Effect of *Hominis Placenta* Pharmacopuncture for a Patient with Mild Cognitive Impairment: A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial

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Objectives: Mild cognitive impairment (MCI) is condition of cognitive decline shown in transition from normal aging to dementia. *Hominis placenta* pharmacopuncture (HPP) is a treatment that combines effects of medication and acupuncture by injecting Hominis placenta into acupoints. The objective of this study was to evaluate the efficacy and safety of HPP for MCI.

Methods: This was a randomized, double-blind, placebo-controlled, two-center clinical trial. Eligible patients were randomly allocated to either the HPP group or the placebo group. HPP or saline as placebo was administered to participants for eight weeks. Changes in symptoms were observed. The primary outcome was difference in mean change of Korean Version of the Montreal Cognitive Assessment (MoCA-K) score between the HPP group and the placebo group. Cognitive function, overall status of mood and sleep, and quality of life (QoL) were also assessed. Safety assessment and economic analysis were then conducted.

Results: Thirty participants were enrolled. One participant in the placebo group dropped out. The score of MoCA-K increased after treatment. Its mean change was smaller in the HPP group than in the control group. HPP ameliorated Global Deterioration Scale and Korean Dementia Rating Scale subtests for attention, organization, and memory compared to the placebo. However, none of them was significantly different between the two groups. Mood, sleep, and QoL all improved more in the HPP group than in the placebo group, although differences between the two groups were not statistically significant. There was no adverse event probably related to the drug. HPP treatment needed KRW 345,000 more than the placebo group in improving Geriatric Quality of Life scale-Dementia score by one point for one year.

Conclusions: Although HPP treatment did not significantly improve cognition, it changed behavioral and psychological symptoms in MCI.

Key Words: *Hominis placenta*, Pharmacopuncture, Mild cognitive impairment, Efficacy, Economic analysis, MoCA.

I. INTRODUCTION

Mild cognitive impairment (MCI) refers to the intermediate stage of transition from normal aging to dementia with memory impairment compared to normal elderly, but the ability to perform independent daily activities is preserved. MCI is a time point for early diagnosis and treatment to reduce the onset of dementia, and has important significance in that it can delay or prevent progression to dementia[1]. Currently, treatments for patients with MCI are largely divided into pharmacological treatment and non-pharmacological treatment. Pharmacological treatment has not yet been fully developed, and long-term use of the drug has to bear the risk of side effects[2].

Pharmacopuncture is different from simple injection therapy in that it obtains both the effects of drugs and acupuncture at the same time by injecting 0.1 to several ml of pharmacopuncture fluid into the acupuncture points or trigger points. The selection of pharmacopuncture fluid is based on the characteristics and efficacy of herbs such as qi-flavor theory (氣味論), and the selection of treatment sites is based on the meridian and collateral theory (經絡論). Currently, pharmacopuncture is widely used in the clinical field of Korean medicine. Various kinds of pharmacopuncture such as Bee Venom, Sweet Bee Venom, Cornu cervi pantotrichum, Mountain Ginseng have been developed and adjusted to various diseases[3].

Hominis placenta (*H. placenta*) is one of the popular pharmacopuncture. *H. placenta* is collected from fresh *placenta* from healthy pregnant women. In traditional medicine, *H. placenta* is known to tonify and replenish (補益) consumption (虛損), and replenish (補) qi (氣), blood (血) and essence (精)[4]. It is known that *H. placenta* pharmacopuncture (HPP) can achieve a synergistic therapeutic effect by combining the effects of drugs and acupuncture[3]. There have been several studies reporting therapeutic effects of HPP.

Case reports were conducted on diverse range of diseases including inflammatory disease, psychiatric disease, muscular disease, etc. Case reports on neurological disease were also reported such as peripheral facial nerve palsy[5], idiopathic oculomotor nerve palsy[6], leg spasticity of stroke patients[7], transverse myelitis[8]. HPP improved memory function and inhibited damaged lesions in brain tissue and pathological protein expression such as Tau protein, glial fibrillary acidic protein (GFAP) protein, and presenilin 1/2 protein in mice under intrahippocampal amyloid-β injection[9]. HPP also decreased amyloid-β deposits and increased brain-derived neurotrophic factor (BDNF) expression in hippocampus of amyloid-β mouse model of Alzheimer's disease[10]. Injection of *H. placenta* was reported to improve memory recall and dendritic growth of normal cortical neurons in mouse model of Alzheimer's disease[11]. In a case study, HPP treatment improved the cognition of a patient diagnosed with MCI, as assessed by an increase in the scores of Korean Version of the Montreal cognitive Assessment (MoCA-K) and Korean Dementia Rating Scale (K-DRS)[12].

