Journal of Pain Research Dovepress

Open Access Full Text Article STUDY PROTOCOL

Efficacy, Safety, and Economic Feasibility of Dokhwalgisaeng-Tang for Degenerative Knee Osteoarthritis: Protocol for a Multicenter, Randomized, Assessor Blinded, Controlled Trial

Wonnam Kim[1,*], Yeon-Cheol Park[2,3,*], Bonhyuk Goo[2], Jung-Hyun Kim[2], Dongwoo Nam[3,4], Eunseok Kim[5,6], Hyun-Jong Lee[7], Dong-Hyun Pyun[8,9], Hae Sun Suh[8–10], Yoonsung Lee[11], Man S Kim[11], Byung-Kwan Seo[2,3], Yong-Hyeon Baek[2,3]

[1]Division of Pharmacology, School of Korean Medicine, Pusan National University, Yangsan, Republic of Korea; [2]Department of Acupuncture & Moxibustion, Kyung Hee University College of Korean Medicine, Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea; [3]Department of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, Republic of Korea; [4]Department of Acupuncture & Moxibustion, Kyung Hee University College of Korean Medicine, Kyung Hee University Medical Center, Seoul, Republic of Korea; [5]Division of Clinical Medicine, School of Korean Medicine, Pusan National University, Yangsan, Republic of Korea; [6]Department of Acupuncture and Moxibustion Medicine, Pusan National University Korean Medicine Hospital, Yangsan, Republic of Korea; [7]Department of Acupuncture & Moxibustion, College of Korean Medicine, Daegu Haany University, Daegu, Republic of Korea; [8]Department of Regulatory Science, Graduate School, Kyung Hee University, Seoul, Republic of Korea; [9]Institute of Regulatory Innovation Through Science (IRIS), Kyung Hee University, Seoul, Republic of Korea; [10]College of Pharmacy, Kyung Hee University, Seoul, Republic of Korea; [11]Clinical Research Institute, Kyung Hee University Hospital at Gangdong, School of Medicine, Kyung Hee University, Seoul, Republic of Korea

*These authors contributed equally to this work

Correspondence: Yong-Hyeon Baek, Department of Acupuncture & Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea, Tel +82 2 440 6099, Fax +82 2 440 714, Email byhacu@khu.ac.kr

Purpose: Knee osteoarthritis (KOA) is one of the most prevalent degenerative joint diseases worldwide. The herbal decoction, Dokhwalgisaeng-tang (DHGST), has been commonly used in East Asia to treat osteoarthritis. However, there is insufficient evidence to draw clear conclusions concerning its effectiveness and safety for patients with KOA. We aim to determine the efficacy, safety, and economic feasibility of DHGST compared with Celecoxib, an oral COX-2 inhibitor, for patients with degenerative KOA.

Trial Design and Methods: This multicenter, randomized, noninferiority trial, involving 160 participants who will be randomized using block randomization with 1:1 allocation, will compare DHGST and Celecoxib. The total trial period is 24 weeks after random allocation, comprising 12 weeks of treatment and 12 weeks of follow-up. Participants with KOA will be administered 200 mg of DHGST (treatment group) or Celecoxib capsules (control group) for 12 weeks. Efficacy and safety evaluations will be conducted at weeks 0, 4, 8, and 12, and 24. The primary outcome measurement is the Korean Western Ontario McMaster score at week 12. Changes in pain intensity using a 100 mm visual analog scale, changes in quality of life using a EuroQol 5-dimension 5-level self-report survey, and patient satisfaction will also be measured to evaluate effectiveness between the two groups. A trial-based economic feasibility evaluation will be conducted to analyze treatment cost-effectiveness from societal and healthcare system perspectives. Drug safety will be assessed through adverse reactions and laboratory test findings.

Discussion: This trial protocol has the following limitations. Applying a double-dummy design is not possible, as the tablet and granule forms can easily be distinguished visually, and achieving participant blinding is challenging. The trial findings are intended to inform participants, physicians, and other stakeholders in determining whether DHGST could be used as an alternative therapeutic option for KOA.

Trial Registration Number: KCT0008424 (Clinical Research Information Service of the Republic of Korea), registered on 12 May 2023.

