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Original Article

The effects of herbal medicine (Jujadokseo-hwan) on quality of life in patients with mild cognitive impairment: Cost-effectiveness analysis alongside randomized controlled trial

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ABSTRACT

Background: Mild cognitive impairment (MCI), the early stage of dementia, requires effective intervention for symptom management and improving patients' quality of life (QoL). Jujadokseo-hwan (JDH) is a Korean herbal medicine prescription used to improve MCI symptoms, such as memory deficit. This study evaluates the improvement in QoL through JDH. Alongside a clinical trial, it estimates the cost-effectiveness of JDH, compared to placebo, for MCI over 24 weeks.

Methods: Changes in QoL were measured using the EuroQol-5 Dimensions (EQ-5D) and Korean version QoL-Alzheimer's Disease (KQOL-AD). Direct medical and non-medical costs were surveyed and incremental cost-effectiveness ratios (ICER) per QALY for JDH were produced.

Results: In total, 64 patients were included in the economic evaluation (n = 35 in JDH, n = 29 in placebo). In the JDH group, EQ-5D and KQOL-AD improved by 0.020 (p = .318) and 3.40 (p = .011) over 24 weeks, respectively. In the placebo group, they increased by 0.001 (p=.920) and 1.07 (p=.130), respectively. The ICER was KRW 76,400,000 per QALY and KRW 108,000 per KQOL-AD for JDH, compared to the placebo group.

Conclusion: JDH is not considered a cost-effective treatment option compared with placebo; however, it positively affects QoL improvement in patients with MCI.

1. Introduction

Dementia is a global public health issue that imposes a heavy economic burden worldwide.[1] Dementia is a progressive neurocognitive disorder requiring assistance with daily activities due to the deterioration of intellectual, social, or occupational functions.[2,3] Consequently, social and informal care costs for patients are considerable, accounting for a large proportion of total dementia management costs.[4,5] The societal costs of dementia increase with the severity of the disease, requiring higher patient care.[6-10] Therefore, slowing or preventing transition to the advanced stage effectively reduces the economic impact.[11] In this context, increasing attention is being paid to mild cognitive impairment (MCI), which is a precursor of dementia.[12,13]

MCI is an intermediate phase between normal aging and dementia that deteriorates one or more domains of cognition, including memory, attention, language, visuospatial skills, and executive function.[14-16] Patients can perform routine activities, such as eating, dressing, bathing, or walking, unlike dementia, but they have problems performing daily instrumental functions such as cooking, shopping, using public transportation, or handling money.[17,18] Neuropsychiatric disturbances such as depression, anxiety, and apathy are commonly observed in patients with MCI.[19] These cognitive, functional, and psychiatric symptoms are associated with a low quality of life (QoL) in patients with MCI.[20-22] Furthermore, patients with cognitive deficits, such as memory deficit (amnesia)

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or non-cognitive symptoms, have a high risk of developing dementia.[23-25]

Although not all patients progress to dementia, about 50% of patients with MCI develop dementia within three years and about 80% develop dementia within six years.[15] The major treatment strategy for MCI is disease-modifying, which can reduce the prevalence of dementia.[26-28] Interventions targeting biomarkers, including beta-amyloid plaques, neurofibrillary tangles, and inflammation, that contribute to neurodegeneration are theoretically considered as a potential pharmacotherapy for MCI.[29] Clinical trials have been actively conducted to evaluate the effectiveness of amyloid therapy, anti-inflammatory agents, and antioxidants.[30] However, none of these therapeutic options decreased the risk of conversion from MCI to dementia with certainty.[31]

As no clinically-evidenced treatments have been determined to date, interventions for symptom and QOL improvement are a priority for now.[32] Symptoms have been addressed as risk factors for the progression of MCI to dementia.[33,34] Furthermore, cognitive complaints and psychological symptoms, particularly depression, in MCI increase patient dependency,[31,35] which can be a predictor for cost burden in the MCI phase.[6] This is because patient dependency imposes a higher caregiver burden and requires extensive consumption of medical services.[36,37] Depression and patient dependency are closely associated with lower QoL in patients.[36-38] Appropriate options for alleviating symptoms or raising QoL may maintain or enhance patient independence, thereby relieving caregivers' distress and providing economic benefits to the patient or society. For this reason, symptom control and QoL improvement are crucial for the treatment of MCI.

