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Effectiveness of an integrative medicine approach to improve cognitive dysfunction and dementia
An observational study

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Abstract

Despite the urgent need to control dementia, an effective treatment has yet to be developed. Along with the Korean government's policy of cooperation between conventional medicine (CM) and Korean medicine (KM), integrative medical services for dementia patients are being provided. This study aimed to compare the integrative medical clinic (IMC) for dementia used by Dongguk University Hospitals (DUH) with other service models and to review the characteristics and treatment outcomes of patients who had visited DUH over the past 5 years. Patients' electronic medical records from May 2015 to June 2020 were searched and their data were analyzed to evaluate the IMC's service model. Patient demographic and clinical characteristics, diagnostic tests, and treatment patterns for CM and KM were collected. The proportion of patients who did not show worsening cognitive function was described in detail. A strength of the DUH integrative medicine clinic is its ability to manage both KM and CM patients in the same space at the same time. Among the 82 patients who visited the clinic during our study period, 56 remained for data analysis after we excluded patients who met the exclusion criteria; nineteen patients had diagnoses of mild cognitive impairment. Among collaboration patterns, the first visit to the IMC had the highest proportion (55.4%). Among diagnosed tests in CM, laboratory tests and neuropsychological tests were used the most. In KM, a heart rate variability test was frequently used. The most common CM treatment prescribed was anticonvulsants, with 22 patients (39.2%) receiving donepezil, whereas the most frequent KM treatments were acupuncture (82.1%) and herbal medicine (78.6%). Twelve patients were followed up with the Mini-Mental State Examination, and 8 demonstrated either no worsening or improved cognition (baseline Mini-Mental State Examination range: 21–26). All 8 patients had mild cognitive impairment including 6 with amnestic, multidomain impairment. This study searched for a way to improve cognitive dysfunction and dementia using an integrative approach, and it shows promising results for mild cognitive impairment. However, more precisely designed follow-up studies are needed to address the present work's limitations of a retrospective study design and a small sample size.

Abbreviations: CAM = complementary and alternative medicine, CDR = Clinical Dementia Rating, CM = conventional medicine, CT = conventional therapy, DUH = Dongguk University Hospitals, DUIOMH = Dongguk University Ilsan Oriental Medicine Hospital, EEG = electroencephalogram, GDS = Global Deterioration Scale, HRV = heart rate variability, IMC = integrative medical clinic, IMP = integrative medicine program, KM = Korean medicine, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, SCD = subjective cognitive decline, TEAM = Traditional East-Asia Medicine.

Keywords: cognitive dysfunction, dementia, integrative medicine, retrospective study, TEAM

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1. Introduction

With the general aging of the global population, the number of patients with dementia is increasing rapidly worldwide. In Korea in particular, the prevalence of dementia is expected to increase substantially as the nation transitions from an aging to a "super-aged" society, where more than 21% of the population is aged 65 years or older.[1] In fact, the prevalence of dementia is higher in Korea than it is in other countries in the Asia-Pacific region, although there are some differences in age among these countries' populations.[2] Unfortunately, effective curative treatments and disease-modifying therapies have yet to be developed for dementia. Although some approved drugs are known to relieve symptoms, these drugs cannot sustain their beneficial effects beyond 9 months.[3,4]

Researchers have proposed various noninvasive methods of improving cognitive function including modifying food intake and exercising. Cross-sectional research has shown the beneficial effects of moderate caffeine intake on cognitive and mood states in patients with vascular cognitive impairment,[5] and a review identified correlations between acetyl-l-carnitine intake and cognitive function improvement in dementia patients.[6] An RCT reported that a combination of shiatsu (traditional oriental tools for acupressure) and physical activity improved depression in Alzheimer disease (AD),[7] and another study reported on the effectiveness of intensive ergotherapy including hand motor rehabilitation and visual-perceptual treatment for neurorehabilitation in patients with mild intellectual disability.[8] There have been indications that transcranial magnetic stimulation effectively improves cognitive function, apathy, memory, and speech function in patients with early mild AD[9] and that noninvasive brain stimulation can be applied to various neuropsychiatric disorders including dementia by modulating synaptic plasticity and functional connectivity.[10] However, the validity of such techniques remains a topic of debate that requires further study.

