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Original Article

Effect of herbal medicine (Jodeungsan) on migraine: A double-blind randomized clinical trial

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ABSTRACT

Background: Migraine is a relatively common disease that has a significant effect on the daily activities of affected individuals. The purpose of this study was to explore the effects of herbal medicine (Jodeungsan, JDS) on migraine.
Methods: Sixty-four patients with migraine were recruited and randomized to either the JDS or placebo group at a 1:1 ratio. The subjects received JDS or placebo daily for four weeks. The primary outcome was a change in the number of headache attack days (HADs), and the secondary outcome measures were the headache impact test (HIT), migraine-specific quality of life (MSQoL), the deficiency and excess pattern identification questionnaire (DEPIQ), the cold and heat pattern identification questionnaire (CHPIQ), and the blood stasis pattern questionnaire (BSPQ).
Results: In all, 61 of the 64 patients took the investigational drugs for four weeks. The number of HADs did not significantly differ between the JDS and placebo groups at the end of the study. However, the HIT and MSQoL results showed significant improvement over the baseline in both groups.
Conclusion: JDS did not have a significant effect on chronic migraine. Larger studies are needed to confirm this result.
Trial registration: Clinical Research Information Service (https://cris.nih.go.kr/): KCT0003121.
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1. Introduction

Migraine is a common condition experienced by one in nine adults worldwide. The prevalence in South Korea and overseas is estimated to be 7–35%.[1,2] The annual prevalence in adults in South Korea is 6.5% and 31.5% of them experience severe migraine.[1]

Migraine treatment can be divided into acute-phase treatment, to reduce pain during the attack period, and preventive treatment, which is administered during the migraine-free period. Various pharmacologic treatments are also recommended for migraine prophylaxis such as an antidepressant (amitriptyline), anti-epileptics (topiramate, divalproex sodium), beta-blockers (propranolol, metoprolol), a calcium channel blocker (flunarizine), and intramuscular injection of botulinum toxin.[3]

In Traditional Korean Medicine (TKM), herbal medicine and acupuncture have been commonly used for migraine with many studies reporting acute analgesic effects and a long-term preventive effect on migraine incidence which lasts about three months.[4,5] Most of the clinical studies on migraine involving TKM have been conducted in China. A review study found the following to be the most frequently applied herbs, and all have shown positive effects: Chengung (*Cnidii rhizoma*), Baekji (*Angelicae dahuricae radix*), Baekjakyak (*Paeoniae radix*), Cheonma (*Gastrodiae rhi-*

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zoma), Jogudeung (*Uncariae ramulus cum uncus*), and Siho (*Bupleuri radix*).[6]

The present study investigated the effect of Jodeungsan (JDS), which is clinically used to treat chronic headaches, including migraine, in Korea and Japan. Many studies have reported the application of JDS to treat headache or vertigo in middle-aged or older patients with hypertension[7] and chronic headache in patients with cerebrovascular disorders.[8] In addition, JDS is composed of herbal medicines that are effective in treating migraine. However, the evidence-based effect of JDS on migraine has not been determined in a well-designed clinical trial. Thus, this study investigated whether JDS is effective on migraine through a randomized clinical trial with cost-effective analysis.

2. Methods

2.1. Study design

The present study was a prospective, double-blind, placebo-controlled, multi-institution clinical study that was conducted on migraine patients visiting the Wonkwang University Gwangju Medical Center (WUGMC), Kyunghee University Korean Medicine Hospital, and Semyung University Jechun Korean Medicine Hospital.

2.1.1. Protocol registration

The protocol was registered with the Clinical Research Information Service (CRIS) of the Korean National Institute of Health (KCT0003121) after the first subject was enrolled.

2.1.2. Ethical statement

The study was approved by the Institutional Review Board at each institution (WUGMC, IRB 2017–16; Kyunghee University, KOMCIRB-171,018-HR-040; Semyung University, IRB 1710–17). We informed the eligible participants of the study contents, especially including adverse responses to the drugs. The participants signed a consent form and provided their information about demographic factors and medical history.