Pharmacological approaches such as cholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and NMDA antagonists (memantine), approved for dementia, have not been shown to alleviate cognitive symptoms in MCI.[28,39] However, non-pharmacological treatments, including cognitive-behavioral training, dietary supplementation, and exercise, can be helpful for symptom management.[31,39] Complementary and alternative medicine (CAM) is also considered a symptomatic therapy in South Korea.[40-42] In Korean Medicine, as a representative of CAM in Korea, herbal preparation products, acupuncture, electroacupuncture, and moxibustion have been predominantly used to improve memory loss, daily dysfunction, and anxiety in patients with cognitive impairment.[43]

Jujadokseo-hwan (JDH, or ZhuziDushu Wan in Chinese) is a known Korean herbal prescription in Korea and China that improves memory deficit symptoms.[44] Its prescription originated from the 16th century Ming Dynasty and was recorded as a treatment for forgetfulness in Donguibogam, a traditional Korean medicine book published in 1613.[45] JDH consists of seven single herbal drugs, including components that enhance memory and cognition: P*oria Sclertum cum Pini Radix, Poly galae Radix, Gingseng Radix, Citri Unshius Pericarpium, Acori Graminei Rhizoma, Angelicae Gigantis Radix, and Glycyrrhizae Radix et Rhizoma*.[46] In *vivo* studies investigating the memory-enhancing mechanism of JDH revealed that it protects against nerve injury caused by oxidative stress or beta-amyloid and activates the brain by increasing cerebral blood flow, enhancing brain ability, memory, and learning.[47,48] In Korea, JDH tablet has been approved for the treatment of forgetfulness by the Korean Ministry of Food Drugs Safety and is currently marketed as an over-the-counter medicine under the product name of 'Shimsahwan'.[49]

Several herbal medicine prescriptions, including JDH, have been suggested as candidates in a recent Korean medicine study exploring treatments for cognitive disorders.[46] Considering the memory-enhancing mechanism of JDH, it has the potential to be considered as a useful treatment for MCI. Still, there are insufficient studies designed to prove the effectiveness of JDH in patients with MCI. Therefore, the first randomized clinical trial (RCT; KCT0003570) was performed to explore the effectiveness of JDH for MCI in three hospitals in Korea.[45] This RCT focused on the improvement of memory deficit (amnesia) through JDH compared to placebo with the Seoul Neuropsychological Screening Battery, 2nd Edition (SNSB-II), the Mini-Mental State Examination for Dementia Screening (MMSE-DS), and the Montreal Cognitive Assessment-Korean version (MoCA-K). Furthermore, this study assessed the QoL of patients using two different QoL instruments considering the importance of enhancing QoL for patients with MCI: the KQOL-AD, a cognitive impairment-specific measure, and EQ-5D, a generic QoL measure.

The purpose of this study was to evaluate the improvement in QoL by administering JDH and to assess the cost-effectiveness of JDH for patients with MCI from a healthcare perspective in South Korea.

2. Methods

2.1. Study design

This economic evaluation was conducted using data from the RCT, which evaluated the efficacy and safety of JDH for memory deficit (amnesia) in MCI disorders. The total clinical trial period was 24 weeks, including 12 weeks of the treatment period and an additional 12 weeks of follow-up observation. The recruited participants were asked to visit eight times within 12 weeks of the treatment period. At each visit, they received clinical examinations and were requested to complete the survey questionnaire. The treatment and control groups received JDH or placebo orally three times a day for 12 weeks of the treatment period.

The clinical data used for the economic evaluation were analyzed using per-protocol (PP) analysis, and this cost-effectiveness analysis model was established for a period of 24 weeks from the healthcare perspective period in South Korea.

2.2. Participants

Participants were recruited in a voluntary, competitive enrollment manner in three Korean medicine hospitals in Daejeon, Jeonju, and Gunpo in Korea. The subject identification number was given only if they met the participant conformity assessment criteria. Participants were aged 45 to 85 years and diagnosed with mild MCI according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Participants were required to have scores comparable to those of patients with MCI on several cognitive tests, such as the Clinical Dementia Rating (CDR) (score 0.5), the Global Deterioration Scale (GDS) (score from 2 to 3), and the MoCA-K (score below 22). In addition, participants should have no instrumental impairment (Korean version of Instrumental Activity of Daily Living; K-IADL score below 0.43) and must have received more than six years of education (at least primary education). All participants or their legal representatives should voluntarily agree to sign a written consent.