Because of the limited availability of conventional treatments and the increasing numbers of dementia patients caused by the general aging of populations, there is an increasing need for multidisciplinary approaches to treating dementia and improving patients' quality of life. Complementary and alternative medicines (CAM) such as acupuncture and herbal medicine have shown promising effectiveness alone and in combination with conventional medicine (CM).[11–16]

CAM is increasingly applied in a wide range of diseases.[17–20] According to a US national survey, nearly 40% of adults in general and 74% of Korean adults have used some forms of CAM.[19] Given this trend, there has been increasing interest in developing ways to incorporate CM and CAM into an effective integrative medicine model for use in each nation's health care system. The paradigm governing the relationship between modern CM and CAM has shifted from exclusion to convergence.[21]

Traditional medicine is recognized as one category of CAM in many countries. In East Asian countries such as Korea, Japan, and China, CM and traditional East-Asia medicine (TEAM) are recognized as distinct,[22] but nearly all previous surveys of these countries have classified TEAM as CAM.[23–25]

Under the umbrella of TEAM is Korean medicine (KM), and KM and CM are recognized as 2 distinct medical practices that strictly exclude each other. Researchers have argued that practitioners in each field should only be allowed to practice within their KM or CM fields[23]; this argument includes KM doctors referring their "unsuitable" patients to western medicine facilities and vice versa. This form of medical service—exclusionary pluralism—has the unique strength of allowing collaborations while simultaneously limiting conflicts.

Leading into this study's topic is the question of which disease entity will be most appropriate for incorporating CM and KM? Senile dementia is regarded as an appropriate disease entity for this context because dementia control is limited despite modern Western medicine's dementia research achievements and investments.[26] KM shares its origin with Chinese medicine, it is different in that the points of diagnosis and treatments are more individualized according to the particular physiological and pathological characteristics of the individual; specifically, there are 4 constitutions (*sa-sang*): *tae-yang*, *tae-eum*, *so-yang*, and *so-eum*.[27] Each type has a typical imbalance in the function of internal organ systems, and KM manages each patient based on the pathophysiology of each constitution.

Along with the Korean government's efforts to achieve more cooperative collaboration between CM and KM, the government introduced a demonstration project 2016 called the Medicine-Oriental Medicine Consultation Service. This project led to more engagement between MD and Korean medical doctors with patients with dementia and cognitive dysfunction. However, few researchers have examined integrations between KM and CM for dementia patients.

Therefore, it is worth considering ways to integrate KM into the routine care of dementia in outpatient clinics to control dementia and ultimately enhance public health. Our aim with this paper was to present a clinical pathway of integrative medical services for patients with cognitive dysfunction and dementia between academic medical hospitals (Donguk University Hospitals, DUH; Dongguk University Ilsan Hospital, DUIH; and Dongguk University Ilsan Oriental Medicine Hospital, DUIOMH), analyze the data of patients who have received such medical service, and make suggestions for developing high-quality medical service collaborations between CM and TEAM not only domestically but also across nations.

Our research group examined the data from 5 years of the operation of a clinic offering integrative CM-KM services, and we clinically observed high patient satisfaction and improved cognitive function. Therefore, we hypothesized the following: A CM-KM integrative clinic model is a suitable and promising strategy for treating patients with cognitive impairment. To confirm this, we retrospectively reviewed the data of all patients with cognitive impairment who visited this clinic and statistically analyzed the data from a subgroup of patients.