Thus, this study aimed to explore the efficacy, safety and cost-effectiveness of HPP treatment in patients with MCI.

II. METHODS

1. Trial design

This study is a randomized, double-blind, placebo-controlled, two-center clinical trial to objectively evaluate the efficacy and safety of HPP for MCI. The eligible patients were randomly allocated in 50/50 splits. HPP or placebo pharmacopuncture was administered to participants for eight weeks and changes in symptoms observed before and after eight weeks of administration. This trial was performed in Kyung Hee University Korean Medicine Hospital and Semyung

University Korean Medicine Hospital. The trial was conducted according to the previously published trial protocol and the detailed method is described in the protocol[13].

2. Ethical considerations

The study received ethical approval from the Institutional Review Boards of Kyung Hee University Korean Medicine Hospital and Semyung University Korean Medicine Hospital (KOMCIRB 2019-10-004 and SMCJH 1912-08, respectively). This trial complies with the Declaration of Helsinki. All participants were fully explained the protocol and voluntarily signed the informed consent form.

3. Participants

1) Assessment of eligibility

Participants who voluntarily agreed to the trial were given a subject identification code in order, and underwent a demographic survey, vital sign and laboratory tests, and neuropsychological examinations to determine whether they met the inclusion/exclusion criteria.

2) Inclusion criteria

(1) Male or female adult aged 50 to 80.

(2) A person diagnosed with mild neurocognitive impairment based on Diagnostic And Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[14].

(3) A person who can undergo neuropsychological tests and complete questionnaires.

(4) A person who agrees to participate in the trial after receiving explanations regarding the purpose and procedures involved in the clinical trial and has signed the informed consent form by oneself or one's legal representative.

(5) A person with a score of 0.5 on the CDR.

3) Exclusion criteria

(1) A person with a cranial lesion or brain injury that can cause cognitive decline.

(2) A person with a history of cerebral hemorrhage or cerebral infarction.

(3) A person with brain diseases such as Parkinson's disease, epilepsy, and brain cancer.

(4) A person with a present illness or past history of a major psychiatric disorder such as schizophrenia, delusional disorder, depressive disorder, bipolar disorder, or alcohol or substance abuse disorder as diagnosed using DSM-5.

(5) A person who has participated in other clinical trials within the last month.

(6) A person who had acupuncture treatment for cognitive impairment within the last four weeks.

(7) A person who is currently taking medication related to dementia (If the person is diagnosed with MCI and is taking dementia-related drugs, he/she may participate in the clinical trial after the washout period of 15 days).

(8) A person with a severely destabilizing general medical condition (a doctor in charge will judge the enrollment based on the results of laboratory tests, vital signs, etc.).

(9) A person with clinically serious liver disease or with serum aspartate transaminase and alanine transaminase levels exceeding twice the upper limit of reference value (AST: Male 50, Female 35; ALT: Male 50, Female 35).

(10) A person with chronic renal failure or with serum blood urea nitrogen and creatinine levels exceeding 1.5 times the upper limit of reference value (BUN: 20, Creatinine: Male 1.18, Female 1.02).

(11) Pregnant woman, lactating woman, or woman of childbearing potential who does not use appropriate methods of contraception.

(12) A person who researchers judge to be in-

appropriate for participation in this clinical trial.

(13) A person who is hypersensitive to *H. placenta* and other drugs.

(14) A person with moderate complications other than those involving the heart, liver, and kidney.

(15) A person with psychogenic diseases.

4) Discontinuation criteria

Participants can be excluded from the study when any of the following conditions are met:

(1) In case the participant withdraws their consent to participate in the trial.

(2) In case the participant violates the inclusion criteria or meets the exclusion criteria.

(3) In case the participant has serious adverse events (AEs), or it is difficult to continue the clinical trial due to AEs.

(4) In case it is judged impossible to continue treatment or observe the participant due to an unexpected disease or accident.

(5) In case the participant requests discontinuation or the investigator determines discontinuation due to a worsening cognitive deficit during the clinical trial.

(6) In case cognitive function deteriorates during the clinical trial and CDR becomes 1 or higher.

(7) In case it is determined that there is an unavoidable reason for the participant to discontinue the trial.

(8) In case overall compliance is less than 70%.

4. Interventions

Pharmacopuncture treatment was performed by Korean Medicine Doctor of Neuropsychiatry. 1 mL of *H. placenta* or placebo was injected twice a week into acupoints (GV20, both ST36, CV12). Other drugs and therapies to ameliorate cognitive function were prohibited in principle during the clinical trial period, and in the event of concurrent treatment, the clinical trial director determined whether the partic-

ipant would be excluded from the study and the statistical analyses.

