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Original Article

# Efficacy and Safety of Cheong-A-Won Gagambang (JCE003) on Knee Osteoarthritis: Randomized Controlled Pilot Trial

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**ABSTRACT**

**Background:** The aim of this study was to evaluate the effectiveness and safety of Cheong-A-Won Gagambang (JCE003) treatment for degenerative knee osteoarthritis.
**Methods:** This was a single-center, randomized, double-blind, placebo-controlled pilot clinical trial. There were 36 adults with degenerative knee osteoarthritis who were randomly allocated into JCE003 1,000 mg, JCE003 2,000 mg, or the placebo group (in a 1:1:1 ratio). The participants received 12 weeks of treatment and had scheduled tests every 6 weeks. The primary outcomes were measured using the Korean Western Ontario and McMaster Universities scale, and the secondary outcomes were measured using the visual analog scale, European quality of life-5-dimensions, patient global impression of change, C-reactive protein, and erythrocyte sedimentation rate. Changes between baseline scores and scores following study completion were analyzed.
**Results:** There were 29 participants whose data were analyzed in this study. The change of Korean Western Ontario and McMaster Universities, visual analog scale, European quality of life-5-dimensions scores showed significant improvement in the JCE003 1,000 mg group. The change of patient global impression of change was significantly improved in the placebo group. There were 14 adverse events, but there was no clinically significant relationship with the intake of JCE003 compared with the placebo.
**Conclusion:** Taking JCE003 may be effective at improving knee pain in patients with degenerative knee osteoarthritis and appears to be safe. Based on this study, the concentration and feasibility of the test group may be used when conducting a large-scale clinical trial of degenerative knee osteoarthritis in the future.

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## Introduction

Knee osteoarthritis (KOA) is a condition/disease in which the articular cartilage and surrounding structures are deformed due to an increase in the physical load in the knee joint, and changes in chondrocyte metabolism [1]. In KOA, chondrocytes have a limited capacity to self-heal following persistent inflammation [2].

Generally, non-steroidal anti-inflammatory drugs (NSAIDs) are used as pharmacotherapy for KOA, and intra-articular steroids are used as injection therapy [3]. Although some symptoms improve with the use of NSAIDs, clinical side effects such as liver disease and gastrointestinal conditions/disease may occur [4]. It has been reported that steroid injections confer only temporary improvement of symptoms, and long-term treatment may result in joint deterioration [5]. As a result, the demand for more effective and safe drug treatments is increasing, especially with a focus on traditional Korean medicine (TKM) treatment.

Currently, research on TKM treatment for KOA is being

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conducted using herbal [6,7], and acupuncture treatments such as pharmacoacupuncture [8], acupotomy [9], and warm acupuncture [10,11]. A systematic review in 2019 of herbal medicine treatment for KOA by Kim et al [12] reported there was no statistically significant difference between some commercially available drugs and herbal medicines in the treatment of KOA. However, herbal medicines have been reported to have fewer side effects than commercially available drugs with comparable effects.

There have been 21 clinical studies on Chinese herbal medicine treatment for KOA conducted in Korea; among them, only 3 studies were randomized controlled trials. Based on these 3 reports, this study was conducted using Cheong-A-Won-gagambang [Juglandis semen complex extract (JCE003)] based on Cheong-A-Won, which is a TKM prescription frequently used for bone conditions/diseases caused by liver-kidney deficiency, as recorded in consent supplementation.

Cheong-A-Won is composed of *Juglans sinensis*, *Eucommia ulmoides*, *Psoralea corylifolia*, and *Zingiber officinale*, of which *Psoralea corylifolia* has a toxic component, and its use is controversial because of the associated risk of liver damage [13]. Long-term medication is required for treatment of KOA. In this study, JCE003 was used, where *Psoralea corylifolia* has been replaced with *Acanthopanax sessiliflorum*. It is safe for human consumption and is widely used for the treatment of musculoskeletal conditions/diseases.

In a rat model of KOA (induced by monosodium iodoacetate), anti-inflammatory effects of orally ingested JCE003 were described [14]. In this pilot clinical trial, JCE003 (1,000 and 2,000 mg) or placebo were used. There were 36 men and women, between the ages of 40 and 75 years, who had been diagnosed with KOA and were treated for 12 weeks. The outcomes were measured using evaluation indices including the Korean Western Ontario and McMaster Universities (K-WOMAC) osteoarthritis index, visual analog scale (VAS), European quality of life-5-dimensions (EQ-5D) scale, patient global impression of change (PGIC) scale, C-reactive protein (CRP) level, and erythrocyte sedimentation rate (ESR).

## Materials and Methods

### *Study design*

This was a randomized, double-blind, controlled pilot trial to investigate the efficacy of JCE003 in treating KOA.

From April-August 2019, participants were recruited through indoor and outdoor advertisements at the Cheonan Korean Medicine Hospital of Daejeon University. After the participants had signed informed consent forms, screening tests were performed including a medical history survey, measurement of vital signs, measurement of obesity, clinical pathology tests, and a urine pregnancy test (for women of childbearing age only). If participants met the inclusion/exclusion criteria, they were registered as participants and were assigned to a group through random allocation and assigned to the JCE003 1,000 mg, JCE003 2,000 mg, or placebo group, and were administered treatment for a total period of 12 weeks. The allocation ratio for each group was 1:1:1.