2. Methods

2.1. The integrative medicine clinic for dementia

The DUIH-DUIOMH dementia clinic operates once a week (Thursday, one section) in the form of inter-institutional consultation. This clinic has operated for more than 5 years since its establishment in May 2015. A doctor with more than 10 years of experience as either a medical doctor in the department of neurology or an Oriental medical doctor in the neuropsychology department examines patients in the same space in one of the outpatient rooms of DUIOH. To characterize the clinical pathways offered by the DUIH-DUIOMH integrative medical services for dementia, we searched and reviewed documents including official national reports and presentations from professional associations.[26,28–31]

2.2. Examining patients' records

We retrospectively examined patients' records for dementia dating from the clinic's establishment (May 2015) through June 2020. We determined eligible patients based on the Korean Standard Classification of Diseases (KCD): F00 (Dementia in Alzheimer disease), F01 (Vascular dementia), F02 (Dementia in other diseases classified elsewhere), F03 (Unspecified dementia), F06.7 (Mild cognitive disorder), G30 (Alzheimer disease), G31 (Other degenerative diseases of nervous system, not elsewhere classified), and R413 (Memory disorder). We excluded patients who received treatment from either KM or CM but not both. We collected the patients' demographic and clinical characteristics (diagnosis, follow-up duration, and dementia severity)

and analyzed the patterns of collaborative medical service they received. We also collected the data on which diagnostic tests and treatments both types of doctors had ordered as well as on the potential subset of patients who did not show worsened memory function.

2.3. Statistical analyses

Two researchers initially coded the patients' data using Microsoft Excel and then cross-coded them through crossovers. In descriptive statistical analysis, the mean, and standard deviation are used for continuous variables, while the frequency and percentage are used for categorical variables. We conducted all statistical comparisons of treatment responses in the patients with mild cognitive impairment using *R* Statistical Software version 4.0.3 (*R* Foundation for Statistical Computing, Vienna, Austria). First, we examined Mini-Mental State Examination (MMSE) improvement since each patient's initial visit and then divided the patients into 2 groups depending on whether their MMSE score had improved or worsened over follow-up.

To test for differences in MMSE change between the 2 groups, we performed a nonparametric Wilcoxon rank-sum test at the significance level of .05. We also used the same test to assess the differences in the median lengths of follow-up between the 2 groups. To calculate the differences in MMSE score adjusting for the effect of the follow-up length, we fit a linear regression model in which MMSE change (MMSE at baseline—MMSE at follow-up) was the dependent variable and a group indicator variable (0 for $MMSE_{worsened}$ and 1 for $MMSE_{improved}$) was the explanatory variable, and we added the median follow-up length as a covariate. We examined demographic measures for statistical differences between the 2 groups using Wilcoxon rank-sum tests for continuous variables and Fisher exact tests for categorical variables at significance of .05.

2.4. Ethical considerations

This study complied with the Declaration of Helsinki. It was conducted after obtaining approval from the Institutional Review Board of Dongguk University Ilsan Oriental Medicine Hospital (IRB no. 2020-05-001).

3. Results

### 3.1. Review of clinical pathways of integrative medicine clinic for dementia

The evaluation and treatment for cognitive dysfunction and dementia are standardized. Here, we detail how KM is integrated into the CM (Fig. 1). Based on a research review, our operating method did not greatly differ from those suggested in other guidelines. However, there is very little research on the essence of our clinic operation, wherein a patient can access both types of medical services in the same space at the same time.