In contrast, individuals with diseases other than MCI, such as Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, and hydrocephalus were excluded. People with medical conditions that could possibly cause dementia, jeopardize their health during the test, or affect test results, were also excluded. Volunteers with depression and other mental illnesses were also ruled out. Medication history was also examined to exclude anyone who had been receiving dementia treatment or hormone therapy.

2.3. Clinical outcomes: QoL and QALY

The QoL of patients with MCI was assessed using two different instruments: EuroQol-5 Dimensions (EQ-5D) and the Korean version of the Quality of Life-Alzheimer's Disease (KQOL-AD). The QoL data was collected at baseline, after treatment (at 12 weeks), and after the observation period for follow-up (at 24 weeks).

The EQ-5D is a valid, reliable, and responsive tool for the evaluation of general QoL, developed by the EuroQoL group. Health states measured by EQ-5D were converted into utility weights using the representative sample of Korea.[50] The quality-adjusted life year (QALY) for 24 weeks was obtained by multiplying the survival period by the utility weights.

The Quality of Life-Alzheimer's Disease (QOL-AD) is a widely used questionnaire designed to measure QoL with cognitive impairment ranging from MCI to severe dementia.[51,52] The Korean version of the QOL-AD is a valid and reliable QoL measurement for patients with MCI in Korea (Cronbach's α: 0.860).[53] It consists of 13 questionnaires and asks about physical health, energy level, mood, living situation, memory, interpersonal relationships (family, marriage, friends), self as whole, the ability to do chores and things for fun, money, and life as whole. The score for each question ranges from 1 to 4, and the total score ranges from 13 to 52, with a higher score indicating a higher quality of life.[53,54] Both the patients' self-rating and proxy-rating versions were available,[52,54] but we leveraged the self-reported KQOL-AD questionnaires.

2.4. Costs

To estimate the cost-effectiveness outcome, direct medical and non-medical costs that occurred during the 24 weeks of study were collected. The costs were measured at the 2021 rate of the Korean won (KRW). Since all costs considered and assessed in this study occurred within 24 weeks, no discounting was applied.

Direct medical costs were the costs incurred for visiting Korean medicine hospitals and taking herbal medicine treatments according to the clinical trial protocol. The physician and lab exam fees were identical for both groups and included in the direct medical costs. The costs related to herbal medicine (KRW 3,000 per day) were only added to the direct medical costs of the JDH group.

Round-trip transportation fares for visiting the Korean medicine hospitals eight times were considered the direct non-medical costs. The average travel cost per outpatient visit to a Korean medicine hospital was based on the data on transportation fees according to the type of medical institution in 2008.[55] Using the Statistics Korea price index, the monetary values of 2008 were transformed to the 2021 monetary values.[56]

2.5. Cost-Effectiveness analysis: ICER

Cost-effectiveness analysis compares the additional costs to the improved effectiveness of the new treatment intervention (in comparison with its alternative). The incremental cost-effectiveness ratios (ICER) were calculated for a trial period of 24 weeks for the cost estimates over each QoL outcome of QALYs and KQOL-AD.

$$\text{ICER} = \frac{\triangle\, Cost\,(JDH) - \triangle\, Cost\,(Placebo)}{\triangle\, QoL\ outcome\ (JDH) - \triangle\, QoL\ outcome\ (Placebo)}$$

2.6. Sensitivity Analysis

Sensitivity analysis was performed to assess whether the study results were stable, even as the assumptions applied to the study were changed. We performed a sensitivity analysis from a societal perspective, in which productivity loss costs for both employees and household workers were considered in addition to direct costs.

Table 1
Baseline Characteristics of Participants.