Randomization was performed by stratified block randomization method in the experimental groups 1 and 2 and the control group at a ratio of 1:1:1 to ensure a balanced distribution over the 3 groups. Subjects who met all registration criteria were randomly assigned a randomization identification code (KOA-R-001-036) in the order generated by a computer randomized program. The randomization identification code indicated whether JCE003 1,000 mg, 2,000 mg, or placebo were given. As this pilot study was designed to be a double-blind trial, the participants, researchers, and assessors collecting the data were blinded to the group allocation. The information of intervention assignment was stored in the 3rd Department of Statistics at the hospital where the randomization code was placed in an opaque envelope. With the exception of disclosure to individual patients in an emergency situation, randomization and blinding were not disclosed to researchers until the end of the trial.

Subjects who were eligible for participation in the clinical trial were invited for Visit 1 within 1-4 days of screening (Week 0). Baseline assessment of the evaluation items was performed at Visit 1. Subjects took the treatment for 12 weeks without knowing whether they had received JCE003 or the placebo, and underwent further investigations and tests scheduled for Visits 2 and 3 (Week 6, and 12) according to the study schedule (Table 1).

The experimental drug JCE003 (Han Kook Shin Yak Pharmaceutical Co., Nonsan, Korea) was used at a concentration of 1,000 or 2,000 mg and consisted of *Juglans sinensis*, *Eucommia ulmoides*, *Zingiber officinale*, *Acanthopanax sessiliflorum*, D-sorbitol solution, sucrose, cyclodextrins, citric acid, sodium benzoate, and purified water. The placebo drug was consisted of D-sorbitol solution, sucrose, cyclodextrins, citric acid, sodium benzoate, and purified water. The experimental drug and the placebo were in the form of a soft brown extract, and was packaged in the same silvery white paper. To maintain the double-blind nature of the study, JCE003 1,000 mg, 2,000 mg, and the placebo were similar in appearance, smell, and taste, and were therefore indistinguishable to clinical trial subjects and researchers alike. The participants took the treatment twice a day, one sachet at a time, after meals (Table 2).

The primary outcome measure was based on the K-WOMAC score. The secondary outcome measures were based on the VAS, EQ-5D, and PGIC scores, CRP, and ESR.

This study was approved by the Institutional Review Board of Cheonan Korean Medicine Hospital of Daejeon University (study approval no.: DJUMC-2018-BM-09-3) and registered with the Clinical Research Information Service (https://cris.nih.go.kr/cris/index/index.do, registration no.: KCT0003552). The study was conducted in accordance with the Declaration of Helsinki.

### *Participants*

There were 41 participants recruited between April 2019 and August 2019. After a full explanation of the purpose of the trial, method, randomization probabilities, inconvenience, guaranteed secrecy, compensation, and right for withdrawal, the participants signed the informed consent form as an agreement.

Male and female patients aged 40-75 years who met the inclusion

Table 1. Participant Timeline.

| | Study period | | | |
|---|---|---|---|---|
| Visit | Screening | 1 | 2 | 3 |
| Week* | −2−0 | 0 | 6 | 12 |
| Enrollment: | | | | |
| Investigation of demographic characteristics | ✔† | | | |
| Eligibility screen performed | ✔ | | | |
| Informed consent given | ✔ | | | |
| Allocation | | ✔ | | |
| Interventions : | | | | |
| JCE003 1,000 mg treatment | | ✔ | ✔ | ✔ |
| JCE003 2,000 mg treatment | | ✔ | ✔ | ✔ |
| Placebo treatment | | ✔ | ✔ | ✔ |
| Assessments : | | | | |
| VAS used for knee pain | | ✔ | ✔ | ✔ |
| K-WOMAC | | ✔ | ✔ | ✔ |
| EQ-5D | | ✔ | ✔ | ✔ |
| PGIC | | | ✔ | ✔ |
| Checked X-ray for both knees | ✔ | | | |
| AST, ALT, GGT, total cholesterol, LDL, TG, glucose, total bilirubin, BUN, creatinine, CRP, ESR, CBC | ✔ | | ✔ | ✔ |
| RA factor, uric acid | ✔ | | | |
| Checked for adverse events | | | ✔ | ✔ |
| Confirmation of concomitant medicine change | | ✔ | ✔ | ✔ |
| Confirmation of adherence to medication regimen | | | ✔ | ✔ |

* The error range for each visit is set to ±5 days.
† Scheduled interventions or assessments were conducted.
K-WOMAC, Korean western ontario and Mcmaster universities; EQ-5D, Euro quality-of-life 5 dimension; PGIC, patient global impression of change; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; LDL, low density lipoprotein; TG, triglyceride; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; CBC, complete blood cell count; RA, rheumatoid arthritis; VAS, visual analogue scale.

and exclusion criteria were enrolled. The inclusion criteria were as follows: (1) Kellgren-Lawrence (K-L grade) Grade 1 or Grade 2 on the bilateral knee joint X-ray; and (2) no change in arthritis medication within the last 1 month after taking arthritis medications. The exclusion criteria were as follows: (1) arthritis due to factors other than degenerative factors which was determined by the researcher; (2) history of a lower limb fracture within the last 3 months; (3) received intra-articular injection of a drug such as hyaluronic acid or a steroid within 3 months from the start of the trial; (4) continued to take steroids, NSAIDs, or health supplements that may affect joint health such as glucosamine, methylsulfonylmethane, green-lipped or mussel oil extract, or herbs within the last month; (5) severe gastrointestinal symptoms such as heartburn or indigestion; (6) habitual alcohol consumption; (7) presence of clinically significant cardiovascular, immune system, infectious, and neoplastic conditions/diseases, other than joint