3.2. Patient characteristics

Among 82 patients who visited the DUIH-DUIOMH integrative medical clinic, we analyzed the data on 56 patients who met the study inclusion criteria (Table 1). Of these 56 participants, 37 (66.07%) were female, and their median age was 70.7 years (range, 37–92 years). The largest group of patients had mild cognitive impairment (MCI) (n = 19; 33.9%), followed in order by Alzheimer disease (17 patients, 30.4%), memory disorder (12, 21.4%), and vascular dementia (5, 8.9%). Memory disorder corresponds to R413 in the KCD and was diagnosed based on subjective cognitive decline (SCD), that is, when the patient had a subjective complaint of cognitive decline but objective test results were within the normal range on an objective cognitive test and the patient had no limitations in activities of daily living (ADLs).[32] The KCD used to diagnose patients in Korea is based on the International Classification of Disease, but the KCD does not include any diagnosis that accurately corresponds to SCD. The R code includes cases in which no specific diagnosis has been made even after all tests have been performed; among them, R41.3—indicating other amnesia—was used for diagnosis.[33,34]

Because of the heterogeneity of MCI, we categorized patients with MCI as amnestic or non-amnestic based on the presence of memory loss and as having cognitive impairments in single or multiple domains.[35] Based on these classifications, we divided the patients into 4 subgroups: single-amnestic MCI, single-non-amnestic MCI, multi-amnestic MCI, and multi-non-amnestic MCI. We measured the patients' cognitive domain performance using the Seoul Neuropsychological Screening Battery, and we considered a patient's performance abnormal if it fell below the 16th
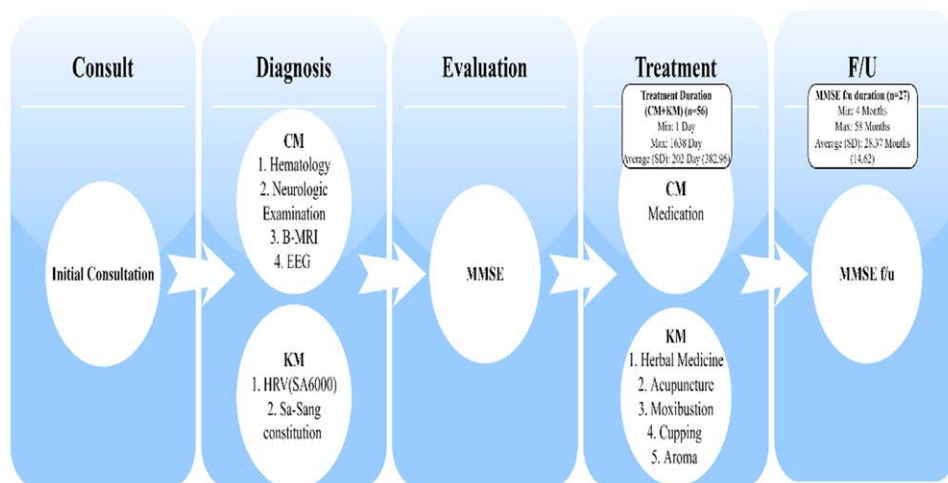
Figure 1. Method of integrating KM in CM. We detail how KM is integrated into the CM. Diagnosis, evaluation, treatment, and follow-up procedures were summarized from the first visit to the clinic. The treatment duration and MMSE f/u duration of this clinic were described. Treatment Duration (n = 56): Min 1 day, Max 1638 day, Average (SD) 202 day (382.96). MMSE f/u Duration (n = 27): Min 4 months, Max 58 months, Average (SD) 28.37 months (14.62). B-MRI = Brain Magnetic Resonance Imaging, CM = conventional medicine, EEG = electroencephalogram, HRV = heart rate variability, KM = Korean medicine, MMSE = Mini-Mental State Examination, SD = standard deviation.

Table 1

Demographic and clinical characteristics (n = 56).