	JDH (n = 35)	Placebo (n = 29)	P-value[a]
Age (mean)	66.5	67.1	.783
Years of education (mean)	11.9	9.9	.036
Sex (n(%))			
Male	15 (42)	8 (27.6)	.205
Female	20 (57.1)	21 (72.4)	
Smoking (n(%))			
No	25 (71.4)	23 (79.3)	.332
Quit for more than 6 months	10 (28.6)	5 (17.2)	
Yes	-	1 (3.4)	
Drinking (n(%))			
No	25 (71.4)	25 (86.2)	.155
Yes	10 (28.6)	4 (13.8)	
Employment status (n(%))			
Paid employment	11 (31.4)	15 (42.9)	.277
House-hold worker	15 (42.9)	10 (28.6)	
Unemployed	8 (22.9)	4 (11.4)	
MMSE-DS	25.4 ± 2.9	24.7 ± 3.4	.389
EQ-5D score	0.859 ± 0.11	0.879 ± 0.08	.490
KQOL-AD score	30.03 ± 6.41	29.45 ± 4.93	.691

EQ-5D, Euroqol five-dimension scale; JDH, Jujadokseo-hwan; MMSE-DS, Korean version of Mini Mental State Examination for Dementia Screening; KQOL-AD, Korean Quality of Alzheimer's Disease

[a] P-value was calculated using the independent t-test or chi-square test.

The lost productivity costs were calculated by multiplying the lost times, hourly compensation, and the rate of employees or household workers. Data on lost hours due to absenteeism were self-reported in the cost questionnaire survey during the trial. The survey was conducted at the first visit (baseline), at the end of treatment (12 weeks), and at the end of the study (24 weeks). Hourly wages for employees were calculated using the 2020 national statistics data on Statistics Korea.[57] It was converted into the year 2021 KRW monetary value using the year-on-year nominal wage growth rate.[58] The hourly value of housework in 2014 was KRW 10,569 and transformed to the 2021 monetary value using the average annual growth rate of the value of unpaid housework.[59,60] We assumed that both the JDH and placebo groups had the same proportion of employees and household workers, which was calculated based on the participants' characteristics.

2.7. Statistical Analysis

All data were presented descriptively as frequency (%), mean, and standard deviation. To examine the homogeneity between the intervention and control groups, baseline characteristics were compared using the independent t-test or chi-square test. We conducted paired t-tests to evaluate the improvement in outcomes after the intervention. The difference-in-differences test was used to compare changes between baseline and endpoints for JDH in comparison with placebo. A p-value$<$.05 was considered statistically significant (two-tailed). IBM SPSS statistics version 25 (IBM Corp., Armonk, NY, USA) was used for all data analyses.

3. Results

After screening 140 individuals, we found that 80 were eligible for participation in the clinical trial. They were randomly assigned to the intervention group with JDH treatment (n = 43) or the placebo group (n = 37). A total of 64 participants (80%) completed all the visits (n = 35 for JDH and n = 29 for the placebo group) within 24 weeks, and their data was used for the economic evaluation analysis.

Table 1 below shows the demographic characteristics, MMSE-DS scores, and QoL scores at baseline. There were no significant differences between the JDH and placebo groups at baseline, except for education years (Table 1).

Table 2
Quality of life Outcomes within the JDH and Placebo during follow-up (per protocol).

		JDH (n = 35)		Placebo (n = 29)		p-value
		Mean ± SD (p-value)		Mean ± SD (p-value)		
EQ-5D	Baseline	0.859 ± 0.11		0.876 ± 0.08		
(range 0–1)	12 weeks	0.880 ± 0.10	(.272)	0.890 ± 0.09	(.479)	
	24 weeks	0.880 ± 0.12	(.318)	0.878 ± 0.09	(.920)	
	Change[a]	0.020 ± 0.12		0.001 ± 0.10		.519
KQOL-AD	Baseline	30.03 ± 6.41		29.45 ± 4.93		
(range	12 weeks	32.00 ± 5.93	(.001)	31.41 ± 4.70	(.008)	
13–52)	24 weeks	33.43 ± 7.79	(.011)	30.52 ± 5.34	(.130)	
	Change[a]	3.40 ± 7.46		1.07 ± 3.69		.110
QALY	For 12 weeks[b]	0.2017 ± 0.0219		0.2051 ± 0.0151		
	For 24 weeks[b]	0.4046 ± 0.0405		0.4092 ± 0.0288		
	Change[c]	0.0080 ± 0.0386		0.0047 ± 0.0316		.713

Abbreviations: EQ-5D, Euroqol five-dimension scale; KQOL-AD, Korean Quality of Alzheimer's Disease; QALY, Quality Adjusted Life Years.
[a] Change was difference between baseline and 24 weeks, within the group.
[b] QALY for 12 or 24 weeks was calculated by using the area under the curve.
[c] QALY change was an increase in QALY by intervention during 24 weeks of study.