Table 2. Composition of JCE003 1,000 mg, 2,000 mg, and Placebo

| | JCE003 1,000 mg | JCE003 2,000 mg | Placebo |
|---|---|---|---|
| Juglans sinensis (g) | 2.381 | 4.762 | - |
| Eucommia ulmoides (g) | 2.381 | 4.762 | - |
| Acanthopanax sessiliflorum (g) | 2.381 | 4.762 | - |
| Zingiber officinale (g) | 1.191 | 2.382 | - |
| D-sorbitol solution (g) | 1.666 | 1.666 | 1.666 |
| Sucrose (g) | 1.5 | 1.5 | 1.5 |
| Cyclodextrin (g) | 0.134 | 0.134 | 0.134 |
| Citric acid (g) | 0.02 | 0.02 | 0.02 |
| Sodium benzoate (g) | 0.012 | 0.012 | 0.012 |
| Purified water (g) | 8.334 | - | 16.484 |
| Sodium carboxymethylcellulose (g) | - | - | 0.06 |
| Caramel color (g) | - | - | 0.04 |
| Ginseng scent (g) | - | - | 0.084 |
| Total (g) | 20 | 20 | 20 |

pain, at the time of enrollment; (8) suspected of having liver disease, kidney disease, or blood conditions/disease as observed from the results of the blood test; (9) habitually take psychotropic drugs and narcotic analgesics that affect the sensation of pain; (10) pregnant or lactating women; (11) judged by researchers to be inappropriate for this study; (12) food allergies; or (13) participated in other clinical trials within 30 days.

### *Sample size*

This study was a pilot clinical trial to determine the feasibility of running a large randomized clinical trial. Considering the feasibility and precision of the estimated mean and variance, Julious [15] suggested an empirically optimal sample size of 12 per group for a pilot study and a parallel design [15]. Therefore, the final number of subjects was 12 per group, totaling 36 subjects.

### *Statistical analysis*

A normality test was performed for continuous data, analysis of variance was performed if the normality assumptions were met, and a non-parametric method, the Kruskal-Wallis test, was used. Post-tests were performed using Dunnett's method. Analysis of covariance using the basal value as a covariant was performed to test the mean difference in outcome measure changes after 12 weeks of treatment compared with the baseline among the 3 groups.

For category type data, the chi-square test and the Fisher's exact test were used. Using the generalized formula of Cohen's d presented by Rosnow et al [16], the magnitude of the effect of visit-specific changes compared with the base values in intergroup differences were analyzed. To investigate the tendency of changes in the degree of pain due to medicines, the time of visit (visit, continuous type) and group (Group), the interaction between the time of visit and the group (Group × Visit), the default value ($Y_1$) was fixed effects, and a linear mixed effects model (LME) was performed in which the subjects had random effects. The regression coefficient and standard error of the fixed effect estimated by the LME model; the value of the t test statistic, the *p* value, and the standard error of the random effect are presented together. The results of the analysis of variance of the fixed effects (the 3$^{rd}$ sums of squares, expected squares, the F value and its degrees of freedom, and *p* value used for the significance test of each effect) are presented. The missing values for the efficacy variables were imputed using the last observation carried forward method.

## Results

From April-August 2019, of the 41 subjects recruited at Cheonan Korean Medicine Hospital of Daejeon University, a total of 36 subjects were judged to be suitable (using the screening test results) to be included in the clinical trial. One of the 36 randomly assigned study subjects withdrew their consent and dropped out,

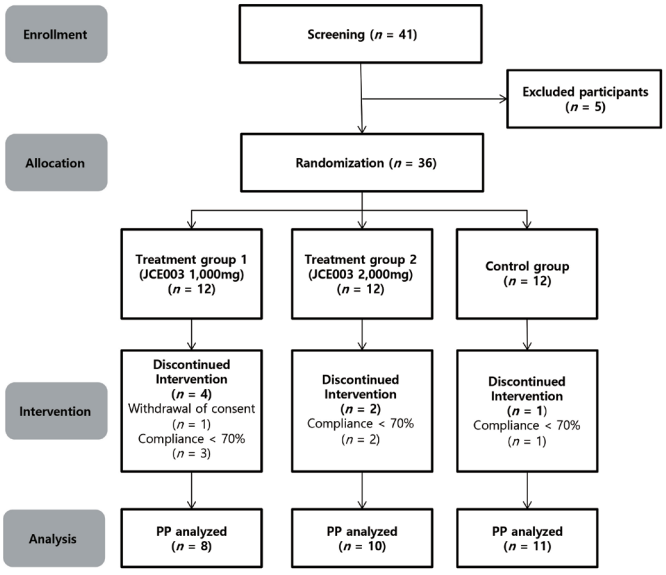


Fig. 1. Flow chart of clinical trial.

and 35 completed the study. Six of the 35 patients were excluded from the analysis group due to compliance resulting in a total compliance < 70%, and therefore data from 29 patients (in the per protocol analysis group) underwent statistical analysis (Fig. 1).

### *General characteristics of the participants*

There were no statistically significant differences between the 3 groups for all indicators measured. The average duration of knee joint pain was 70.6 months in the placebo group, which was different from the values of 45.8 and 49.3 months in the other 2 groups; however, no statistical difference was observed (Table 3).