Variable	N (%)
Male/female	19 (33.9)/37 (66.1)
Age, mean (range)	70.0 (37–92)
Diagnosis	
Mild cognitive impairment*	19 (33.9)
Amnestic, multiple domain	12
Amnestic, single domain	3
Nonamnestic, multiple domain	2
Nonanmestic, single domain	1
Alzheimer disease	17 (30.3)
Memory disorder	12 (21.4)
Vascular dementia	5 (8.9)
Dementia, mixed dementia	2 (3.5)
Others†	1 (1.8)[1]
MMSE (n = 44)	
20–26	23 (41.0)
0–19	10 (17.8)
CDR (n = 43)	
0 (normal)	1 (2.3)
0.5 (uncertain)	22 (51.1)
1 (mild)	15 (34.8)
2 (moderate)	3 (6.9)
3 (severe)	2 (4.6)
GDS (n = 43)	
2 and 3 (mild cognitive impairment)	29 (67.4)
4 (mild dementia)	6 (13.9)
5 (moderate dementia)	3 (6.9)
6 (moderate severe dementia)	1 (2.3)
7 (severe dementia)	2 (4.6)
SNSB	Mean (range)
Attention	37.85 (0.14–99.71)
Language	43.95 (0.04–80.54)
Visuospatial function	25.02 (0.01–78.16)
Memory	16.99 (0.03–78.08)
Frontal/executive function	36.54 (0.02–95.78)
K-IADL	3.4 (0–21)

CDR = Clinical Dementia Rating, GDS = Global Deterioration Scale, K-IADL = K-instrumental activities of daily living, MMSE = Mini Mental State Examination, SNSB = Seoul Neuropsychologic Screening Battery.
*Classification data was available for 18 patients.
†Dementia in Creutzfeldt-Jakob disease: 1 (1.8%).

Table 2

Pattern of collaboration until visiting dementia IMC (n = 56).

Pattern	N (%)
Number of patients who visit dementia IMC as first visit	31 (55.35)
Number of patients who were referred to dementia IMC from Dept of ONP	13 (23.21)
Number of patients who were referred to dementia IMC from Dept of Neurology	12 (21.42)

Dept = Department, IMC = Integrative Medical Clinic, ONP = Oriental Neuropsychiatry.

Table 3

Demographic and clinical characteristics of patients with mild cognitive disorder (n = 19).

Variable	N (%)
Male/female	7 (36.84%)/12 (63.15%)
Age, mean (range)	70.05 (57–92)
MMSE (n = 18)	(*4 (22.22%): MMSE > 26)
20–26	13 (72.22%)
0–19	1 (5.55%)
CDR (n = 16)	
0 (normal)	1 (6.25%)
0.5 (uncertain)	13 (81.25%)
1 (mild)	2 (12.5%)
2 (moderate)	0
3 (severe)	0
GDS (n = 16)	
2 and 3 (mild cognitive impairment)	14 (87.5%)
4 (mild dementia)	2 (12.5%)
5 (moderate dementia)	0
6 (moderate severe dementia)	0
7 (severe dementia)	0
SNSB (n = 16)	
Attention	44.00
Language	37.92
Visuospatial function	24.84
Memory	17.73
Frontal/executive function	34.45
K-IADL (mean) (n = 16)	0.24
ApoE ε4−/ApoE ε4+ (n = 14)	10/4

CDR = Clinical Dementia Rating, GDS = Global Deterioration Scale, K-IADL = K-instrumental activities of daily living, MMSE = Mini Mental State Examination, SNSB = Seoul Neuropsychologic Screening Battery.

percentile. Among the 18 MCI patients, 15 were amnestic type, and 12 of these patients were impaired in multiple domains. Regarding comorbidities, 25 (44.6%) patients had hypertension and 12 (21.4%) had diabetes mellitus.

To screen for dementia, we administered the MMSE to 44 patients. We could not administer the MMSE to some patients because they had only visited the clinic once without a follow-up or because they did not provide informed consent; the average MMSE score was 16.3. Additionally, we tested 43 patients for their Clinical Dementia Ratings (CDRs), and 15 scored 1 point, indicating mild dementia; 5 patients scored 2 or 3 points, indicating moderate or severe dementia, respectively. We also administered the Global Deterioration Scale (GDS): Of the group we tested, 43 scored 2 to 3 points, which indicated mild cognitive impairment, and 6 had indications of moderate to severe dementia based on scores of 5 or higher. The mean number of patient visits was 5.1 (range, 1–39), and the mean duration of follow-up was 201.8 days (range, 1–1638 days). Approximately half of patients visited the integrative medicine clinic as their first visit, and 13 had been referred by a KM specialist in the Oriental neuropsychiatry department (Table 2).