Keywords: degenerative joint disease, Dokhwalgisaeng-tang, noninferiority trial, randomized controlled trial

Received: 8 September 2024
Accepted: 21 October 2024
Published: 28 October 2024

Introduction

Knee osteoarthritis (KOA) is one of the most prevalent degenerative joint diseases worldwide. In two population-based national studies, prevalence rates for degenerative KOA in middle-aged and older adults were estimated to be 35.1% in Korea and 37.4% in the United States of America.[1,2] The cost for KOA-related healthcare has increased by 5.7% annually since 1996, amounting to USD 8 billion in 2016.[3] KOA contributes to functional limitations, stiffness, and pain, which impair certain activities and affect quality of life in many older adults.[4] The clinical features of KOA include joint symptoms and pathological changes associated with radiographic features such as the presence of osteophytes.[5,6] The management options available for KOA include several pharmacological and non-pharmacological therapies. Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first-line treatment to relieve pain. However, patients with long-term NSAID usage can experience persistent pain and disability. One study reported that >50% of patients discontinued treatment within a year.[7] Moreover, it has been reported that there was a three-fold increase in the risk of stroke with the use of NSAIDs, a four-fold increase in the risk of cardiovascular death, and a two-fold increase in all-cause death versus placebo.[7–9] Therefore, intermittent or periodic dosing of NSAIDs is recommended in preference to long-term administration.

Dokhwalgisaeng-tang (DHGST; Duhuojisheng-tang in Chinese) is a herbal decoction consisting of 16 herbs that has been used in traditional East Asian medicine for a long time. In the classic Korean medical text, Donguibogam, it is written that it is used for low back and knee pain caused by liver and kidney Yin insufficiency.[10] Even today, it is widely used in clinical settings in Korea, China and Taiwan to improve pain and function due to osteoarthritis. Also, various experiments and clinical studies on Dokhwalgisaengtang have reported its effectiveness in treating osteoarthritis.[10–12] In an experimental osteoarthritis model, DHGST significantly inhibited histological degeneration, vascular endothelial growth factor, and hypoxia-inducible factor-1α expression induced by anterior cruciate ligament transection.[13] Recent systematic reviews and meta-analyses have reported the beneficial effects of DHGST with or without conventional treatments for KOA, lumbar disc herniation, and postmenopausal osteoporosis.[11,14,15] A prospective follow-up study reported that DHGST improved joint function and quality of life in patients with KOA.[16] While DHGST appears effective for KOA, reaching a clear conclusion concerning its effectiveness and safety is challenging. Further high-quality studies are needed to determine whether DHGST can also be used safely and effectively to treat KOA.

In this multicenter, randomized, non-inferiority trial, we aim to compare between Celecoxib, the standard treatment drug for KOA, and DHGST to determine the efficacy, safety, and cost-effectiveness of DHGST for patients with KOA.

Trial Design and Methods

Methods and Design

This will be a multicenter, randomized, assessor blinded, non-inferiority, controlled trial with two parallel arms (1:1 ratio). The trial will be conducted at Kyung Hee University Korean Medicine Hospital in Gangdong, at Kyung Hee University Medical Center, at Pusan National University Korean Medicine Hospital, and at Daegu Haany University Korean Medicine Hospital in Daegu. The efficacy, safety, and economic feasibility of DHGST for patients with degenerative KOA will be assessed in relation to an oral COX-2 inhibitor (Celecoxib), which is frequently prescribed in conventional medicine. The trial protocol has been approved by the Institutional Review Board (IRB) of each site (approval number: KHNMCOH 2022–08-001, KOMCIRB 2022–07-001-001, PNUKHIRB 2022–10-001-001, and DHUMC-D-22023-ANS-01) and is registered at the Clinical Research Information Service of the Republic of Korea (registration number: KCT0008424). All trial procedures will be performed by the investigators in accordance with Declaration of Helsinki and Korean Good Clinical Practice guidelines.

Investigational Product

The investigational product of DHGST for clinical trials was manufactured at the Herbal Medicine Production Center (GMP) of the National Institute for Korean Medicine Development (NIKOM, Gyeongsan, Korea), following the same process as the product approved by the Ministry of Food and Drug Safety (MFDS) of Korea. The dried extracts were produced through a series of steps including extraction, filtration, concentration, vacuum drying, pulverization, process

inspection, and yield calculation. The DHGST dried extract, lactose monohydrate, and corn starch were then mixed through a blending process and subjected to granulation (granulating, drying, and sizing) before being packaged into 5g film pouches. Celecoxib was purchased from Pfizer Korea (Seoul, Korea). Repackaging as an Investigational Product for use in clinical trials was performed by KMEDHub (Daegu, Korea). The Investigational Product used in this clinical trial were labeled in accordance with the labeling standards of Investigational Product and provided to four clinical trial institutions.