Table 3
Costs for 24 weeks per person (2021KRW).

	JDH	Placebo
Costs for 24 weeks per person (KRW)		
Direct medical cost	862,000	610,000
Direct non-medical cost	23,000	23,000
Lost productivity cost for employee	8,800	11,100
Lost productivity cost for household worker	8,800	8,900
Total costs for 24 weeks per person (KRW)		
Base-case[a]	885,000	633,000
Sensitivity analysis[b]	902,000	653,000

JDH, Jujadokseo-hwan
[a] Base case included direct costs from a healthcare perspective.
[b] Sensitivity analysis scenario considering both direct costs and productivity loss costs from a societal perspective.

3.1. Quality of life outcomes

Table 2 below shows the QoL scores of the EQ-5D and KQOL-AD at each follow-up point. The QoL scores in JDH sequentially increased for both EQ-5D and KQOL-AD during the 24 weeks of study. In the placebo group, the QoL scores increased during the 12 weeks of administration and slightly decreased thereafter for the follow-up period. During 24 weeks of study, the improvement in EQ-5D scores was greater in the JDH group than in the placebo group, but there was no statistically significant difference between them (p = .519). For the KQOL-AD scale, the score significantly increased in JDH (p = .011) from baseline. However, the change in KQOL-AD was not statistically different from that in the placebo group (p = .110).

On the other hand, the increased QALYs during 24 weeks for the JDH group (0.0080 QALYs) was approximately 1.7 times greater than the increased QALYs in the placebo group (0.0047 QALYs) (Table 2).

3.2. Costs

The cost estimates generated during 24 weeks of study periods are summarized in Table 3 below. The direct medical cost of the JDH group was 1.4 times greater than that of the placebo group because of the daily dosage cost of KRW 3,000 for JDH (Table 3). The direct non-medical costs were identical, as both groups were required to visit hospitals eight times. Therefore, the total cost was approximately 40% greater in the JDH treatment group than in the placebo group (Table 3).

The average loss of work productivity during 12 weeks of treatment was 0.25 hours and 0.43 hours per person in the JDH and the placebo group respectively. During the subsequent 12 weeks of observation, the average missing work time was similar between the two groups (0.43 and 0.44 hours). According to the survey, the employment rate of participants was 44% in the treatment period and 47% in the follow-up period. Based on the employment rate, missing work time, and hourly wages, the lost work productivity costs during 24 weeks were KRW 8,800 in the JDH and KRW 11,100 in the placebo group.

The average loss time of household work for participants was 0.64 hours vs. 0.60 hours during 12 weeks of treatment periods and 0.79 hours vs 0.85 hours during the 12 following weeks of observation, respectively. The household service worker rate was 38% over 24 weeks. The lost household work productivity costs during the 24-weeks were KRW 8,800 in the JDH and KRW 8,900 in the placebo group. The total costs, including both direct and indirect costs for the JDH group (KWR 902,000) were 1.38 times greater than the placebo group (KRW 653,000) (Table 3).

3.3. Cost-effectiveness analysis

The ICER results are presented in Table 4 below. The base case model analyzed from the healthcare perspective showed that the incremental direct costs of using the JDH for treating patients with MCI was KRW 76,400,000 for increasing one QALY compared to placebo (Table 3). With regard to a one-point increase in KQOL-AD, the incremental cost during 24 weeks was KRW 108,000 (Table 4).

Considering both direct and indirect costs, the result of ICER for 24 weeks was an 75,600,000 KRW/QALY and 107,000 KRW/KQOL-AD for providing JDH in patients with MCI compared to the placebo group (Table 4).