During the review period, we identified MCI prevalence of 23% (19 of 82) at the DUIH integrative dementia clinic. The demographic and baseline clinical characteristics of these patients with MCI are listed in Table 3.

3.3. Diagnostic evaluation

Table 4 details the findings from the diagnostic evaluations we performed in this study. In addition to taking the patient's medical history and performing a physical examination, both of which are common in CM as well as in KM, a doctor of neurology ordered most diagnostic tests. For 49 patients (87.5%), we conducted basic laboratory testing as well as measuring most of those patients' lipid panels and vitamin B, folate, and homocysteine levels. Most patients (32; 57.1%) underwent apolipoprotein E genotyping, 44 (78.5%) completed the MMSE, and we took the CDRs and collected the Korean version of the independent activities of daily living measures (K-IADLs) for 43 (76.7%) patients. Thirty patients (53.5%) completed the Seoul Neuropsychological Screening Battery of dementia tests that measure attention, language, visuospatial function, memory, and frontal/executive function. Regarding apolipoprotein genotyping, the largest portion of patients (n = 17) had apoE ε3/ε3, followed in order by those with apo ε3/ε4 (n = 9), apo ε2/ε3 (n = 3), apo ε2/ε4 (n = 2), and apo ε4/ε4 (n = 1). Among patients who underwent brain MRI, 31 showed changes in brain atrophy, 15 showed old infarcts, and 13 patients showed microbleeding or small vascular disease.

Table 4

Diagnostic test used for patients (n = 56).

Tests evaluated from CM	N (%)	Tests evaluated from KM	N (%)
Laboratory test		HRV	42 (75)
Hematology*	49 (87.5)		
HbA1c	43 (76.7)		
Lipid panel†	48 (85.7)		
Vitamin B12	46 (82.1)		
Folate	45 (80.3)		
Homocysteine	44 (78.5)		
ApoE genotyping	32 (57.1)		
Brain MRI	48 (85.7)		
MMSE	44 (78.5)		
NPI	44 (78.5)		
CDR	43 (76.7)		
K-IADL	43 (76.7)		
EEG	39 (69.6)		
SNSB	30 (53.5)		

ApoE = Apolipoprotein E, CDR = Clinical Dementia Rating, CM = conventional medicine, EEG = electroencephalogram, HbA1c = Hemoglobin A1c, HRV = heart rate variability, K-IADL = K-instrumental activities of daily living, KM = Korean medicine, MMSE = Mini Mental State Examination, MRI = Magnetic Resonance Imaging, NPI = Neuropsychiatric Inventory, SNSB = Seoul Neuropsychologic Screening Battery.
*Hematology: CBC (WBC, RBC, WBC, RBC, Hb, Hct, PLT, WBC Differential Count [Neutro, Lympho, Mono, Eosino, Baso]), AST, ALT, BUN, Creatine.
†Lipid panel: LDL, HDL, Total cholesterol.

Table 5

Baseline characteristics according to ApoE status (n = 32).

	Absence ApoE ε4− (N = 20)	At least one ApoE ε4+ (N = 12)
Age, yr (range)	69.3 (56–92)	72.1 (57–90)
Sex, female/male	12/8	8/4
Diagnosis (%)		
MCI	10 (50)	4 (33)
Alzheimer disease	3 (15)	5 (41.6)
Memory disorder	5 (25)	2 (16.6)
Vascular dementia	2 (10)	1 (8.3)
MMSE (mean)	22.22	22.92
CDR (mean)	0.63	0.87
SNSB³ (mean)		
Attention	37.18	42.01
Language	36.10	33.32
Visuospatial function	25.41	14.35
Memory	18.97	10.84
Frontal/executive function	29.89	25.26
K-IADL (mean)	0.28	0.57

ApoE = Apolipoprotein E, CDR = Clinical Dementia Rating, K-IADL = K-instrumental activities of daily living, MCI = mild cognitive impairment, MMSE = Mini Mental State Examination, SNSB = Seoul Neuropsychologic Screening Battery.