Participants

Inclusion Criteria

Inclusion criteria will comprise the following participants: (i) aged 40–70 years; (ii) with KOA-related knee pain present for >3 months; (iii) diagnosed with KOA according to American College of Rheumatology classification criteria for osteoarthritis of the knee, with Kellgren-Lawrence (K-L) grades I–III, as observed on plain knee radiographic images; (iv) with a total Korean Western Ontario and McMaster (K-WOMAC) score of ≥30, as assessed during the screening visit; (v) who agree to discontinue any existing treatment and are able to cooperate with the trial protocol; (vi) who voluntarily agree to participate in the trial; and (vii) with unilateral or bilateral KOA, where the target lesion is decided according to the following criteria:

1. The knee with the higher K-L grade
2. If the K-L grade is the same bilaterally, the knee with the higher level of pain, as indicated by the participant during the screening interview
3. If criteria for (1)–(2) are the same, the right knee will be evaluated

Exclusion Criteria

Exclusion criteria will be as follows: (i) patients with a history of knee joint trauma within the last 6 months; (ii) patients with a history of knee joint surgery or a plan for surgery during the clinical trial period; (iii) patients with a history of any intra-articular injection treatment within the last 3 months; (iv) patients who are suspected of any of the following diseases, based on physical or diagnostic medical examinations, namely, rheumatoid arthritis, autoimmune disease, septic arthritis, inflammatory joint disease, gout, recurrent pseudogout, Paget's disease, joint fracture, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary osteochondrosis, genetic diseases (eg hyperkinesia), or collagen gene abnormalities; (v) patients with musculoskeletal disorders that the researchers deem likely to affect the trial outcome (eg hip or spine-related issues); (vi) patients receiving treatment for mental disorders such as depression and schizophrenia; (vii) patients with liver disease (aspartate transaminase or alanine transaminase levels >2 times the normal range); (viii) patients with renal disease (creatinine clearance, <30 mL/min); (ix) patients with other diseases that may interfere with treatment, such as serious gastrointestinal or cardiovascular diseases, uncontrolled hypertension or diabetes mellitus, serious kidney or liver diseases, or hemorrhagic diseases; (x) patients with concomitant diseases or hypersensitivity reactions for whom the prescription of NSAIDs is contraindicated; (xi) pregnant or lactating women; (xii) patients whom the researcher deems are not suitable for herbal medicine treatment; and (xiii) patients who have participated in another clinical trial within 4 weeks of the start of the clinical trial or who are currently participating in another clinical trial.

Procedure

In total, 160 participants will be recruited via media platforms (eg hospital websites, newspapers, subways, and online advertisements). Participants who meet the eligibility criteria will be recruited competitively at four institutions. All participants will be informed that they can participate voluntarily and can withdraw their consent at any time during the trial period. They will also be provided with essential information concerning the trial protocol, including the purpose, the selection of participants, interventions based on random allocation, schedules, expected benefits and risks, alternative treatment options, and confidentiality in relation to the trial. Those who voluntarily agree and provide their written informed consent form will be screened through the eligibility criteria. Participants meeting the eligibility criteria will be

Table 1 Schedule of Enrolment, interventions, and Assessments

	Study Period					
	Enrollment	Allocation	Post-allocation			Follow-up
Time point (Weeks)	−2 ~	0†	4†	8†	12†	24†
Visit	V1	V2	V3	V4	V5	V6
ENROLMENT:						
Eligibility screen	X	X				
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Dokhwalgisaeng-tang	◆—	——	——	——	——	—◆
Celecoxib	◆—	——	——	——	——	—◆
ASSESSMENTS:						
K-WOMAC		X				X
100-mm Pain VAS	X	X				X
EQ-5D-5L	X	X				X
Satisfaction assessment		X				X
Economic feasibility		X				X
Vital sign	X	X	X	X	X	X
**Laboratory test and electrocardiography*	X				X	
Concomitant medications		X	X	X	X	X
***Pregnancy test*	X					
Cold-Heat Pattern identification		X	X	X	X	X
****Medication Adherence*			X	X	X	

Notes: †Allows (±7D) on specified days, *Complete blood cell count, Blood chemistry examination and urinalysis, **Urine HCG test performed only on women of childbearing age, ***Compare, check and record the remaining amount of investigational drug.
Abbreviations: VAS, Visual Analogue Scale; K-WOMAC, Korean Western Ontario and McMaster; VAS, Visual Analogue Scale; EQ-5D5L, European Quality of Life 5-dimension 5-level scale.

randomly allocated to either a DHGST or Celecoxib group. After a random allocation, five visit sessions for 24 weeks, including 12 weeks of treatment and 12 weeks of follow-up, will be conducted according to scheduled appointments (Table 1).

Interventions

A packet of DHGST contains 5 g of dried extracts of a mixture of 16 herbs in a fixed ratio (Table 2). A capsule containing 200 mg of celecoxib will be used as a control medicine. The participants in the DHGST group will take 5 g of DHGST (one packet) 3 times a day, 30 min after each meal as the investigation drug. The participants in the Celecoxib group will take 200 mg of Celecoxib (one capsule) once a day, 30 min after breakfast. The participants will be provided with 4 weeks supply of medication at each visit, during 12 weeks of the trial period. Owing to the large difference in terms of the weights of the two drugs, double-blinding is difficult and only assessor-blinding will be possible.