### *Compliance assessment*

During each visit interval (Visit 1–2, Visit 2–3), the dose of the treatment that could be taken and the remaining amount that was not taken were confirmed. The medicine compliance was expressed as a percentage (%) by dividing the number of sachets of medicine taken by the number of sachets of medicines that should have been taken. The medication compliance standard is 80%, and in this trial, medication compliance was 88.9% in the JCE003 1,000 mg group, 82.7% in the JCE003 2,000 mg group, and 91.3% in the placebo group. There were no statistically significant differences in medication compliance between the three groups.

### *K-WOMAC*

The baseline K-WOMAC score of the JCE003 1,000 mg group was 40.2 (± 16.7), which was statistically significant different compared with the JCE003 2,000 mg [26.4 (± 13.9)] and the placebo groups [22.9 (± 12.8); $p$ <0.05]. Using analysis of covariance the range of change after 12 weeks, compared with the baseline, may have been overestimated in the JCE003 1,000 mg group when compared to the other groups. Therefore, baseline K-WOMAC scores were adjusted for statistical analysis, and the score in each of the 3 experimental groups were 31.9, 28.2, and 27.3. The adjusted Visit 2 – Visit 1 values were −7.4, −9.6, and −3.4 for the JCE003 1,000 mg, JCE003 2,000 mg, and placebo groups, respectively, and the Visit 3 – Visit 1 values were −12.0, −6.8, and 1.2, respectively.

Table 3. Demographic Characteristics Based on the Screening Phase: Per-Protocol Analysis Set.

| Variable | Placebo ($n$ = 11) | JCE 1,000mg ($n$ = 8) | JCE 2,000mg ($n$ = 10) | Test statistic |
|---|---|---|---|---|
| Sex | | | | |
| Male | 2 (18%) | 1 (12%) | 2 (20%) | FE-test $p$ = 1.0000 |
| Female | 9 (82%) | 7 (88%) | 8 (80%) | |
| Age (y) | | | | |
| Mean (SD) | 57.9 (±6.5) | 53.6 (±6.5) | 55.0 (±8.3) | KW =1.5 $p$ = 0.4774 |
| Median [range] | 60.0 [46.0-65.0] | 52.0 [46.0-64.0] | 52.0 [47.0-67.0] | |
| Height (cm) | | | | |
| Mean (SD) | 158.6 (±6.0) | 159.4 (±4.1) | 161.3 (±5.2) | KW =1.6 p = 0.4383 |
| Median [range] | 157.9 [150.6-168.7] | 160.9 [153.4-165.2] | 159.8 [155.9-173.7] | |
| Weight (kg) | | | | |
| Mean (SD) | 61.7 (±9.3) | 62.4 (±7.9) | 64.0 (±12.2) | =0.1 $p$ = 0.8714 |
| Median [range] | 57.6 [51.4-81.0] | 61.5 [53.0-74.0] | 64.3 [45.1-81.3] | |

Table 3. (continued).

| Variable | Placebo ($n$ = 11) | JCE 1000mg ($n$ = 8) | JCE 2000mg ($n$ = 10) | Test statistic |
|---|---|---|---|---|
| Body mass index (kg/m$^2$) | | | | |
| Mean (SD) | 24.5 (±3.6) | 24.6 (±3.1) | 24.6 (±4.4) | KW =0.1<br>$p$ = 0.9601 |
| Median [range] | 23.4 [20.6-34.2] | 23.8 [20.5-29.9] | 25.0 [18.0-31.8] | |
| Systolic blood pressure (mmHg) | | | | |
| Mean (SD) | 122.6 (±12.9) | 124.8 (±15.2) | 126.2 (±16.6) | =0.2<br>$p$ = 0.8591 |
| Median [range] | 121.0 [106.0-140.0] | 121.5 [105.0-149.0] | 133.5 [101.0-149.0] | |
| Diastolic blood pressure (mmHg) | | | | |
| Mean (SD) | 75.4 (±11.2) | 74.5 (±10.3) | 73.7 (±8.7) | =0.1<br>$p$ = 0.9320 |
| Median [range] | 75.0 [57.0-92.0] | 74.5 [61.0-90.0] | 76.5 [59.0-85.0] | |
| Pulse (bpm) | | | | |
| Mean (SD) | 70.1 (±9.3) | 69.8 (±13.4) | 73.6 (±6.4) | =0.5<br>$p$ = 0.6374 |
| Median [range] | 74.0 [52.0-81.0] | 68.0 [57.0-96.0] | 73.5 [63.0-85.0] | |
| Takes exercise | | | | |
| Yes | 8 (73%) | 4 (50%) | 5 (50%) | FE-test<br>$p$ = 0.5147 |
| No | 3 (27%) | 4 (50%) | 5 (50%) | |
| A smoker | | | | |
| Yes | 0 (0%) | 0 (0%) | 0 (0%) | FE-test<br>$p$ = 1.0000 |
| No | 11 (100%) | 8 (100%) | 10 (100%) | |
| Drinks alcohol | | | | |
| Yes | 3 (27%) | 1 (12%) | 3 (30%) | FE-test<br>$p$ = 0.7484 |
| No | 8 (73%) | 7 (88%) | 7 (70%) | |
| Duration of knee joint pain (mo) | | | | |
| Mean (SD) | 70.6 (±101.3) | 45.8 (±32.7) | 49.3 (±48.0) | KW =0.0<br>$p$ = 0.9758 |
| Median [range] | 48.0 [3.0-360.0] | 48.0 [6.0-84.0] | 30.0 [6.0-144.0] | |
| Kellgren-Lawrence grading scale | | | | |
| Grade 1 | 7 (64%) | 5 (62%) | 7 (70%) | FE-test<br>$p$ = 1.0000 |
| Grade 2 | 4 (36%) | 3 (38%) | 3 (30%) | |

Changes in the K-WOMAC score at the time of visit showed a statistically significant difference ($p < 0.05$). The interaction between the population and the time of visit was not statistically significant, however, the change in the JCE003 1,000 mg group after 12 weeks from baseline was statistically significant compared with the other groups ($p < 0.05$; Fig. 2).

