-WOMAC) and confirmed its validity. Participants will be evaluated using K-WOMAC at every visit.

The patient global assessment score is a measure of a patient's subjective improvement after treatment [39]. Participants will select 1of 5 options (much improved, minimally improved, no change, minimally worse, much worse) regarding KOA at every visit.

The European quality of life 5-dimension 5-level scale (EQ-5D-5L) is an instrument that assesses health-related quality of life, and

consists of a descriptive system and the EQ-VAS. The descriptive system has 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), with 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems). The EQ-VAS records a patient's self-rated health on a vertical line that has end points labelled as 0 (worst health) and 100 (best health) [40]. We will evaluate participants using this scale at visits 2, 5, and 8.

Additional assessments

The participants will be allocated into cold-heat and deficiency-excess patterns based on a traditional Korean medicine questionnaire (34 questions) developed by Kwon et al [41]. We will perform subgroup analysis and compare the efficacy of medications (GB and celecoxib) depending on the patterns.

All data on costs will be collected using a questionnaire at every visit. It will include direct health care-related costs of treatment and indirect costs, such as transportation expenses, nursing fees, and costs due to lost work days.

We will determine the quality-adjusted life years of participants by asking them to compare living with KOA for 5 years and living without health problems for 1 to 5 years. We will also determine quality-adjusted life years by asking them to compare living with GB or celecoxib with acupuncture treatment. These data will be compared to assess the utility of medications.

Sample size

A previous study reported the mean change of pain on the VAS in the celecoxib group was 16.3 mm at 4 weeks and 24.2 mm at 8 weeks [42]. Thus, based on simple linear regression, we estimated the mean change at 6 weeks maybe 20 mm.

In addition, the mean change in the level of pain as viewed on the VAS for participants given GCSB-5 was about 11 mm at 4 weeks [42]. By comparing the yield of GB and GCSB-5, we estimated that GB may have 70% of the effect of GCSB-5, and therefore we estimated a mean change in the GB group of about 7.7 mm.

We estimated the standard deviations (SDs) in the GB and celecoxib group would be 20 mm, which is larger than at 4 weeks and smaller than at 8 weeks. Thus, the calculated sample size was 42 per group. To allow for a possible 15% dropout rate, 100 participants will be randomized to each group.

Statistical analysis

Efficacy variables will be analyzed using the intention-to-treat (ITT) and the per-protocol (PP) sets. The Last-Observation-Carried-Forward (LOCF) imputation will be used for missing data from the primary outcome. All variables, excluding the primary outcome, will be analyzed using the available data.

The primary end point will be the mean change of level of pain on the VAS from week 0 to week 6. This value will be presented as a mean and SD, and an independent 2-sample *t*-test will be used to compare the groups. For analysis of secondary outcomes, analysis of covariance will be used to compare groups, with the VAS baseline as a covariate. A 2-way analysis of variance will also be used to assess the interaction between time and group.

The incidence of AEs will be calculated in each group, and the groups will be compared using a chi-square test or Fisher's exact test. To evaluate the values of laboratory test results, weight, and vital signs, continuous data will be presented as the mean and SDs at the time of assessment, and compared to the baseline value using an independent *t*-test or the Mann-Whitney' U test. Categorical data will be presented as frequencies and percentages.

Safety

Participants will be asked to report any adverse events (AEs) occurring during the study period. Although there are no known specific AEs related to use of GB, there is 1 ingredient (Aconite tuber) that may cause AEs such as palpitation, hot flushes, nausea, or glossoplegia. The AEs known to be associated with celecoxib are gastrointestinal disorders, cardiovascular and neuropsychiatric disorders, itching, and rashes. Detailed descriptions of AEs will be recorded in the CRFs, including dates of occurrence and recovery, severity, possible causal relationship with the intervention, and methods used for management. If a serious AE occurs, it will be reported to the Institutional Review Board to determine whether the clinical trial should continue or stop.

In addition, laboratory tests on blood, urine, kidney function, and liver function will be performed at the screening phase and after treatment (week 6). Vital signs (blood pressure, heart rate, and temperature) will be measured at every visit.

Withdrawal criteria

Dropouts or early termination are defined in the following events:

1) Violation in processing eligibility criteria.
2) Serious AEs or a request by the participant to discontinue because of AEs.
3) Identification of an undiscovered systemic disease.
4) Withdrawal of participation request, by the participant or by legal representative, due to unsatisfactory treatment effect.
5) Violation of the protocol by the participant or researcher.
6) Withdrawal of consent by the participant.
7) Failure to participate in follow-up.
8) Use of unpermitted medication or treatment that may affect the results of the study.
9) Compliance less than 80% during the treatment period.
10) Inappropriate progress, as determined by the researcher.