Table 2 Components of DHGST Granules

Scientific Name (Latin Name)	Amount (g)
Aralia continentalis Kitagawa (Araliae Continentalis Radix)	0.7
Angelica gigas Nakai (Angelicae Gigantis Radix)	0.7
Paeonia lactiflora Pallas (Paeoniae Radix)	0.7
Loranthus chinensis Danser (Loranthi Ramulus Et Folium)	0.7
Rehmannia glutinosa Liboschitz ex Steudel (Rehmanniae Radix Preparata)	0.5
Cnidium officinale Makino (Cnidii Rhizoma)	0.5
Panax ginseng C. A. Meyer (Ginseng Radix)	0.5
Poria cocos Wolf (Poria Sclerotium)	0.5
Achyranthes bidentata Blume (Achyranthis Radix)	0.5
Eucommia ulmoides Oliver (Eucommiae Cortex)	0.5
Gentiana macrophylla Pallas (Gentianae Macrophyllae Radix)	0.5
Asiasarum heterotropoides F. Maekawa var. *mandshuricum* F. Maekawa (Asiasari Radix et Rhizoma)	0.5
Saposhnikovia divaricata Schischkin (Saposhnikoviae Radix)	0.5
Cinnamomum cassia Presl (Cinnamomi Cortex)	0.5
Zingiber officinale Roscoe (Zingiberis Rhizoma Recens)	0.5
Glycyrrhiza uralensis Fischer (Glycyrrhizae Radix et Rhizoma)	0.3
Dry weight of DHGST water extract	1
Excipients (inactive constituent)	
Lactose Monohydrate	2.7
Corn Starch	1.3
Total	5

Abbreviation: DHGST, Dokhwalgisaeng-tang.

Concomitant Treatment and Participant Drop-Out

The participants may concurrently use drugs considered unrelated to degenerative KOA according to the researcher's judgment. The following drugs and treatments for degenerative KOA cannot be administered concurrently during the 12 weeks of the trial period: (i) analgesics, NSAIDs (including topical agents and patches); (ii) antidepressants, anticonvulsants, and cyclobenzaprine administered for pain control; (iii) intra-articular steroid injections; (iv) intravenous, intramuscular, and oral steroid preparations; and (v) acupuncture, moxibustion, cupping, or physical therapy for the purpose of pain control.

Participants will be dropped from the trial if they meet the following criteria during the trial: (i) new serious protocol violations regarding selection/exclusion criteria are discovered during clinical trial; (ii) it is difficult to proceed with the clinical trial due to serious adverse events (AEs) in the participants or when a participant requests discontinuation of the trial due to AEs; (iii) a participant is found to have systemic diseases that were not detected during the pre-treatment tests and evaluations; (iv) a participant is administered a drug that is expected to affect the evaluation of the safety and efficacy of the investigational drug for clinical trials; (v) a participant requests discontinuation of administration of the investigational drug during the clinical trial or withdraws consent to participate in the trial; (vi) pregnancy or lactation is confirmed during the trial; (vii) it is impossible to track a participant during the test period; (viii) in situations where a serious violation of the clinical trial protocol occurs; and (ix) in other situations where the principal investigator or researcher determines that the trial should be stopped.

Primary Outcome Measurement

The primary outcome measurement to assess efficacy will be changes in total K-WOMAC scores, calculated using baselines scores and scores at 12 weeks (end of the trial period). Differences in terms of changes in total K-WOMAC scores between the two groups will be compared. K-WOMAC is comprised of 24 items, which are divided into three subcategories: pain, stiffness, and physical function. There are five items for pain, two items for stiffness, and 17 items

for physical function. All items are evaluated on a 5-point Likert scale (0, no pain or no difficulty; 4, worst imaginable pain, or difficulty such that help is required). The total K-WOMAC score is derived from the sum of each subcategory, ranging from 0–96.

Secondary Outcome Measurements

The secondary outcome measurements will include changes in total K-WOMAC scores calculated at 4, 8, and 24 weeks and at the baseline, changes in knee pain using a 100 mm pain VAS, changes in quality of life assessed using a EuroQol 5 Dimension 5 Level (EQ-5D-5L) self-report survey, participant satisfaction assessment, and economic feasibility.

Changes in Total K-WOMAC Scores at 4, 8, and 24 weeks

Changes in the total K-WOMAC score will be calculated from scores at 4, 8, and 24 weeks and at the baseline.

Changes in the 100 mm Pain VAS

Knee pain severity will be evaluated using the 100-mm pain VAS at each visit from visit 1 (baseline) to visit 5 (follow-up). Participants will be questioned concerning their pain severity at rest, during exercise, and at night.

Changes in the EQ-5D-5L

The Korean version of the EQ 5D-5L, which is a 20-cm scale with scores ranging from 0 to 100 (0, worst health condition imaginable; 100, best health condition imaginable),[17] will be used to assess the participants' general health status at each visit from visit 1 (baseline) to visit 5 (follow-up). The EQ-5D-5L consists of five questions concerning morbidity, personal care, daily activities, pain/discomfort, and anxiety/depression, with each question rated from 1 to 5 (1, no problem; 2, slight problems; 3, moderate problems; 4, severe problems; 5, extreme problems).