### *VAS*

The adjusted baseline VAS scores in the 3 groups were 57.0, 53.4, and 54.5, with no statistically significant differences. The difference in the mean value of change between Visit 2, Visit 3, and Visit 1 between the 2 experimental JCE003 groups and the placebo group

was not statistically significant. The interaction between group and visit time was not statistically significant, however, the change in VAS score in the JCE003 1,000 mg group after 6 and 12 weeks from baseline was statistically significant compared with that in the other groups ($p < 0.05$, $p < 0.001$; Fig. 3).

### *EQ-5D*

The adjusted baseline EQ-5D scores in the 3 groups were 0.74, 0.75, and 0.75, which indicated no statistically significant difference between groups. The change of EQ-5D according to the time of visit showed a statistically significant difference ($p < 0.005$). The interaction between group and visit time was not statistically significant, however, the change in EQ-5D score in the JCE003 1,000 mg group after 12 weeks from baseline was statistically significant compared with the other groups ($p < 0.05$; Fig. 4).

### *PGIC*

The adjusted baseline PGIC scores in the 3 groups were 3.00, 3.30, and 3.64, which indicated no statistically significant differences. The interaction between group and visit time was not statistically significant, however, the change in PGIC score in the placebo group after 12 weeks from baseline was statistically

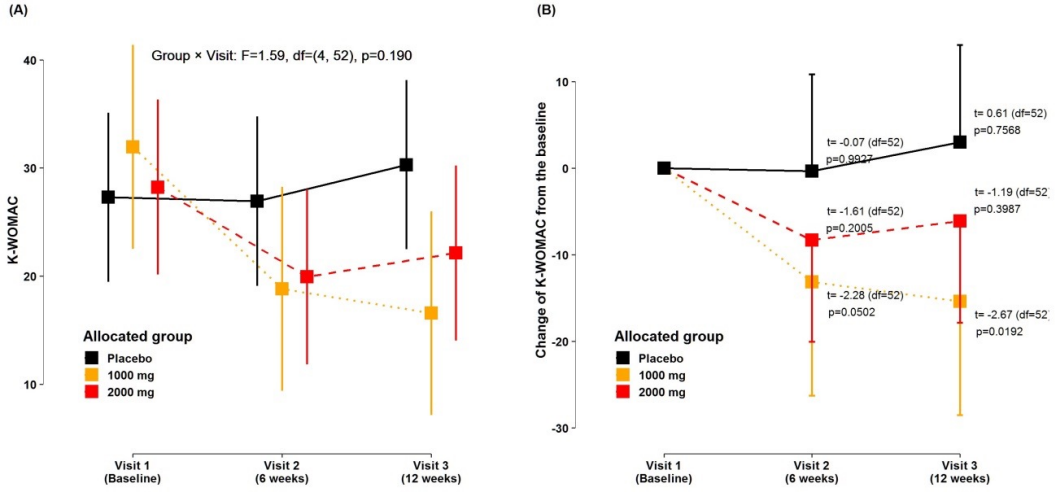


Fig. 2. Change of K-WOMAC from the baseline. (A) Estimated marginal means of K-WOMAC score at each visit according to each allocated group. (B) Mean changes of K-WOMAC score from the baseline to 6, 12 weeks for each allocated group: Dunnett's method was applied to obtain adjusted $p$-values and 95 % CIs.
K-WOMAC, Korean western ontario and Mcmaster universities.

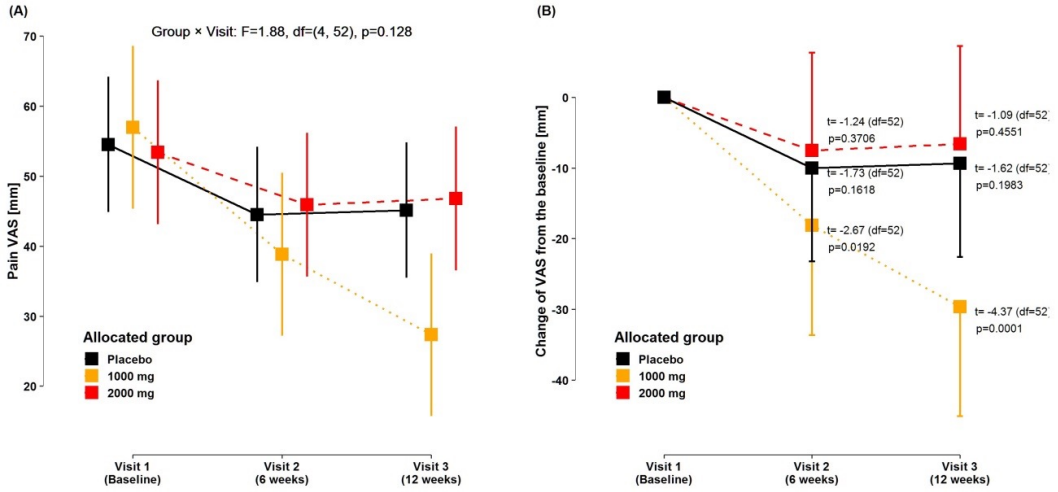


Fig. 3. Change of VAS score from the baseline. (A) EMMs of EQ-5D score at each visit according to each allocated group. (B) Mean changes of EQ-5D score from the baseline to 6, 12 weeks for each allocated group: Dunnett's method was applied to obtained adjusted $p$-values and 95 % CIs.
VAS, visual analogue scale; EQ-5D, Euro quality-of-life 5 dimension.