5. Sample size calculation

Since there was no previous clinical trial on *H. placenta* for this indication, the results of previous studies on herbal medicines using MoCA scores[15] were cited. According to the previous study comparing MoCA scores after herbal medicine or placebo treatment of patients with MCI, calculation using a standard formula[16] yielded a sample size of 10 for each group, with 80% statistical power at 5% level significance (α=0.05, 1-β=0.8). Assuming a dropout rate of 30% considering the eight-week-long administration and follow-up period, the final sample size was determined to be 15 for each group, 30 in total.

6. Randomization and allocation concealment

Block randomization was performed on participants who met the inclusion/exclusion criteria. The randomization number was generated by an independent statistics expert using R. The generated number was placed in a lightproof, sealed envelope and kept in a locked chamber that was accessible only to people authorized to be unblinded. After completion, database lockout was performed, and then the random number table with intervention group or control group labelled either A or B was provided to the investigator responsible for statistical analysis. After the statistical analysis was completed, the group information marked either A or B was disclosed.

7. Blinding

This clinical trial was designed to be double-blinded by separating the pharmacopuncture practitioner and assessor from the process of transferring *H. placenta* from ampule to syringe and controlling the bias as much as possible. To avoid participant

bias as much as possible, the syringe was covered by translucent tape on the surface to avoid the participant from noticing the color of the liquid. The practitioner injected the same amount of *H. placenta* or saline with the needle at the same acupoints so that both practitioner and participant would not infer allocation. The validity of the blinding was assessed by an investigator who was not involved in either allocation or performance of the pharmacopuncture treatment.

8. Outcome measurement

This study aimed to explore the efficacy, safety and cost-effectiveness of HPP treatment in patients with MCI. It evaluated its efficacy on cognitive functions using MoCA-K, Mini-Mental Status Examination for Dementia Screening (MMSE-DS), K-DRS, Clinical Dementia Rating (CDR), and Global Deterioration Scale (GDS). It also assessed diverse dimensions of the patients such as mood change, sleep disturbance and quality of life (QoL) using the Korean version of Beck Depression Inventory-II (K-BDI-II), State-Trait Anxiety Inventory (STAI), State-Trait Anger Expression Inventory (STAXI), Insomnia Severity Index (ISI), Euro Quality of Life-5 Dimensions (EQ-5D), Euro Quality of Life-visual analogue scale (EQ-VAS), and Geriatric Quality of Life scale-Dementia (GQOL-D). Incremental cost-effectiveness ratio was also acquired from the collected data.

1) Primary outcome

The primary outcome was the difference in mean change of MoCA-K scores between intervention group and control group. The MoCA-K is a tool that was originally developed by Nasreddin et al.[17] to screen for MCI, which was translated into Korean and validated[18]. The maximum score is 30 points, and one point is added when the participant has been educated for less than six years to correct dif-

ferences in cognition due to academic background. Reliability of the original tool was Cronbach's α = .83[17] and that of the translated tool was Cronbach's α = .81~.84[18].

2) Secondary outcomes

Secondary outcomes were (1) differences in mean change of MMSE-DS, K-DRS, CDR, GDS, K-BDI-II, STAI, STAXI, ISI, EQ-5D, EQ-VAS, and GQOL-D scores between intervention group and control group, and (2) direction of intra-group change of mean of K-DRS, MMSE-DS, MoCA-K, CDR, GDS, K-BDI-II, STAI, STAXI, ISI, EQ-5D, EQ-VAS, and GQOL-D scores in pre- and post-treatment evaluation. K-DRS, MMSE-DS, MoCA-K, GDS, K-BDI-II, STAI, STAXI, ISI, EQ-5D, EQ-VAS, and GQOL-D scores were assessed at baseline and 8 weeks, and CDR score was assessed at baseline, 4 weeks, and 8 weeks.

(1) Korean Dementia Rating Scale (K-DRS)

The K-DRS[19] is the Korean version of the Dementia Rating Scale[20], which consists of five subtests suitable for examining general cognitive functions: attention, execution, organization, memory, and conceptualization. The score ranges from 0 to 144 points. The correlation with MMSE-K was 0.82, and two-week test-retest reliability was 0.96[19].

(2) Mini-Mental Status Examination for Dementia Screening (MMSE-DS)

The MMSE-DS was developed by Han et al. (2010) to measure cognitive function in the elderly. The scores obtained are calculated by adding all the scores obtained based on the 19 questions. The maximum score is 30 points, and the cutoff score varies according to age, gender, and education. The Pearson correlation coefficient between 4-week interval test-retest results was 0.935 ($p < 0.001$).