2.2. Participant selection

2.2.1. Inclusion criteria

The inclusion criteria for the participants were as follows: Individuals diagnosed with migraine based on the criteria of the International Headache Society (ICHD-III beta version)[9] and aged 19–75 years were selected. The ICHD-III beta version diagnostic consists of headache persistence, headache characteristics, and accompanying symptoms for 4–72 hours. Migraine is divided into two categories based on the presence of the aura. The main common symptoms of migraine are characterized by one-sided moderate to severe pain, pulsation, and deterioration due to daily life, accompanied by nausea, vomiting, and sensitivity to light and sound. We also included subjects who were able to adequately communicate with clinical investigators and complete the questionnaire and headache report, after providing written consent to participate.

2.2.2. Exclusion criteria

We excluded the following individuals: persons who were currently taking a drug that may have affected headache (e.g., tricyclic antidepressant, monoamine oxidase inhibitor, high-dose [≥100 mg/d] magnesium, corticosteroid, botulinum toxin) and persons with a history of ischemic heart disease, liver or renal dysfunction, alcohol or drug addiction, pregnancy, or lactation. The use of tricyclic antidepressants, monoamine oxidase inhibitors, high-dose magnesium corticosteroids, local anesthetics and botulinum toxin was prohibited during participation in the study. Low-dose aspirin, analgesics, and anti-inflammatory drugs were permitted in cases of severe headache, and all concomitant medications were recorded in the case record.

2.3. Randomization and blinding

After screening, eligible participants were randomly assigned to either the JDS group or the placebo group in a 1:1 ratio. Random numbers were generated through computerized block randomization with block size four using the SAS package (SAS ver. 9.1.3, SAS Institute Inc., Cary, NC, USA). An independent researcher who was not involved in data collection or analysis conducted randomization. The participants and investigators were blinded to the participants' group assignments until the completion of the statistical analysis. The informed consent and explanatory note stated that the study aimed to compare the outcome of real drug or placebo drug.

2.4. Sample size calculation

To calculate the number of participants required in each group, the number of headache attack days (HAD) was used as the dependent variable. In previous studies,[10,11] the clinically significant difference in the number of HAD between the two groups was estimated as five days, with a standard deviation of 5.8 days. This was then applied to the following equation at a 5% confidence level and 80% testing power. The results indicated that the required number of patients in each group was 22. Considering an expected dropout rate of 30%, the final number of participants recruited for each group was 32. The total number of participants in this study was 64. The equation used is as follows:

$$n_1 = kn_2 \quad n_2 = \frac{\left(z_{\alpha/2} + z_{\beta}\right)^2 \sigma^2 (1 - 1/k)}{\epsilon^2} \approx 22$$

$$n^* = n/(1 - 30\%) = 22/0.7 = 31.43$$

2.5. Intervention

The participants were randomly assigned to the JDS or the placebo group and took the drugs orally, JDS (7.5 g) or placebo (7.5 g), three times a day for four weeks. The investigational drugs were provided at two-week intervals. The JDS is a light-gray granular product of Jeil Herb (Tsumura), Co. Ltd. It was composed of eleven medicinal plants: Uncariae Ramulus et Uncus (1.0), Citri Unshius Pericarpium (1.0), Pinelliae Tuber (1.0), Liriopis seu Ophiopogonis Tuber (1.0), Poria Sclerotium(1.0), Ginseng Radix (0.7), Saposhnikoviae Radix (0.7), Chrysanthemi Indici Flos (0.7), Glycyrrhizae Radix et Rhizoma (0.7), Zingiberis Rhizoma (0.7), Gypsum Fibrosum (1.7).

The JDS is registered to reduce the symptoms of chronic headache in Korean Ministry of Food and Drug Safety. The placebo was produced to be similar to the JDS obtained from Jeil Herb Co. Ltd. The participants and investigators could not visually distinguish the JDS from the placebo.

2.6. Outcome measures

2.6.1. Primary outcome measures

The primary outcome was the change in the number of HAD, which was measured three times: before drug administration, and after two and four weeks of drug administration.