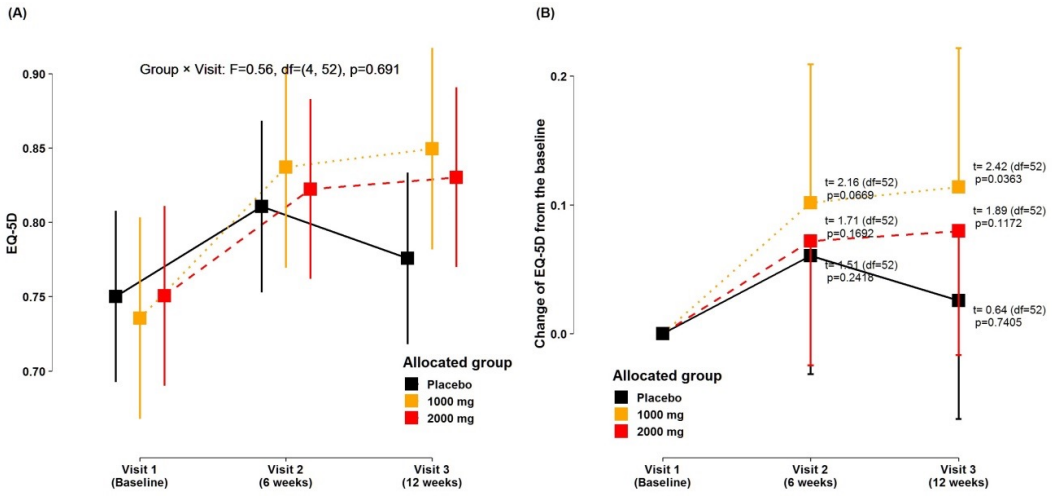


Fig. 4. Change of EQ-5D score from the baseline. (A) EMMs of VAS score at each visit according to each allocated group. (B) Mean changes of Pain VAS score from the baseline to 6, 12 weeks for each allocated group: Dunnett's method was applied to obtain adjusted *p*-values and 95 % CIs. VAS, visual analogue scale; EQ-5D, Euro quality-of-life 5 dimension.

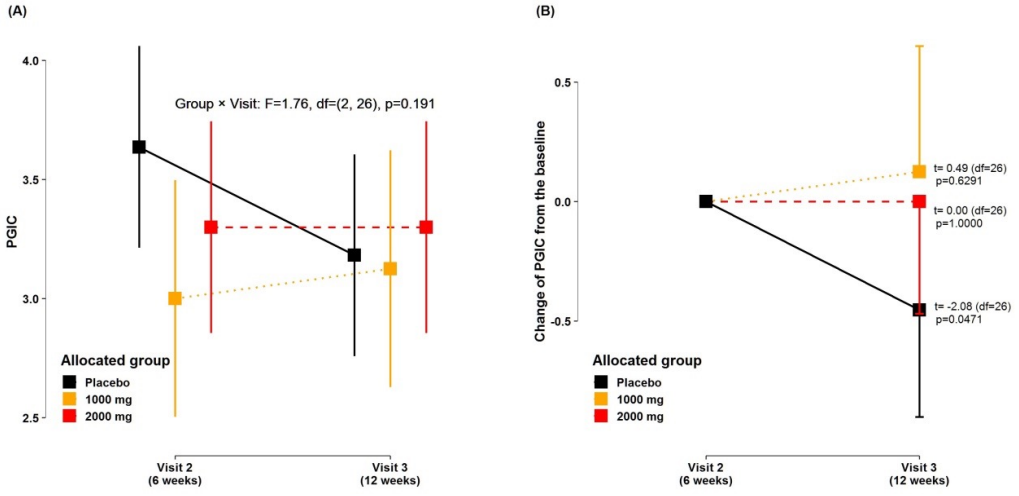


Fig. 5. Change of PGIC from the baseline. (A) EMMs of PGIC score at each visit according to each allocated group. (B) Mean changes of PGIC score from the baseline to 6, 12 weeks for each allocated group: Dunnett's method was applied to obtained adjusted *p*-values and 95 % CIs. PGIC, patient global impression of change.

significant compared with the other groups ($p < 0.05$; Fig. 5).

### *CRP*

The adjusted baseline CRP levels in the three groups were 0.89, 1.18, and 1.06, which indicated no statistically significant difference between groups. The interaction between group and visit time was not statistically significant. In addition, the change in concentration of CRP in the 3 groups after 6 and 12 weeks from baseline was not statistically significant (Fig. 6).

### *ESR*

The adjusted baseline ESR levels in the three groups were 12.75, 17.50, and 15.64, which indicated no statistically significant differences. The interaction between group and visit time was not statistically significant. In addition, the change of ESR in the 3 groups after 6 and 12 weeks from baseline was not statistically significant (Fig. 7).