(3) Global Deterioration Scale (GDS)

GDS is designed to classify the clinical severity of patients who are suspected to have dementia or are

diagnosed with dementia. It is a revised version of the GDS designed by Reisberg et al.[22] and they showed that the inter-tester reliability is 0.95[22].

(4) Clinical Dementia Rating (CDR)

The CDR scale was developed by Hughes et al.[23] to measure the degree of cognitive and social function of dementia patients. The Korean version translated by Choi et al.[24] was used in this study. This tool evaluates dementia severity by compiling reports from the patient and the caregiver regarding six areas of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

(5) Korean version of Beck Depression Inventory-II (K-BDI-II)

The 21-item BDI was developed by Beck et al.[25] to measure the severity of depression. Items of the K-BDI-II are scored on a 4-point Likert scale ranging from 0 to 3 points, and a higher score means more severe depression.

(6) State-Trait Anxiety Inventory (STAI)

It is a measure that can evaluate state anxiety and trait anxiety simultaneously and was developed by Spielberger et al.[26]. In order to measure anxiety experience, it evaluates state anxiety (20 questions) and trait anxiety (20 questions), each on a 4-point scale. The score ranges from 20 to 80, and a higher score means higher anxiety.

(7) State-Trait Anger Expression Inventory (STAXI)

The STAXI is a scale developed by Spielberger[27] and consists of 44 questions that evaluate state anger (10 questions), trait anger (10 questions), and anger expression (24 questions). Each item is measured on a 4-point scale.

(8) Insomnia Severity Index (ISI)

This is a subjective measure of insomnia developed by Morin (1993), and a self-reporting measure that assesses the type and severity of insomnia, sleep satisfaction, disturbance of daytime function, and

sufferings from sleep disorders. Total score ranges from 0 to 28 and higher scores indicate more severe symptoms of insomnia.

(9) Euro Quality of Life-5 Dimensions (EQ-5D), Euro Quality of Life-visual analogue scale (EQ-VAS)

Euro Quality of Life (EuroQol) Group developed it as a tool for measuring health-related QoL[29]. It consists of a description part and evaluation part. Evaluation part consists of EQ-5D index and EQ-VAS. EQ-VAS using a visual analogue scale is designed to indicate one's current health status on a vertical line graded from 0 (the worst imaginable health) to 100 (the best imaginable health).

(10) Geriatric Quality of Life scale-Dementia (GQOL-D)

GQOL-D is a scale to measure the quality-of-life of dementia patients, especially AD. It is designed to comprehensively cover all different sub-areas from other quality-of-life tools for the elderly[30]. This scale consists of a total of 15 items, including 13 items that measure physical health, psychological health, social relations, and environment and 2 items that respectively measure overall health and overall life satisfaction.

9. Economic analysis

This study used GQOL-D score as the clinical performance index, and direct medical cost (Korean medicine service), direct non-medical cost (round-trip transportation fare), and indirect cost as costs. Direct medical cost included pharmacopuncture costs for HPP group and body acupuncture costs applied for the control group. Direct nonmedical costs included only round-trip transportation fare for treatment visits. Indirect costs were productivity loss, which were obtained data from the national reports regarding dementia and MCI[31-33]. To determine the health outcomes of cost-effectiveness, the difference

in difference analysis was performed to confirm the significance of the mean change in GQOL-D scores between two groups. The additional monetary values per increasing one GQOL-D point for HPP treatment group compared to the control group during 8 weeks was measured. For sensitivity analysis, another cost-effectiveness analysis was conducted by projecting the model over a period of one year. The effect of 8-week-long HPP treatment was also assumed to be retained for one year while receiving HPP treatment at the same frequency as in the clinical trial (104 times per year). Economic analysis was conducted by the experts (E Cho and JE Lee).

10. Statistical analysis

For the analysis of efficacy, intention-to-treat (ITT) analysis was conducted. ITT set included participants who administered at least one investigational product, underwent efficacy evaluation at least once, and did not violate the inclusion/exclusion criteria as described in the protocol. The continuous data were presented as mean and standard deviation by 95% confidence interval, and categorical data was presented as frequency and percentage. Chi-square an-

alysis was performed for group comparison of dichotomous variables (e.g. sex, occupational status, education year, and educational background) and categorical variable (e.g. CDR), and independent t-test was performed for group comparison of continuous variables. The paired t-test was performed for intra-group variation. For CDR sum of boxes (CDR-SB), repeated measures analysis of variance was used to compare the difference of the changes over time.