2.6.2. Secondary outcome measures

Secondary outcome measures were headache impact test (HIT), migraine-specific quality of life (MSQoL), and pattern identification, which were assessed before drug administration and after

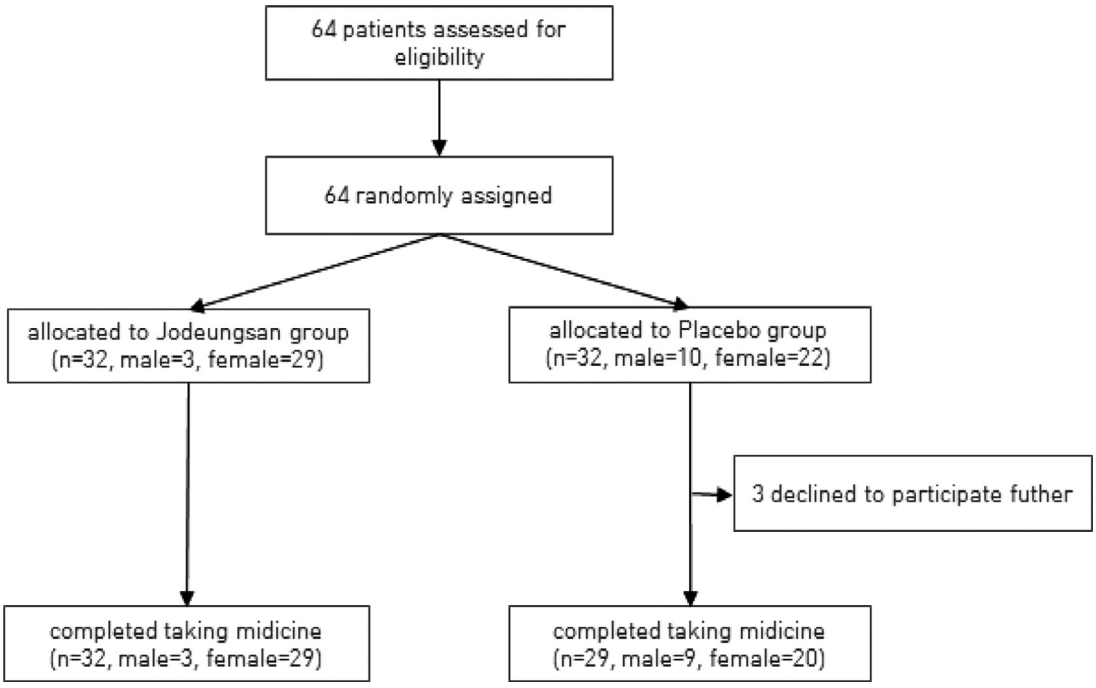

Fig. 1. Flowchart outlining study design.

four weeks of drug administration. For the HIT, the participants were guided to subjectively report the level of perceived headache and difficulty in daily activities. A higher score of HIT indicated a greater negative effect on daily activities. The MSQoL questionnaire consists of 25 questions. A higher score of MSQoL indicated higher quality of life.

We also examined the direct medical cost (medical examination, consultation, and cost of drug) and the direct non-medical cost (transportation cost) for the cost-effectiveness analysis. We conducted a cost-effectiveness analysis based on the estimated budget for each item prior to the clinical trial and got the other cost information from the clinical trial institution.

In addition, we investigated the differences in symptoms classification patterns based on the TKM theory using the Deficiency and Excess Pattern Identification Questionnaire (DEPIQ), Cold and Heat Pattern Identification Questionnaire (CHPIQ), and the Blood Statis Pattern Questionnaire (BSPQ) between both groups.

2.7. Statistical analysis

SPSS V22 (SPSS Inc., Chicago, IL, USA) was used to analyze all collected data. The intention-to-treat (ITT) population was used for the efficacy analysis. For safety analysis, all randomized participants who took at least one dose of any investigational drug were included. To test the effect of JDS, the HAD, HIT, and MSQoL were considered dependent variables, and a repeated measures ANOVA with a sex covariate was performed. We further disaggregated and analyzed the results by sex to determine the difference in the experience of migraine symptoms in relation to sex.

For the cost-effectiveness analysis, we used two methods of calculating the summary measure, the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER). We also used HAD as an effective indicator. We included only direct medical and non-medical costs, but not indirect costs (e.g. nursing fees), to calculate the AECR and ICER from a limited social perspective. The analysis period was four weeks of the clinical trial.

In addition, we performed Chi-square tests to investigate the differences in symptoms classification patterns using three pattern identification inventories, the DEPIQ, CHPIQ, and BSPQ.