### *Adverse events*

A total of 14 adverse events were observed during the study period (Table 4). They were judged to be mild reactions that did not interfere with most activities of daily life. The adverse events were basal conditions/diseases of the subject and had little causal relationship with the administration of the placebo or treatment. No clinically significant abnormal findings were observed in the

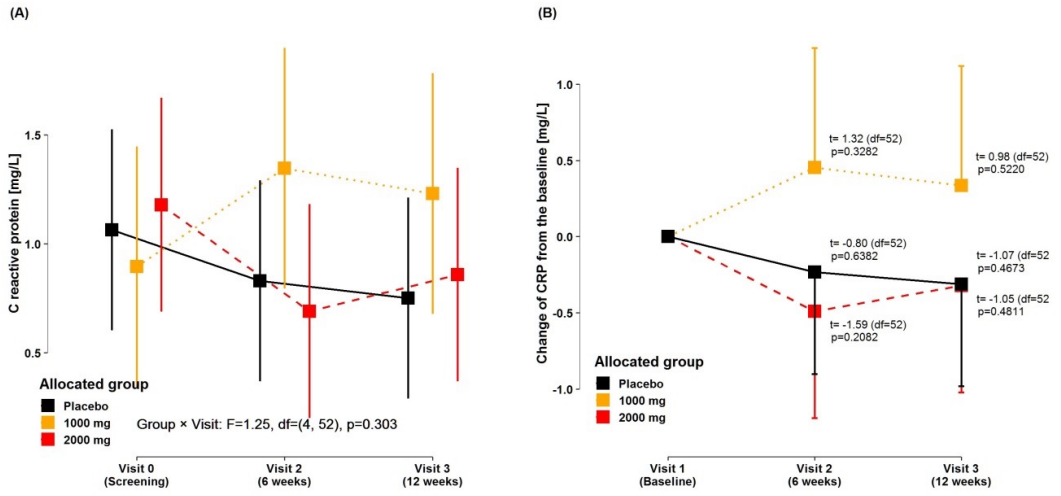


Fig. 6. Change of CRP from the baseline. (A) EMMs of CRP at each visit according to each allocated group. (B) Mean changes of CRP from the baseline to 6, 12 weeks for each allocated group: Dunnett's method was applied to obtain adjusted *p*-values and 95 % CIs.
CRP, C-reactive protein.

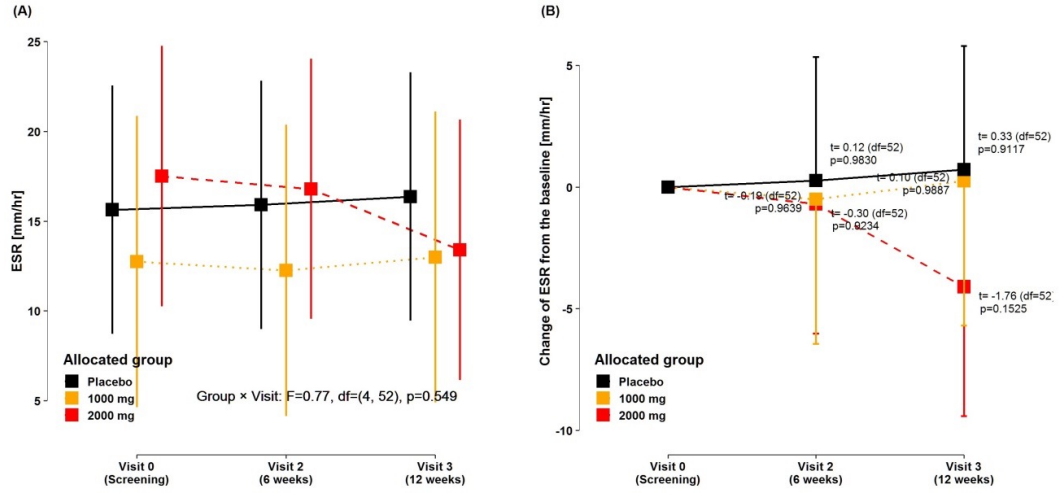


Fig. 7. Change of ESR from the baseline. (A) EMMs of ESR at each visit according to each allocated group. (B) Mean changes of ESR from the baseline to 6, 12 weeks for each allocated group: Dunnett's method was applied to obtain adjusted p-values and 95 % CIs.
ESR, erythrocyte sedimentation rate.

blood test results, including liver function and renal function tests performed before and after taking the drug, and signs of vitality, and the apparent safety of JCE003 during the 12-week dosing period could be confirmed.

## Discussion

In this pilot clinical trial, a total of 36 men and women aged 40-75 years who were diagnosed with K-L Grade I or II KOA upon radiological examination were treated with JCE003 1,000 mg or JCE003 2,000 mg or placebo for 12 weeks.

Subsequently, the efficacy and safety were evaluated. There was no statistically significant difference in the baseline demographic and sociological characteristics, vital signs, and secondary efficacy evaluation index between the 3 randomly assigned groups. However, the baseline of K-WOMAC and the primary efficacy evaluation index for JCE003 1,000 mg, JCE003 2,000 mg and placebo groups were 22.9, 40.2, and 26.4, respectively, indicating significantly higher values in the JCE003 1,000 mg group. The higher K-WOMAC values in the JCE003 1,000 mg group suggests that it is effective in improving the symptoms of KOA.

The baseline of each evaluation index was set to the CRP and ESR values ascertained at the time of screening, the K-WOMAC, VAS, and EQ-5D values evaluated at Visit 1, and the PGIC values were measured at Visit 2. After taking the study drug, evaluation indices were remeasured at Visit 2 and Visit 3 to evaluate drug efficacy.