III. RESULTS

As described in Fig. 1, 34 participants were screened and 4 participants were excluded. A total of 30 participants who were diagnosed as MCI and met eligibility criteria were randomly assigned to either of HPP group and placebo group. Every participant in HPP group completed the whole visits, while 14 participants in placebo group finished the visits. One participant in placebo group withdrew before the completion of the trial due to AEs, resulting in a dropout rate of 3.33%.
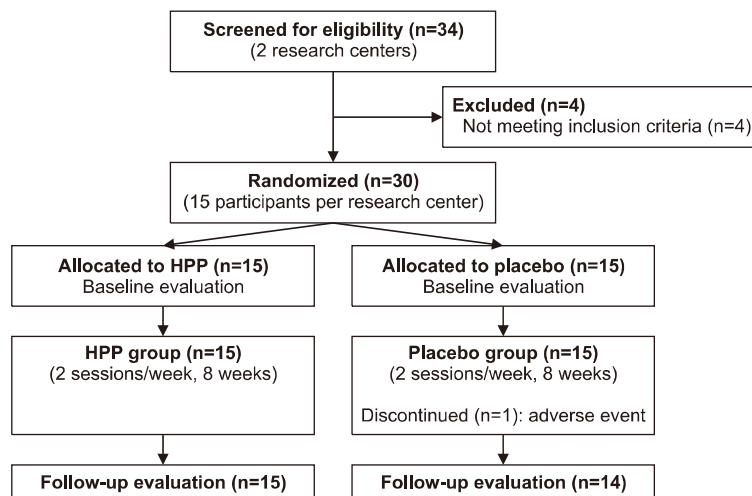

Fig. 1. Flowchart of participants through the study.

1. Demographic data

The groups were similar at baseline in terms of demographic characteristics and clinical characteristics (Table 1). There were one male (6.67%) and fourteen females (93.33%) in HPP group and two males (13.33%) and thirteen females (86.67%) in placebo group. The average years of education was not significantly different (12.13±2.97 vs 11.40±4.45, p= 0.6000) and the highest percentage of respondents in both groups answered that they graduated high school. There was no significant difference between two groups in terms of age, sex, duration of MCI,

Table 1. Sociodemographic Data of the Participants

	HPP group (n=15)	Placebo group (n=15)	p-value
Sex (%)			
Male	1 (6.67%)	2 (13.33%)	0.5428
Female	14 (93.33%)	13 (86.67%)	
Age (yr)	59.53±5.37	61.20±5.32	0.4004
Duration of MCI (yr)	4.93±2.66	5.07±3.51	0.9076
Occupation status (%)			
Employed	10 (66.67%)	12 (80.00%)	0.2912
Unemployed	0 (0%)	1 (6.67%)	
Other	5 (33.33%)	2 (13.33%)	
Years of education (%)	12.13±2.97	11.40±4.45	0.6000
Education (%)			
Under elementary school	0 (0%)	1 (6.67%)	0.2322
Elementary school	2 (13.33%)	1 (6.67%)	
Middle school	0 (0%)	3 (20.00%)	
High school	9 (60.00%)	5 (33.33%)	
University	4 (26.67%)	5 (33.33%)	
Height	159.34±4.85	156.24±7.90	0.2059
Weight	59.36±8.92	59.19±7.61	0.9548
MoCA-K	25.27±2.40	24.27±2.91	0.3141
MMSE-DS	27.60±1.12	26.40±2.03	0.0575
CDR-SB	1.50±0.53	1.47±0.48	
K-DRS	135.07±3.99	135.07±4.54	1.0000
Attention	36.47±0.83	36.53±0.83	0.8283
Execution	35.2±2.04	34.47±2.61	0.3997
Organization	5.87±0.52	6.00±0.00	0.3343
Conceptualization	35.27±2.94	36.13±1.68	0.3324
Memory	22.20±1.66	21.93±1.79	0.6753
GDS	2.60±0.51	2.93±0.59	0.1094

CDR-SB: Clinical Dementia Rating-sum of boxes, GDS: Global Deterioration Scale, HPP: *Hominis placenta* pharmacopuncture, K-DRS: Korean Dementia Rating Scale, MCI: mild cognitive impairment, MMSE-DS: Mini-Mental Status Examination for Dementia Screening, MoCA-K: Korean Version of the Montreal Cognitive Assessment.

height, weight, vital signs and laboratory tests. As examined from neuropsychiatric tests including MoCA-K, K-MMSE-DS, CDR sum of boxes, K-DRS and GDS, the cognitive features of both groups did not show significant difference at baseline.