3. Results

3.1. Baseline characteristics

In this study, 64 patients were screened and met the inclusion/exclusion criteria. Thus, all 64 patients were enrolled and three of them were dropped out of the placebo group (Fig. 1). There were no statistical differences between the two groups on baseline characteristics including age, height, weight, period of illness, past treatment experience, use of analgesics, socioeconomic status, HAD, HIT, MSQoL, and except distributions of all three-pattern identification sex distribution ($p < 0.05$) (Table 1).

3.2. Outcome measures

3.2.1. Primary outcome

There were no statistically significant differences between the groups at four weeks in any of the measured outcomes. The number of HAD decreased after four weeks of drug administration, but this trend was not statistically significant in either group (Table 2).

3.2.2. Secondary outcome

There was no significant difference in HIT and MSQoL scores between the groups after four weeks. However, the interference of migraine in daily activities decreased after four weeks of drug administration compared with the baseline in both groups. The HIT and MSQoL scores of the JDS group were lower than those of the placebo group, but the difference was not statistically significant (Table 2).

Table 1
Characteristics of participants.

Characteristic		Jodeungsan (JDS) group (n = 32)	placebo group (n = 32)	p-value
Sex				0.03*
Male (%)		3 (9.37)	10 (31.25)	
Female (%)		29 (90.63)	22 (68.75)	
Age (years)		42.84 (38.53, 47.16)	42.16 (37.90, 46.40)	0.82†
Social economic status				0.47*
High (%)		5 (27.80)	8 (38.10)	
Middle (%)		12 (66.70)	13 (69.90)	
Low (%)		1 (5.60)	0 (0.0)	
Not reported (%)		14 (43.75)	11 (34.37)	
Period of illness (years)		101.72 (62.07, 141.37)	107.66 (56.88, 158.43)	0.85†
Prior treatment experience				0.50*
With experience (%)		7 (21.88)	6 (18.75)	
No experience (%)		25 (78.12)	26 (81.25)	
Use of analgesic tablet (last 4 weeks)		4.38 (2.78, 5.99)	5.30 (3.00, 7.61)	0.47†
HAD		5.06 (3.63, 6.48)	4.88 (3.46, 6.29)	0.85†
HIT		59.06 (56.91, 61.20)	58.13 (55.27, 60.97)	0.59†
MSQoL		67.12 (62.07, 72.17)	64.75 (60.56, 68.93)	0.46†
DEPIQ	Deficiency (%)	3 (9.4)	4 (12.5)	0.92*
	Middle (%)	27 (84.4)	26 (81.3)	
	Excess (%)	2 (6.3)	2 (6.3)	
CHPIQ	Cold (%)	6 (18.8)	4 (12.5)	0.33*
	Middle (%)	25 (78.1)	24 (75.0)	
	Heat (%)	1 (3.1)	4 (12.5)	
BSPQ	BS (%)	–	–	–
	Non-BS (%)	32 (100.0)	32 (100.0)	

Data are presented as n (%) or mean (95% CI). HAD, headache attack days; HIT, headache impact test, MSQoL, migraine specific quality of life; DEPIQ, Deficiency and Excess Pattern Identification Questionnaire; CHPIQ, Cold and Heat Pattern Identification Questionnair; BSPQ, Blood Statis Pattern Questionnaire.
* p-value by chi-square
† p-value by independent t-test.

Table 2
Changes in primary and secondary outcomes in the Jodeungsan (JDS) and placebo groups between the baseline and week 2 or 4.