Treatment Satisfaction Assessment

A treatment satisfaction questionnaire will be used to collect information concerning treatment, intention to engage in additional treatment, and willingness to recommend the treatment to other patients, using a 10-point scale on visits 8 (end of treatment), 9, and 10 (end of follow-up). The participants will score each question using a scale ranging from 1 (very unsatisfied) to 10 (very satisfied).

Economic Feasibility Evaluation

A trial-based economic feasibility evaluation will be conducted to analyze the cost-effectiveness of the treatment from both societal and healthcare system perspectives. A cost minimization analysis will be performed if no significant differences in terms of efficacy and/or safety are observed. The final outcome measure will be the incremental costs, which will involve determining cost differences between DHGST and Celecoxib. This trial will examine incurred costs categorized according to direct medical costs, direct non-medical costs, and indirect costs at visits 1 (baseline), 8 (end of treatment), 9, and 10 (end of follow-up). Direct medical costs will be estimated using data obtained from medical institutions and costs paid by the participants. The participants will complete a questionnaire to evaluate direct non-medical costs such as transportation, care-giving costs, and participant time. In terms of indirect costs, a validated Korean version of the Institute for Medical Technology Assessment Productivity Cost Questionnaire will be used to estimate productivity loss costs.[18] Participant time costs and indirect costs will be calculated according to Statistics Korea's wage data.

Safety Assessment

Any new clinical symptoms, signs, and/or abnormal laboratory test results that appear during the trial period will be investigated for safety. AEs are defined as all abnormal events occurring within the trial period, regardless of medication. AEs will be evaluated to determine whether they are related to the investigational drug and will be classified into the following six levels: definitely related, probably related, possibly related, unlikely, not related, and unknown.

Randomization and Allocation Concealment

The 160 participants will be randomized to either a DHGST or Celecoxib group using block randomization with 1:1 allocation. Using SAS (SAS Institute Inc., Cary, NC, USA) software, an independent statistician will perform generation of randomization sequencing, with a block size of 4. The random codes will be enclosed in opaque, sealed envelopes, and prepared by an independently blinded manager and the principal investigator. After screening, all participants will receive a random number upon opening their envelopes.

Blinding

We intend to conduct an open-label trial design given the formulated forms used in this trial are tablets and granules, as achieving participant blinding is not possible. However, group assignment information will not be provided to the evaluators and statisticians that undertake the objective analyses.

Data Collection and Management

All research records, including the source documents, will be handled and cross-checked by two separate researchers, including the case report form. All of the clinical trial datasets acquired during the trial will be maintained with anonymity and confidentiality. Trial documents may be preserved or discarded in accordance with management standards of each IRB. Periodic monitoring of the trial procedure and documents will be conducted to ensure the quality of the trial through adherence to Korean Good Clinical Practice guidelines.

The clinical trial will be monitored by the Korean Medicine Clinical Trial Center at Kyung Hee University Korean Medicine Hospital. Personnel responsible for monitoring will collaborate with investigators to ensure the proper execution of the clinical trial and adherence to the protocol as well as to all relevant regulatory requirements. Monitoring personnel will assess the coherence of the case records and supporting data, as well as the accuracy of the case report details. In instances where discrepancies in supporting data, inadequacies in written content, or ethical conflicts arise, the validity of the relevant elements will be evaluated with the assistance of the data manager. Independent data monitoring is scheduled to take place at a minimum of three intervals: prior to the enrollment of the initial participants, after the acquisition of one-third of the predetermined dataset, and following the finalization and verification of all data entries. However, the interim monitoring frequency may be adjusted in accordance with the risk profile of each trial site.

Statistical Considerations

This is the first clinical trial aiming to determine that DHGST is not inferior to the clinically used Celecoxib administration in the treatment of participants with KOA. One study that compared between Celebrex capsules and herbal medicine in patients with degenerative KOA showed that the pooled standard deviation (σ) for the K-WOMAC index was 21.508.[19] In another study, the minimum clinically important difference for the WOMAC index for degenerative KOA was reported to range from 9.1 to 9.6.[20] In this trial, the noninferiority margin for changes in total K-WOMAC scores between the two groups is set at 9.5. Considering a 1:1 ratio, a 20% dropout rate, and 80% power, it is calculated that at least 80 participants will be needed per group.

An efficacy assessment will be conducted for both the full analysis set (FAS) and the per protocol (PP) analysis group. However, if performed analyses requirements are not met, the FAS analysis will be used as the main analysis method, and a PP analysis will be performed for participants who adhere to >70% of the intended treatment schedule. Demographic evaluation will be conducted using the FAS analysis group and, in the case of safety evaluation, raw data will be analyzed without data correction. Demographic characteristics will be described per group using descriptive statistics. Continuous variables will be presented as frequency, mean and standard deviation, or as median and interquartile range. Continuous data will be compared and tested between the two groups using independent *t*- or Mann–Whitney *U*-tests. For categorical data, chi-square or Fisher's exact tests will be used for the comparisons.