2. Cognition

In terms of MoCA-K, the primary outcome, the mean change of MoCA-K of HPP group was smaller than that of placebo group, and was not statistically significant (p=0.2924) (Table 2). MoCA-K score of both groups increased after treatment.

Neither mean change of the secondary outcome relevant to cognitive function was statistically significant except MMSE-DS (p=0.026) which was larger in the placebo group. Only GDS more decreased in HPP group after treatment but its difference was insignificant (p=0.7943). As for K-DRS, subtests for attention, organization, memory were increased more in HPP group and subtests for execution and conceptualization increased more in the placebo group,

Table 2. Difference in the Mean Change in Cognitive Parameters Before and After the Clinical Trial (Visit 1-Visit 6) between *Hominis placenta* Pharmacopuncture (HPP) Group and the Placebo Group

	HPP group (n=15)	Placebo group (n=15)	p-value
	Mean±sd	Mean±sd	
MoCA-K	1.73±1.16	2.27±1.53	0.2924
p-value	<0.0001	0.0001	
MMSE-DS	0.73±1.44	2.00±1.51	0.0260
p-value	0.0682	0.0002	
GDS	-0.53±0.74	-0.47±0.64	0.7943
p-value	0.0148	0.0135	
K-DRS	2.60±6.62	3.07±5.76	0.8383
p-value	0.1505	0.0583	
Attention	0.07±0.46	-0.07±1.03	0.6527
Execution	0.47±2.95	1.13±2.56	0.5139
Organization	0.13±0.52	-0.07±0.26	0.1943
Conceptualization	0.6±3.56	0.93±2.15	0.7587
Memory	1.4±2.95	1.13±1.64	0.7674

GDS: Global Deterioration Scale, HPP: *Hominis placenta* pharmacopuncture, K-DRS: Korean Dementia Rating Scale, MMSE-DS: Mini-Mental Status Examination for Dementia Screening, MoCA-K: Korean Version of the Montreal Cognitive Assessment.

but all of their difference had no statistical significance between two groups (Table 2).

As the CDR items were categorical data, chi-square analysis was conducted. All the participants scored 0.5 points at screening visit and visit 8. Afterward, two people in each group scored 0 point and the rest of the participants remained 0.5 points, whose difference was statistically insignificant (p=1.000). The score of CDR-SB decreased in both groups as the visits continued. As a result of the repeated measured ANOVA, there was no significant difference in the change over time between two groups (p=0.8630) (Table 3).

3. Accompanying symptoms related to mood, sleep and quality of life

None of the outcome measures related to mood, sleep and QoL was not statistically significant at visit 1. There was no statistical significance between two groups in terms of the changes from visit 1 to visit 16 (K-BDI-II, p=0.9450; STAI state anxiety p=0.7309, trait anxiety p=0.6284; STAXI state anger p=0.0896, trait anger p=0.6630; ISI p=0.7861) . Parameters on mood, such as K-BDI-II, STAI and STAXI, improved more in HPP group, especially STAXI worsened in placebo group. Sleep disturbance assessed by ISI was also enhanced in HPP group, while that of placebo group deteriorated (Table 4).

EQ-5D and EQ-VAS measured general health-related QoL, while GQOL-D was developed to assess disease-specific QoL of patients with dementia. In HPP group, EQ-5D decreased but EQ-VAS and GQOL-D increased after treatment. All three measures increased in placebo group. The mean change of EQ-VAS and that of GQOL-D were larger in HPP group, while the mean change of EQ-5D was larger

Table 4. Difference in the Mean Change in Parameters Regarding Mood, Sleep, and Quality of Life Before and After the Clinical Trial (Visit 1-Visit 16) between *Hominis placenta* Pharmacopuncture (HPP) Group and the Placebo Group

	HPP group (n=15)	Placebo group (n=15)	p-value
	Mean±sd	Mean±sd	
K-BDI-II	-1.73±8.25	-1.53±7.46	0.9450
p-value	0.4294	0.4395	
STAI			
State anxiety	-1.47±7.34	-0.60±6.29	0.7309
p-value	0.4517	0.7173	
Trait anxiety	-1.73±7.71	-0.47±6.40	0.6284
p-value	0.3988	0.7818	
STAXI			
State anger	-2.47±5.42	0.20±1.90	0.0896
p-value	0.0999	0.6893	
Trait anger	0.33±2.66	0.80±3.12	0.6630
p-value	0.6354	0.3377	
ISI	-0.27±5.23	0.27±5.43	0.7861
p-value	0.8462	0.8519	
QoL-related outcome			
EQ-5D	-0.01±0.08	0.44±1.58	0.2846
p-value	0.6145	0.2957	
EQ-VAS	1.87±10.53	1.67±14.10	0.9652
p-value	0.5035	0.6541	
GQOL-D	2.60±4.47	1.33±5.86	0.5112
p-value	0.0408	0.3934	