Quality assurance

To guarantee consistency among the 3 institutions, all staff participating in this clinical trial will receive uniform training before the onset of the study. This training will include education about the diagnosis of KOA, participant eligibility criteria, standard operation procedures of the trial, information about medications, manipulation techniques used during acupuncture, and outcome measures.

If the protocol is revised, it will be handled by Korean Medicine Clinical Trial Center of Kyung Hee University Korean Medicine Hospital as the central coordinating facility. Any protocol amendments will be reviewed and approved by the ethics committee before the study application and published via Clinical Research Information Service.

No formal data monitoring committee will be convened for this study. However, regular monitoring will be conducted at each institution to ensure the quality of the trial. A clinical research associate from the Korean Medicine Clinical Trial Center of Kyung Hee University Korean Medicine Hospital will perform cross-checks of the CRFs against source documents, and will evaluate whether the study is being performed according to the protocol.

Data collection and management

All data will be collected in the standardized original CRFs, with no missing data or omission of data. The reasons for any

corrections to the CRF will be explained together with a date and signature of the researcher. Double data entry of CRFs will be checked by 2 independent staff members, and these data will be compared. The records obtained from this clinical trial will be kept confidential in the appointed place, and only authorized staff will have access. After completion of the study, all documents will be retained for 3 years at the participating institutions.

Ethics approval and registration

The protocol was planned using Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines and the revised Standards of Reporting Interventions in Controlled Trials of Acupuncture to guarantee clarity of clinical trial. The procedures of protocol complied with the Declaration of Helsinki and the Korean Good Clinical Practice, and these have been approved by the Institutional Review Board of each clinical trial site (protocol no.: SUHCJ; SMCJH 1806-03, KHUHGD; KHNMCOH 2018-05-008, DUIOH; DUIOH 2018-05-001) and registered in Clinical Research Information Service (KCT0003264) on October 15th, 2018.

Discussion

The purpose of KOA management is to improve a patient's quality of life by reducing pain and increasing mobility [4]. In an effort to achieve these results, and replace current pharmacological treatments with a treatment that has few side effects, practitioners of traditional Korean medicine have used interventions such as acupuncture, moxibustion, and herbal medicines [43].

GB was developed from Gyejitang by blending Atractylodis lanceae rhizoma and Aconite tuber, representative herbal medicines used for clinical treatment of KOA [44]. GB mainly consists of "warm or hot" medicinal herbs, such as Cinnamomi cortex, Zingiberis rhizoma, and Aconite tuber. These components increase vascular permeability and leukocyte migration, resulting in the promotion of the immune system and increased metabolism [30,31,45,46]. Glycyrrhizae radix and Atractylodis lanceae rhizoma inhibit the release of cytokines and the expression of proteins related to inflammation [47-49]. Paeoniae radix reduces pain by relieving muscle strain [50,51], and Zizyphi fructus relaxes the gastrointestinal tract and harmonizes the different herbs [52]. Thus, based on these previous studies, GB appears to be suitable for treating patients who suffer from various symptoms and functional disabilities due to KOA [53]. However, no pragmatic trial has yet provided clinical evidence of its efficacy and safety. There was a study protocol using GB treatment in patients with KOA, but the placebo was set as a control group [32]. We thought that previous study design had a difficulty to provide the clinical evidence.

In traditional Korean medicine clinical practice, various interventions, such as acupuncture, moxibustion, and herbal medicines, are generally given at the same time rather than as a single treatment and this is in addition to Western medical treatments. Thus, the design of this clinical trial had accounted for this and will perform acupuncture as a basic therapy for both groups. This research is a pragmatic clinical trial that will determine whether a particular treatment will be effective when applied in the clinical setting [54,55].

Clinicians have widely used celecoxib to treat osteoarthritis, so it was selected as the active control intervention. Celecoxib is an NSAID that prevents the transformation of arachidonic acid to prostaglandin precursors by the selective inhibition of cyclooxygenase-2. It is less likely to cause gastrointestinal complications than non-selective anti-inflammatory drugs, so short-term use (less than 6 months) is generally acceptable without the need for a proton pump inhibitor. Nevertheless, the gastrointestinal problems caused by celecoxib have been reported, and celecoxib may also increase the risk of adverse cardiovascular events [56,57].

A limitation of this trial is the possibility of bias due to inadequate blinding. However, it is impossible to blind participants and researchers to the identification of the medication, because the appearances of GB and celecoxib are clearly different. In addition, a placebo was not in the design of this trial. Therefore, to overcome this an independent researcher, who will be blinded to group allocations will perform all assessments to reduce the risk of bias.

In this study, we aim to evaluate the efficacy and safety of GB in a manner that would reflect as closely as possible the conditions of daily medical practice. The results of this trial will help patients and caregivers to select a method that is most suitable for the treatment and management of KOA.

Acknowledgments

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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