The primary outcome measure in this trial is changes in the K-WOMAC score after 12 weeks compared with baseline. The mean and standard deviation will be presented to reflect the amount of change, and comparisons between the groups will be performed using an independent *t*-test. Among the secondary outcome measures, continuous data will

be analyzed in the same manner as the primary outcome measure. Descriptive statistics (frequency, percentage) will be presented for categorical data, and the two groups will be compared using chi-square or Fisher's exact tests. Trends over time and time-by-treatment interactions will be analyzed using repeated measures analysis of variance (ANOVA).

A cost-minimization analysis will be undertaken to evaluate the lowest-cost alternative on the assumption that the effects on the DHGST and Celecoxib groups will be equal or non-inferior, and that side-effects are also similar or non-inferior. Analysis will be performed from a healthcare system perspective (direct medical costs related to treatment will be estimated) and from a societal perspective (transportation costs, care-giving costs, and productivity loss costs will be estimated in addition to direct medical costs).

For the safety analysis, all AEs reported during the trial will be tabulated and the occurrence rate will be calculated. The proportion of participants who develop AEs in each group will be compared using chi-square or Fisher's exact tests.

Discussion

Osteoarthritis is one of the most prevalent musculoskeletal diseases and affects >250 million people worldwide.[21] KOA accounts for 83% of the global osteoarthritis burden.[21] An evaluation of KOA is based on a radiographic classification and K-L grading approach.[22] Patients with KOA at K-L grades 3 and 4 are considered potential knee arthroplasty candidates.[23] Moreover, an increasing number of patients are receiving total knee arthroplasty.[24] Currently, there is no complete treatment method for osteoarthritis, and concurrent treatment in non-surgical stages and intensive post-operative care are suggested to alleviate medical costs and improve quality of life.[25–28]

Guidelines for osteoarthritis recommend NSAIDs as first-line therapy.[29–32] NSAIDs are a chemically diverse family of agents that inhibit the synthesis of prostaglandins and thromboxane A through cyclooxygenase (COX) blockage.[29] NSAIDs work through inhibiting COX-1 and COX-2 isozyme activity, which contributes to the symptomatic relief of musculoskeletal pain.[29,33] However, long-term NSAID treatment is limited, mainly owing to gastrointestinal, renal, and cardiovascular side-effects.[34] Selective COX-2 NSAIDs are safer alternatives to conventional NSAIDs, owing to their enhanced gastrointestinal safety profile; however, they are associated with increased cardiovascular risks.[35,36] AEs may also be experienced after using hyaluronic acid, steroids, opioid drugs, or patches that contain narcotics.[37]

In Taiwan, a large-scale pharmaco-epidemiologic study of 20,059 patients with osteoarthritis reported that, among a total 32,069 prescriptions, DHGST was most used (26.6%).[12] In vivo, DHGST treatment has been reported to inhibit the NLRP3/NF-κB signaling pathway and relieve inflammatory factors and pathological changes in the knee synovium in a papain-induced osteoarthritis model.[38] A further study reported that the inhibitory effect of DHGST on NLRP3 activation was mediated through Notch1 signaling.[39] A randomized controlled trial suggested that DHGST in addition to Tuina manipulation may alleviate pain, improve stiffness, and quality of life in patients with KOA.[40] A systemic review and meta-analysis of DHGST reported that, in combination with other treatments, physical function improved and pain was reduced in patients with KOA. However, the safety of DHGST is unclear owing to the small number of trials.[11]

This study is a clinical trial to evaluate the efficacy, safety, and economic feasibility of DHGST compared to celecoxib in participants with KOA-related symptoms. Although DHGST has been widely used in traditional medicine for a long time, there is a clear limitation in proving its efficacy due to the lack of evidence-based clinical trials. In modern medicine, the use of NSAIDs is essential in the treatment of patients with osteoarthritis. In particular, celecoxib is a widely used standard treatment for patients with osteoarthritis because it has lower gastrointestinal and cardiovascular risks compared to NSAIDs such as ibuprofen and naproxen.[41] Therefore, this clinical trial aims to demonstrate non-inferiority of DHGST compared to standard treatments with proven efficacy, taking ethical issues into account. In addition, this study will evaluate additional benefits, such as fewer side effects or quality of life improvement, compared to celecoxib through safety and economic evaluation.

A limitation of this protocol is that it is not possible to apply a double-dummy design. In this trial, the form of capsules and granules can easily be distinguished visually; therefore, it is difficult to achieve participant blinding in the trial.