EQ-5D: Euro Quality of Life-5 Dimensions, EQ-VAS: Euro Quality of Life-visual analogue scale, GQOL-D: Geriatric Quality of Life scale-Dementia, HPP: *Hominis placenta* pharmacopuncture, ISI: Insomnia Severity Index, K-BDI-II: Korean version of Beck Depression Inventory-II, QoL: quality of life, STAI: State-Trait Anxiety Inventory, STAXI: State-Trait Anger Expression Inventory.

Table 3. The Change of CDR of Intervention Group and the Placebo Group during the Clinical Trial

	Screening			Visit 8			Visit 16			p-value[†]
	HPP	Placebo	p-value*	HPP	Placebo	p-value*	HPP	Placebo	p-value*	
CDR										
0	0	0	-	0	0	-	2	2	1.000	
0.5	15	15		15	15		13	13		
Total	15	15		15	15		15	15		
CDR-SB	1.50±0.53	1.47±0.48		1.27±0.42	1.27±0.50		0.97±0.48	1.07±0.56		0.8630

CDR: Clinical Dementia Rating, CDR-SB: Clinical Dementia Rating-sum of boxes, HPP: *Hominis placenta* pharmacopuncture.
*p-values refer to chi-square test, compared with the placebo group, [†]p-values are for repeated measured analysis of variance (ANOVA) comparing with the placebo group.

in placebo group. None of inter-group difference of these results was statistically significant (EQ-VAS, p=0.9652; GQOL-D, p=0.5112; EQ-5D, p=0.2846) (Table 4).

4. Safety

There was no significant difference between groups in regard to vital signs such as systolic blood pressure, diastolic blood pressure, temperature and pulse (p>0.05 respectively). Changes of all variables from the first visit to the final visit were also not statistically significant between two groups (p>0.05 respectively). Changes of AST, ALT, BUN and Creatinine from the first visit to the final visit were insignificantly different in both intra-group analysis and inter-group analysis (p>0.05 respectively) (Table 5).

The AEs that are likely to be related to the drug were two cases in the HPP group, while the events that were probably not related were 5 cases and the events definitely not related were 3 cases. In placebo group, the AEs that were probably not related were 5 cases and the events definitely not related were 4 cases. There was no significant difference in the occurrence of the AEs between the groups. Compliance was 100% in HHP group and 94.17% in placebo group (p=0.3259).

Table 5. Difference in the Mean Change in Laboratory Tests Before and After the Clinical Trial (Visit 1-Visit 16) between *Hominis placenta* Pharmacopuncture (HPP) Group and the Placebo Group

	HPP group (n=15)	Placebo group (n=15)	p-value
	Mean±sd	Mean±sd	
AST	-1.27±8.60	-1.5±6.62	0.9357
p-value	0.5773	0.4118	
ALT	-3.93±15.74	-3.21±10.30	0.8862
p-value	0.3494	0.2641	
BUN	1.07±2.41	1.14±4.74	0.9575
p-value	0.1089	0.3836	
Creatinine	0±0.10	-0.02±0.10	0.5655
p-value	0.9801	0.4236	

ALT: Alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, HPP: *Hominis placenta* pharmacopuncture.

5. Incremental cost-effectiveness ratio (ICER)

HPP treatment spent approximately South Korean won (KRW) 53,000 for 8 weeks compared to the placebo group in improving the GQOL-D score by one point for patients with MCI. The sensitivity analysis, assuming that the final GQOL-D score for HPP treatment maintained for a year, resulted that HPP treatment spent approximately KRW 345,000 for a year compared to the placebo group in improving GQOL-D score by one point.

6. Blinding test

Out of 15 participants in HPP group, 10 participants responded that the drug was HPP, while 8 participants reported that the drug was HPP out of 14 participants in placebo group. The difference of response between two groups was insignificant (p=0.5974), implying that blinding in this trial was successful.

IV. DISCUSSION

This study assessed the efficacy and safety of HPP treatment compared with placebo pharmacopuncture over 8-week period, in patients with MCI. Cognitive function of both groups slightly increased after administration but there was no significant difference between two groups as well. Accompanying symptoms such as mood and sleep disturbance, and QoL improved more in HPP group than in the placebo group, but their difference was statistically insignificant. Compared to the saline placebo treatment, HPP treatment increased the QoL score in patients with MCI, and it was predicted to take an additional KRW 345,000 per year to increase the GQOL-D by one point.