The anti-inflammatory and arthritic effects of JCE003 have

Table 4. Adverse Events in the Trial.

| Symptom | Group | Intensity | Causal Relationship | Action related to the intervention | Treatment | Outcome |
|---|---|---|---|---|---|---|
| Skin allergy | P | Mild | Probably not related | No change | Pharmacotherapy | Cured |
| Lumbar sprain | P | Mild | Definitely not related | No change | No action | Recovering |
| Cold | P | Mild | Definitely not related | No change | Pharmacotherapy | Recovering |
| Ear pain | 1,000* | Mild | Definitely not related | No change | No action | Cured |
| Dizziness | 1,000 | Mild | Definitely not related | No change | No action | Cured |
| Thoracic sprain | 2,000† | Mild | Definitely not related | No change | No action | Cured |
| Vaginitis | P | Mild | Definitely not related | No change | Pharmacotherapy | Recovering |
| Housewife eczema | P | Mild | Definitely not related | No change | No action | Recovering |
| Lumbar disc disorder | 1,000 | Mild | Definitely not related | No change | No action | Recovering |
| Infectious enteritis | 1,000 | Mild | Definitely not related | No change | No action | Recovering |
| Esophagitis | 1,000 | Mild | Definitely not related | No change | Pharmacotherapy | Recovering |
| Ankle pain | P | Mild | Definitely not related | No change | No action | Cured |
| Hand & foot numbness | 2,000 | Mild | Definitely not related | No change | No action | Cured |
| Chest discomfort | P | Mild | Definitely not related | No change | Pharmacotherapy | Cured |

* 1,000 = JCE003 1,000 mg.
† 2,000 = JCE003 2,000 mg.
P, placebo.

been reported in previous in vitro and in vivo studies [14,17]. The amount of tumor necrosis factor alpha produced, and the amount of interferon gamma and tumor necrosis factor alpha mRNA expressed in lipopolysaccharides-treated RAW 264.7 cells were significantly lower compared with the control group.

In animal experiments, significant changes in reactive oxygen species levels, glutathione peroxidase, and nuclear factor erythroid 2-related factor 2 levels were reported, which are antioxidant-related enzymes and proteins, and interleukin 1-beta and cyclooxygenase-2, which are inflammatory cytokines in joint tissues [14].

In this 12-week randomized controlled pilot trial, the JCE003 1,000 mg group showed a statistically significant beneficial change in K-WOMAC, VAS, and EQ-5D scores after 12 weeks compared with the baseline, and the other 2 groups, suggesting that JCE003 1,000 mg is effective in improving the symptoms of KOA. Moreover, although it was not statistically significant, even in the JCE003 2,000 mg group when only the tendency was seen, the improvement tendency of the evaluation indexes, such as K-WOMAC, VAS, and EQ-5D scores, and the ESR, was observed. Not all drugs show concentration-dependent effects, in this pilot trial with 2 doses (without a titration curve of JCE003) JCE003 1,000 mg was apparently more effective than JCE003 2,000 mg.

However, the following limitations exist in this study: (1) Only patients with mild KOA of K-L Grade I or II were included in the study; (2) The efficacy could not be determined because this was a pilot study and the sample size was small; (3) The drug administration period was relatively short at 12 weeks, and the drug effect was not observed for a long period of time; (4) No follow-up was performed after the clinical trial was completed, and the sustainability of the drug effect could not be evaluated; and (5) The point at which the exercise intensity is a load on the subject's knee could not be set.

Despite the limited study period and small number of subjects, this pilot clinical trial showed the efficacy and safety of JCE003 1,000 mg treatment for KOA, suggesting its potential as a herbal medicine treatment for KOA in patients with a K-L Grade 1 or 2. However, large-scale clinical trials in the future are necessary with

the following additional assessments: (1) the addition of evaluation indicators such as knee joint range of motion and pain evaluation according to movement; (2) stratified analysis of symptom intensity; (3) supplementary methods for controlling external variables such as diet and exercise; and (4) a longer clinical study period.

## Conclusion

To examine the efficacy and safety of JCE003 for KOA, 36 patients diagnosed with KOA who visited Cheonan Korean Medicine Hospital of Daejeon University from April–August 2019 were recruited. The conclusions obtained by measuring K-WOMAC, VAS, and EQ-5D scores, PGIC, CRP concentration, and ESR after being randomly assigned to JCE003 1,000 mg, JCE003 2,000 mg or placebo group to take the drug for 12 weeks were: (1) In the primary efficacy evaluation, the amount of change in K-WOMAC after 12 weeks of taking the clinical trial drug in the JCE003 1,000 mg group was statistically significant beneficial compared with other groups; (2) In the secondary efficacy evaluation, the change in VAS and EQ-5D scores after 12 weeks of taking the clinical trial drug in the JCE003 1,000 mg group, and the change in PGIC after 6 weeks of taking the clinical trial drug in the placebo group were statistically significant compared with other groups; and (3) A total of 14 adverse events occurred, however, the relevance to the intervention was small, and no abnormal findings were observed in the blood tests and vital signs taken before and after the intervention, thus confirming the safety of JCE003 in this pilot trial.

## Author Contributions

Conceptualization: HJK and JHK. Methodology: HJK and HL. Formal investigation: HJK, JHK and HL. Data analysis: HJK, JHK and HL. Writing original draft: HJK. Writing – review and editing: HJK, JHK and HL

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

## Ethical Statement

Not applicable.

## Data Availability

All relevant data are included in this manuscript.

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