Conclusion

This trial is intended to be undertaken to provide evidence of the efficacy, safety, and economic feasibility of DHGST for participants with KOA. The trial findings are likely to assist patients, physicians, and other stakeholders in determining whether DHGST is an alternative therapeutic option for patients with KOA.

Funding

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant number: RS-2020-KH087677).

Disclosure

The author(s) report no conflicts of interest in this work.

References

1. Hong JW, Noh JH, Kim DJ. The prevalence of and demographic factors associated with radiographic knee osteoarthritis in Korean adults aged >/= 50 years: the 2010–2013 Korea national health and nutrition examination survey. *PLoS One*. 2020;15(3):e0230613. doi:10.1371/journal.pone.0230613
2. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the third national health and nutrition examination survey 1991–94. *J Rheumatol*. 2006;33(11):2271–2279.
3. Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996–2016. *JAMA*. 2020;323(9):863–884. doi:10.1001/jama.2020.0734
4. Swagerty DL Jr, Hellinger D. Radiographic assessment of osteoarthritis. *Am Fam Physician*. 2001;64(2):279–286.
5. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum*. 1998;41(8):1343–1355. doi:10.1002/1529-0131(199808)41:8<1343::AID-ART3>3.0.CO;2-9
6. Spector TD, Hart DJ, Byrne J, Harris PA, Dacre JE, Doyle DV. Definition of osteoarthritis of the knee for epidemiological studies. *Ann Rheum Dis*. 1993;52(11):790–794. doi:10.1136/ard.52.11.790
7. Choi SH, Kim HC, Jang SG, et al. Effects of a combination of polynucleotide and hyaluronic acid for treating osteoarthritis. *Int J Mol Sci*. 2024;25(3):1714. doi:10.3390/ijms25031714
8. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21–e33. doi:10.1016/S0140-6736(17)31744-0
9. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ*. 2011;342:c7086. doi:10.1136/bmj.c7086
10. Seo C-S, Shin H-K. Development and validation of a high-performance liquid chromatography method for quality assessment of oriental medicine, Dokhwalgisaeng-Tang. *Appl Sci*. 2021;11(17):7829. doi:10.3390/app11177829
11. Zhang W, Wang S, Zhang R, et al. Evidence of Chinese herbal medicine Duhuo Jisheng decoction for knee osteoarthritis: a systematic review of randomised clinical trials. *BMJ Open*. 2016;6(1):e008973. doi:10.1136/bmjopen-2015-008973
12. Chen FP, Chang CM, Hwang SJ, Chen YC, Chen FJ. Chinese herbal prescriptions for osteoarthritis in Taiwan: analysis of national health insurance dataset. *BMC Complement Altern Med*. 2014;14:91. doi:10.1186/1472-6882-14-91
13. Chen CW, Sun J, Li YM, Shen PA, Chen YQ. Action mechanisms of du-huo-ji-sheng-tang on cartilage degradation in a rabbit model of osteoarthritis. *Evid Based Complement Alternat Med*. 2011;2011:571479. doi:10.1093/ecam/neq002
14. Xiong Z, Yi P, Zhang L, Ma H, Li W, Tan M. Efficacy and safety of modified Duhuo Jisheng decoction in the treatment of Lumbar Disc Herniation: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2020;2020:2381462. doi:10.1155/2020/2381462
15. Li J, Wang W, Feng G, et al. Efficacy and safety of Duhuo Jisheng decoction for postmenopausal osteoporosis: a systematic review and meta-analysis. *Evid Based Complement Alternat Med*. 2020;2020:6957825. doi:10.1155/2020/6957825
16. Lai JN, Chen HJ, Chen CC, Lin JH, Hwang JS, Wang JD. Duhuo jisheng tang for treating osteoarthritis of the knee: a prospective clinical observation. *Chin Med*. 2007;2:4. doi:10.1186/1749-8546-2-4
17. Kim TH, Jo MW, Lee SI, Kim SH, Chung SM. Psychometric properties of the EQ-5D-5L in the general population of South Korea. *Qual Life Res*. 2013;22(8):2245–2253. doi:10.1007/s11136-012-0331-3
18. Kim H, Park KS, Yoo JE, Kim S, Han S, Suh HS. Cultural adaptation and validation of the Korean version of the iMTA productivity cost questionnaire. *Healthcare*. 2020;8(2). doi:10.3390/healthcare8020184
19. Park YG, Ha CW, Han CD, et al. A prospective, randomized, double-blind, multicenter comparative study on the safety and efficacy of celecoxib and GCSB-5, dried extracts of six herbs, for the treatment of osteoarthritis of knee joint. *J Ethnopharmacol*. 2013;149(3):816–824. doi:10.1016/j.jep.2013.08.008
20. Strand V, Kelman A. Outcome measures in osteoarthritis: randomized controlled trials. *Curr Rheumatol Rep*. 2004;6(1):20–30. doi:10.1007/s11926-004-0080-6
21. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010. *Lancet*. 2012;380(9859):2163–2196. doi:10.1016/S0140-6736(12)61729-2
22. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. *Clin Orthop Relat Res*. 2016;474(8):1886–1893. doi:10.1007/s11999-016-4732-4