In this study, HPP treatment did not change the cognitive function compared to placebo. The mean

change of MMSE-DS in HPP group was half of that in placebo group, which was the only outcome measure that showed significant inter-group difference. Both intervention decreased the severity of cognitive decline as examined by various scales. Thus, when retesting the effect of HPP in future study, the dose of *H. placenta* extract or other types of pharmacopuncture fluid should be reconsidered.

Unlike cognition, auxiliary symptoms such as emotion and sleep showed improvement compared to placebo. Despite insignificant inter-group difference, these consistent changes in emotion and sleep suggest us the possibility to use HPP on mood- and sleep-related symptoms. Mood and sleep disturbance are major risk factors for progress to dementia[34]. Anger and sleep was degenerated at the end of trial in placebo group. The superiority of HPP observed in this study could be owed to the effect of *H. placenta*. The similar results were reported in the previous studies. In healthy elderly, 8-week-long injection of *H. placenta* increased physical function score more than saline injection[35]. In postmenopausal woman, 2-week-long subcutaneous injection of human placental extract improved sleep and pain compared with the saline injection but did not show difference in cognitive function[36]. These consistent results imply us HPP or *H. placenta* could be applied to management of behavioral and psychological symptoms in cognitive disorders.

GQOL-D was used to perform economic analysis. Although the economic evaluation guideline in Korea recommends using quality-adjusted life year (QALY) to determine the economic value of medical technology, it was difficult to calculate QALY using EQ-5D obtained in limitation within this clinical study. Instead, the current study analyzed the cost-effectiveness of HPP treatment using GQOL-D, dementia-specific QoL scale, and it would capture the QoL of individuals with cognitive impairment more sensi-

tively than EQ-5D which measures general health-related QoL. In the case of dementia, it is important to measure the change in subjective QoL to practically determine treatment's outcome on patients' cognitive function. After 8-week treatment, GQOL-D of HPP group was 35.60±9.83, which was close to the average of GQOL-D of the normal elderly (36.04) reported in the previous study[30]. On the other hand, GQOL-D of placebo group was 34.20±9.70, which was lower than the average of Alzheimer's disease patients' score (34.84). In the previous study, the difference of average scores between normal elderly and Alzheimer's disease patients was 1 point[30]. The mean difference in HPP group and that in placebo group was 2.60±4.47 and 1.33±5.83, respectively. Therefore, it suggests that HPP treatment and body acupuncture treatment could improve QoL of MCI. However, there is still limitation that there were few studies reporting the QoL of dementia patients, so there were insufficient previous studies that can be used as a standard for interpreting GQOL-D. The GQOL-D score of the previous study used as a standard in this study was measured in 2004 and can have time discrepancy[30].

There were technical limitations of this study as follows. First, the number of patients who participated in the clinical trial was not large, so it might be insufficient to examine the effect of HPP in MCI. Even though the sample size was calculated according to the previously published study, the sample size for each group was small compared with other clinical trial on MCI and most of the outcome did not present inter-group difference. A larger number of participants is needed to verify an exact effect in further study. Second, pharmacopuncture treatment was performed in both intervention group and placebo group in the same acupoints which were supposedly effective in treating cognitive function. Even though the saline was administered to the control group, it

can induce therapeutic effect by stimulating the acupoints. Third, the proportion of female participants was overwhelmingly high. Indeed, the average of pre-treatment GQOL-D score of the intervention group (33.00) and that of the placebo group (32.87) were relatively lower than the score of the patients diagnosed with Alzheimer's disease in the previous study (34.84)[30], even though the symptom of MCI was thought to be less severe than Alzheimer's disease. The reason for the low score could be inferred to be the different proportion of females. The gender effect in reporting QoL was previously reported when Short-Form 36-Item Health Survey, one of the questionnaire for health related QoL, was implemented in both healthy and sick elderly people in Korea, where all subscales were lower in women than in men, some of which were significantly different[37].

V. CONCLUSION

To our best knowledge, there has been no previous clinical trial on clinical effect of HPP on cognitive decline in MCI samples. In spite of technical limitations, there were some findings from the clinical trial. 1mL HPP treatment for 8 weeks hardly alleviated cognitive decline compared to placebo. HPP could be presumably effective in emotional status and sleep of patients with cognitive disorder, though. HPP also increased dementia-specific QoL. The type of pharmacopuncture and the trial design should be taken into account in the further study to reveal the effect of pharmacopuncture on cognitive disorders.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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