4. Discussion

This study was performed to identify the effectiveness and economic outcomes of JDH in patients with MCI. First, we assessed QoL using two different QoL-instruments, EQ-5D and KQOL-AD. We observed an improvement in QoL in patients with MCI who received JDH using both questionnaires. After 6 months of receiving JDH compared to baseline, the EQ-5D score increased by 0.02, and the KQOL-AD score increased by 3.4. A statistically significant improvement was seen in KQOL-AD but not EQ-5D, resulting from the difference in the characteristics of the two QoL scales. The EQ-5D is the most widely used generic QoL instrument, but it does not focus on specific diseases. It has problems with ceiling effects

Table 4
Results of Incremental cost-effectiveness ratio (ICER).

QoL	Analysis	Delta[a] △QoL	Delta[a] costs (KRW)	ICER (KRW/QoL)
△[b] QALYs	Base-case[c]	0.0033	252,000	76,400,000
	Sensitivity analysis[d]		250,000	75,600,000
△[b]	Base-case[c]	2.33	252,000	108,000
KQOL-AD	Sensitivity analysis[d]		250,000	107,000

Abbreviations: ICER, Incremental cost-effectiveness ratio; KQOL-AD, Korean Quality of Alzheimer's Disease; QoL, Quality of life; QALYs, Quality Adjusted Life Years.
[a] Delta was the difference between JDH and Placebo.
[b] △ was the difference between baseline and 24 weeks, within group.
[c] Base-case included direct costs from a healthcare perspective.
[d] Sensitivity analysis included productivity loss costs in addition to the base case model.

and especially lacks sensitivity in the domain of mental health.[61] Therefore, the EQ-5D results in this study may not fully demonstrate the effectiveness of JDH on QoL in patients with MCI. On the other hand, the KQOL-AD is a disease-specific QoL instrument developed for patients with mild to moderate dementia and is known to better reflect QoL in patients with cognitive impairment than general QoL measures.[8] In this context, JDH, which significantly altered KQOL-AD scores, might be considered a promising treatment for managing QoL in patients with MCI.

Although KQOL-AD is a reliable and valid QoL-scale for patients with cognitive deficits in Korea,[54] the minimal change in KQOL-AD score that can evaluate the adequacy of MCI treatment is still unknown. To our knowledge, there have been three previous studies in Korea that compared the KQOL-AD scores between patients with MCI (or CDR rating of 0.5) and normal cognitive individuals.[53,62,63] Three studies reported that the KQOL-AD score of normal cognitive individuals was two to four scores higher than that of patients with MCI,[53,62,63] and the difference is similar to a 3.4 point increase in the JDH group in our study. For example, a study had a difference in KQOL scores of 2.98 points (32.62 in MCI vs. 35.60 in normal cognition) that used composite KQOL-AD calculated from patient and proxy scores, in contrast to our study.[53] In the other two studies using patient-rated KQOL-AD similar to our study, the KQOL-AD of MCI and normal cognition was 27.93 vs. 29.50 and 33.9 vs. 30.1, respectively.[62,63] As the calculation methodology for KQOL-AD and baseline characteristics (e.g., age, sex, educational years, MMSE) was different, the QoL scores at the same stage were inconsistent in each study. However, a 3.4 score increase in KQOL-AD in our study, as a result of receiving JDH, may imply a meaningful improvement in QoL, given the differences in KQOL-AD scores between normal cognition and patients with MCI.

Subsequently, we developed and assessed a cost-effectiveness model for JDH in patients with MCI. Our economic model suggested that the incremental cost of using JDH is about 76,400,000 KRW per QALY of patients with MCI compared to placebo. This ICER value was higher than the payer's threshold value, which is usually suggested as GDP per capita (KRW 35,200,000, as GDP per capita in 2021).[64,65] Although the ICER results in our study exceeded the willingness to pay in South Korea, the economic value of JDH should be determined considering the benefits of therapeutic intervention at the MCI phase and how QoL improvement can reduce care burden and save medical resources.

This study has several strengths. First, our study is the first to analyze the cost-effectiveness and provide economic evidence for JDH in patients with MCI. In Korea, effective treatment interventions for MCI are still being explored, and few economic evaluation studies have been conducted. Despite the long history of Korean medicine, evidence for the effectiveness and cost-effectiveness of Korean herbal medicine is still sparse. Therefore, this study will be helpful in policymakers' decision-making and establish the basis for Korean herbal medicine.