23. Goh GS, Schwartz AM, Friend JK, et al. Patients who have Kellgren-Lawrence grade 3 and 4 osteoarthritis benefit equally from total knee arthroplasty. *J Arthroplasty*. 2023;38(9):1714–1717. doi:10.1016/j.arth.2023.03.068
24. Sun W, Yuwen P, Yang X, Chen W, Zhang Y. Changes in epidemiological characteristics of knee arthroplasty in eastern, northern and central China between 2011 and 2020. *J Orthop Surg Res*. 2023;18(1):104. doi:10.1186/s13018-023-03600-3
25. Brophy RH, Fillingham YA. AAOS clinical practice guideline summary: management of osteoarthritis of the knee (nonarthroplasty), third edition. *J Am Acad Orthop Surg*. 2022;30(9):e721–e729. doi:10.5435/JAAOS-D-21-01233
26. Peng H, Ou A, Huang X, et al. Osteotomy around the knee: the surgical treatment of osteoarthritis. *Orthop Surg*. 2021;13(5):1465–1473. doi:10.1111/os.13021
27. Drummer D, McAdam J, Seay R, et al. Osteoarthritis progression: mitigation and rehabilitation strategies. *Front Rehabil Sci*. 2021;2:724052. doi:10.3389/fresc.2021.724052
28. Karia M, Ghaly Y, Al-Hadithy N, Mordecai S, Gupte C. Current concepts in the techniques, indications and outcomes of meniscal repairs. *Eur J Orthop Surg Traumatol*. 2019;29(3):509–520. doi:10.1007/s00590-018-2317-5
29. Magni A, Agostoni P, Bonezzi C, et al. Management of osteoarthritis: expert opinion on NSAIDs. *Pain Ther*. 2021;10(2):783–808. doi:10.1007/s40122-021-00260-1
30. Bruyere O, Honvo G, Veronese N, et al. An updated algorithm recommendation for the management of knee osteoarthritis from the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). *Semin Arthritis Rheum*. 2019;49(3):337–350. doi:10.1016/j.semarthrit.2019.04.008
31. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578–1589. doi:10.1016/j.joca.2019.06.011
32. Ariani A, Manara M, Fioravanti A, et al. The Italian society for rheumatology clinical practice guidelines for the diagnosis and management of knee, hip and hand osteoarthritis. *Reumatismo*. 2019;71(S1):5–21. doi:10.4081/reumatismo.2019.1188
33. D'Arcy Y, McCarberg B. Managing patient pain: a focus on NSAID OTC formulations for relief of musculoskeletal and other common sources of pain. *J Fam Pract*. 2018;67(8 suppl):S67–S72.
34. Essex MN, Zhang RY, Berger MF, Upadhyay S, Park PW. Safety of celecoxib compared with placebo and non-selective NSAIDs: cumulative meta-analysis of 89 randomized controlled trials. *Expert Opin Drug Saf*. 2013;12(4):465–477. doi:10.1517/14740338.2013.780595
35. Zarghi A, Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationships. *Iran J Pharm Res*. 2011;10(4):655–683.
36. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286(8):954–959. doi:10.1001/jama.286.8.954
37. Primorac D, Molnar V, Matisic V, et al. Comprehensive review of knee osteoarthritis pharmacological treatment and the latest professional societies' guidelines. *Pharmaceuticals*. 2021;14(3):205. doi:10.3390/ph14030205
38. Chen W, Wang J, Hua Z, Zhang Y. Du Huo Ji Sheng Tang relieves knee osteoarthritis via suppressing NLRP3/NF-κB inflammatory signals in rats. *Eur J Inflammation*. 2020;18:2058739220942627. doi:10.1177/2058739220942627
39. Chen W-J, Zhuang Y, Peng W, Cui W, Zhang S-J, Wang J-W. Du Huo Ji Sheng Tang inhibits Notch1 signaling and subsequent NLRP3 activation to alleviate cartilage degradation in KOA mice. *Chin Med*. 2023;18(1):80. doi:10.1186/s13020-023-00784-y
40. Chan KH, Ching JYL, Chan KL, et al. Therapeutic effect of Duhuo Jisheng Decoction add-on Tui-na manipulation on osteoarthritis of knee: a randomized controlled trial. *Chin Med*. 2023;18(1):82. doi:10.1186/s13020-023-00737-5
41. Reed GW, Abdallah MS, Shao M, et al. Effect of aspirin coadministration on the safety of celecoxib, naproxen, or ibuprofen. *J Am Coll Cardiol*. 2018;71(16):1741–1751. doi:10.1016/j.jacc.2018.02.036