Outcomes		JDS group (95% CI)(n = 32)		Placebo group (95% CI)(n = 32)		Mean difference‡	p-value
HAD							
Baseline		5.06 (3.63, 6.48)		4.88 (3.45, 6.54)			
Week 2		5.03 (3.94, 6.11)		5.59 (4.31, 6.37)		-0.38 (-1.95, 1.19)	0.63
Difference†		-0.03 (-1.05, 1.11)		0.71 (-1.97, 0.54)			
p-value		0.95		0.25			
Week 4		4.53(3.19, 5.87)		4.97 (3.52, 5.78)			
Difference††		-0.53 (-1.05, 2.11)		0.09 (-1.62, 1.43)		-0.01 (-1.81, 1.78)	0.99
p-value		0.50		0.90			
HIT							
Baseline		59.06 (56.91, 61.20)		57.72 (54.60, 60.84)			
Week 4		53.03 (50.48, 55.57)		53.86 (51.11, 56.61)		-0.42 (-4.23, 3.40)	0.83
Difference††		-6.03 (3.64, 8.42)		-3.86 (0.30, 7.41)			
p-value		0.01***		0.03*			
MSQoL							
Baseline		67.12 (62.07, 72.17)		65.51 (61.01, 70.02)			
Week 4		70.75 (65.43, 76.06)		70.41 (66.17, 74.64)		0.34(-6.73, 7.41)	0.92
Difference††		-3.62 (-6.92, -0.32)		-4.89 (-8.40, –1.38)			
p-value		0.03*		0.01**			
Adverse events							
Indigestion	Mild	Not related	1 (3.12%)	–	–		
		Possibly related	1 (3.12%)	–	–		
	Moderate	–	–	Unlikly related	1 (3.12%)		
Cold	Mild	Not related	2 (6.25%)	Not related	1 (3.12%)		
Vestibularneuronitis	Mild	–	–	Not related	2 (6.25%)		
Nausea	Mild	Possibly related	1 (3.12%)	–	–		
Total			5 (15.62%)		4 (12.50%)		

Values are presented as mean (95% CI).
† difference and p-value by analysis of paired t-test (comparison of baseline and week 2)
†† difference and p-value by analysis of paired t-test(comparison of baseline and week 4).
‡ mean difference and p-value by repeated measures ANOVA with sex as covariate.
* p-value<0.05.
** p-value<0.01.
*** p-value<0.001HAD, Headache Attack Days; HIT Headache Impact Test; MSQoL Migraine Specific Quality of Life.

Table 3
Results of cost-effectiveness assssment.

4 weeks effect	Jodeungsan (n = 32)	Placebo (n = 32)	Difference
Total effect	0.53	-0.09	0.62
Total cost*	808,381 KRW (622 USD)	799,788 KRW (615 USD)	8,593 KRW (7 USD)
ACER	1525,247 KRW (1,173 USD)	-8886,533 KRW (-6,836 USD)	10,411,781 KRW (8,009 USD)
ICER	–	–	13,860 KRW (11 USD)

ACER, Average cost-effectiveness ratio; ICER, Incremental cost-effectiveness ratio; KRW, Korean won (Korean currency); USD, US dollars.
* Direct medical expenses (inspection fee, consultation fee, drug fee) + direct non-medical expenses (transportation costs three times).

3.3. Adverse event

The Adverse events experienced during the trial period are presented in Table 2. In the JDS group, 5 of 32(15.62%) subjects reported mild indigestion, cold symptoms, and nausea. In the placebo group, 4 of 32(12.50%) subjects reported mild indigestion and vestibular neuronitis. All adverse events resolved spontaneously. There were no severe adverse events that necessitated treatment or caused the termination of experimental drug administration.

3.4. Comparisons of outcomes according to sex

When the number of HAD experienced by females was compared before and after drug administration in both groups, the number of HAD in both groups decreased at week 4, however, the difference was not significant. In the within-group comparison, the HIT scores of female participants significantly decreased in the JDS group ($p < 0.05$), but not in the placebo group (Supplement).

3.5. Economic assessment

The total amount of direct medical and non-medical expenses for four weeks in the JDS group was 808,381 Korean won (KRW) which is about 622 USD (based on exchange rate of 1300 KRW per 1 USD), and the control group was 799,788 KRW which is about 615 USD. All costs, except the cost of the drug, were the same in both groups. The average improvement effect of migraine was 0.53 and -0.09 days in the JDS and control groups respectively.

The ACERs are 1,525,247 KRW (0.53 days/808,381 KRW) which is equivalent to 1,173 USD (0.53 days/622 USD), and -8,886,533 KRW (-0.09 days/799,788 KRW) which is equivalent to -6,836 USD (-0.09 days/615 USD) per migraine-relief day for the JDS and control group respectively. The ICER value of JDS group was 13,860 KRW (about 11 USD) per additional migraine-relief day (Table 3).

4. Discussion

4.1. Summary of main results

This clinical trial aimed to evaluate the effectiveness and safety of JDS on migraine. Participants were randomly assigned to the JDS or the control group. The efficacy indicators were evaluated with pre-post changes across groups.