Second, our study assessed the improvement of QoL in patients with MCI as a clinical outcome of JDH. Although most studies evaluated the effectiveness of treatment for MCI using cognitive scales, particularly MMSE,[66] QoL is a more clinically relevant treatment response than standard cognitive scales.[21,51] This is because cognitive tests may not sensitively detect small changes in cognitive function in patients with MCI.[32,67,68] Additionally, deterioration of MCI results from a complex interaction of cognitive, functional, and psychiatric factors,[66] so measuring only cognition may not accurately capture the overall usefulness of interventions for MCI. The KQOL-AD consists of items related to the functional, physical, and psychiatric dimensions, KQOL-AD may present the complex effectiveness of JDH on MCI.

However, this study has several limitations. First, the sample size of the clinical trial was not large enough to suggest therapeutic outcomes with adequate statistical power. Therefore, the improvement in QoL by receiving JDH, measured using EQ-5D and KQOL-AD, might not exhibit a statistically significantly difference compared to placebo. However, this is a common issue in economic evaluation studies set alongside RCT, where only a minimum number of study samples are allowed to participate to obtain significant meaning.

Second, uncertainty may arise in estimating daily activity impairment costs. As there is no standard method to estimate lost productivity costs in household work, this study used the hourly value of household work, which was arbitrarily calculated by synthesizing data from several sources.

Third, it might be insufficient to determine the overall outcomes of JDH on QoL and cost-effectiveness within 24 weeks although six months can be regarded as a mean study duration for cost-effectiveness analysis alongside clinical trials in patients with cognitive deficits.[69] Considering the characteristics of MCI as a progressive and chronic condition, evaluation over long-term observation is desirable to confirm the QoL and economic benefits. Given that the continuous improvement in QoL over 6 months in the JDH, a longer follow-up may lead to meaningful differences in QoL and QALY, resulting in better ICER value favorable to JDH. Further studies should be performed to estimate the long-term prognosis by using, for example, a Markov prediction model.

Finally, our results using placebo-controlled cannot be generalized to the actual clinical setting, where providers or patients are to choose one treatment among various active treatment options. For JDH, it was difficult to identify an active comparator because there is still no clinically proven CAM intervention as a standard treatment for MCI. Many economic evaluations on pharmacotherapy in patients with cognitive deficits have compared a treatment of interest with placebo or no treatment control group.[70-75] In future, further research is needed to compare the QoL and cost of JDH with other Korean Medicine, CAM intervention, and Western medicine treatment as well.

In South Korea, drug reimbursement is determined according to the results of a cost-effectiveness analysis, which can rationally al-

locate limited health care resources. To our knowledge, there are no insured medicines for MCI in Korea. Long-term intervention with non-insured medicines increases the cost burden for patients with MCI, making it difficult to maintain treatment. This can be a significant barrier to implementing timely treatments for patients with MCI, which is a golden opportunity to prevent the transition to dementia. Future research should be conducted that includes a large number of participants and a sufficient time horizon to provide insured medicines based on an economic evaluation of patients with MCI.

In conclusion, this study showed that currently, JDH cannot be a cost-effective intervention option over placebo for patients with MCI in Korea from a healthcare perspective. However, JDH demonstrated an improvement in QoL in patients with MCI. Considering that QoL improvement is an important therapeutic outcome in the long-term treatment plan for patients with MCI, JDH may be a potential treatment option to be considered in the clinical setting.

CRediT authorship contribution statement

Ji-Eun Lee: Conceptualization, Software, Formal analysis, Writing – original draft, Visualization. **Hyung Won Kang:** Investigation, Writing – review & editing. **Sun-A Jung:** Writing – original draft. **So-Young Lee:** Validation. **Ju Yeon Kim:** Investigation. **Da Eun Lee:** Data curation. **Jin-Hyung Joeng:** Data curation. **In Chul Jung:** Investigation, Resources, Writing – review & editing, Funding acquisition. **Eun Cho:** Methodology, Formal analysis, Writing – review & editing, Supervision, Project administration.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Ethical statement

This research was reviewed and approved by the institutional review board of Daejeon University Hospital (DJDSKH-18-DR-16), Wonkwang University Sanbon Hospital (WMCSB 201901-09), and Wonkwang University Jeonju Hospital (WUJKMH-IRB-2018-0006).

Data availability

The data analyzed during this study are not publicly available as they are being collected and analyzed in a clinical trial (KCT0003570).

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