The amount of pre-post changes in HADs, HIT and MSQoL in the JDS group was not significantly greater than those in the control group. In both groups, HIT and MSQoL significantly decreased; however, the number of HAD did not significantly decrease. Although some subjects complained mild symptoms during the trial, they were soon resolved without any additional treatments.

Additionally, as a result of economic assessment based on clinical trial costs, ICER value of JDS was 13,860 KRW (about 11 USD) per additional migraine-relief day.

4.2. Agreement and disagreement with other studies or reviews

Few clinical studies of JDS have been conducted for headaches; however, there was not any RCT study using JDS for migraine. Thus, the results of the current study were not able to be directly compared with those of other studies.

A study has reported that JDS is effective on stroke patients with chronic headaches with a 78.3% improvement rate.[12] In this study, the duration of the drug administration was 8 to 32 weeks (12 weeks on average), two to eight times longer duration than that of the current study. Although the study does not include subcategories such as chronic migraine, chronic tension type headache, and chronic daily headache, it has been found that JDS is effective on overall chronic headaches.

Kimura et al. evaluated the effectiveness of JDS on various symptoms of headache. In the study, the drugs, JDS or yokukansankachimpihange (YKS), were selectively administered according to the different symptoms of headache without a diagnosis of the type of the headache.[13] At the end of the trial, patients were asked to verify the symptoms that have been alleviated after the drug administration. As a result, the patients who were administered with JDS reported that the tension type headache-related symptoms have been more alleviated than the migraine-related symptoms. However, it is difficult to confirm that JDS was ineffective due to the limitation of the study design.

4.3. Implications for clinical practice and research

According to an additional analysis based on gender classification, HIT of women in the JDS group more significantly decreased than that of women in the control group, which implies that JDS could be more effective for women rather than men. It is fascinating to know such an effective drug, especially for women with migraine, because of it's higher prevalence, and severer and more persistent intensity in women.[14,15] However, further study is required to confirm this finding for clinical application because the mechanism that JDS is more effective for women is not yet known, and the number of male subjects was relatively small in our study.

4.4. Potential mechanisms

Although the mechanism by which JDS can improve migraine is not clear, it is presumed to be related to Nitric oxide (NO).[16] NO plays an important role in maintaining homeostasis such as blood pressure control and platelet function regulation. It is also closely related to the pathogenesis of primary headaches, including migraine, by involving pain processing in the central nervous system.[17] One study reported that inhibition of NO synthetase improved migraine.[18] Another study also reported that one of the functions of JDS was to directly remove NO radicals which can cause migraine.[19] However, further studies are required with various candidates of migraine mechanisms.

4.5. Limitation

The limitations of our study were as follows; first, the period of drug intervention was not long enough. One study showed that the effect of JDS differed depending on the period of drug intervention. In the study, the improvement of symptoms appeared after two weeks, and the rate of improvement was the highest between the sixth and ninth week after drug administration, while the period of drug intervention in our study was not enough to show the effect of JDS.[12] Second, our study did not consider the menstruation-related values which might affect the attack time and intensity of migraine, although many studies have reported the influence of menstruation on migraine.[20,21]

4.6. Conclusion

We evaluated the effectiveness of JDS on migraine using a double-blind randomized trial, and this study did not show that JDS was effective on migraine with primary outcome. However, we found a possibility that JDS could be effective on migraine in women. Due to the limitations of our study, further research is required to study the effectiveness of JDS on migraine with more elaborated study designs in the future.

Author contributions

Conceptualization: SKL and JHS. Methodology: SKL and CHK. Investigation: CHK, JHS, HYK, HGS, WSJ, SWK. Formal analysis: SYK, MJK. Writing – original draft: SYK.Writing – review and editing: SYK, SKL. Supervision SKL.

Conflict of interests

The authors declare no conflict of interests.

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Ethical statement

This research has been approved by the Institutional Review Board of the Wonkwang University Gwangju Medical Center (IRB number: 2017–16).

Data availability

The data will be made available by the corresponding author upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2022.100885.

Supplement 1. Changes in primary and secondary outcomes in the Jodeungsan (JDS) and placebo groups between the baseline and week 2 or 4 in female and male subjects.

Supplement 2. CONSORT checklist.

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