Electroencephalography (EEG) was performed for nearly 70% of patients recorded using a 36-channel recording system (Grass Technologies, Warwick, RI), and 23% showed normal findings (9/39). For the EEGs, electrodes were attached according to 10 to 20 international standards, and before the test, the patient was asked to relax and lie down comfortably. Then, recordings were taken with the eyes open and with the eyes closed, with photo stimulation, with hyperventilation, and under induced sleep. An epilepsy specialist evaluated EEG recordings, and 15 patients showed slow waves (eight patients: bilateral frontotemporal area; 5 patients: left temporal; and 2 patients: bilateral temporal).

We then attempted to categorize patients based on the presence of apo/ε4. As Table 5 presents, there was a definitive difference between the 2 groups. KM ordered a heart rate variability (HRV) test for 75% of patients, and mean HRV was 37.8 (range:

Table 6

Treatment used for patients (n = 56).

CM medications	N (%)	KM treatments	N (%)
Anticonvulsant	32 (57.1)	Acupuncture	46 (82.1)
Cerebrotonics*	25 (44.6)	Herbal remedies	44 (78.6)
Antipsychotics	24 (42.8)	Moxibustion	43 (76.7)
Donepezil	22 (39.2)	Cupping therapy	5 (8.9)
Memantine	7 (12.5)	Aroma therapy	1 (1.7)

CM = conventional medicine, KM = Korean medicine.
*Cerebrotonics (the classification code no. 119 [other drugs for the central nervous system] of the Ministry of Health and Welfare of Korea): Rivastigmine, Choline Alfoscerate, pramipexole, levodopa, ropinirole.

11.5–127.5) for the standard deviation of the N–N interval and 2.08 (range: 0.1–8.3) for low frequency/high frequency.

3.4. Evaluation of treatment

Table 6 lists the treatments offered to patients. The drugs CM prescribed most commonly were anticonvulsants (57.1%), followed in order by cerebrotonics, antipsychotics, donepezil, and memantine. Meanwhile, the treatments most commonly performed by KM were acupuncture (84.1%), followed by herbal medicine (78.6%) and moxibustion (76.8%).

Regarding herbal remedies, *gagam-sohabwhangwon* (powder) was the most prescribed, as it was prescribed to 35 patients. *hyungbangjihang-tang* (decoction, powder), *woohwangcheng-simwon* (pill), *bojungikgi-tang* (decoction, powder), *chengsimyeonja-tang* (powder), and *chungsimyeonja-eum* (powder) were respectively used for 14, 9, 9, 3, and 6 patients. According to the chart review, there were no detectable adverse effects from CM or KM treatment.

Among the 12 MCI patients who received CM-KM treatment, 67% (8 of 12) achieved an improved MMSE score, which was statistically significant ($P = .008$) in contrast with the smaller proportion whose MMSE scores declined (see Fig. 2). Meanwhile, there was no statistical difference in the follow-up lengths between the 2 groups ($P = .808$) or in the demographic variables between the 2 groups (Table 7). We conducted a linear regression analysis in which the change in MMSE score was the dependent variable and a group indicator (= 1 for MMSE improved and = 0 otherwise) was the explanatory variable, and we adjusted for the effect of the interval between the baseline and follow-up MMSE measurements. We found a statistically significant difference in the change in MMSE score (change = MMSE at baseline—MMSE at follow-up, $P < .001$) between the 2 groups after we adjusted for the effect of the interval between the baseline and follow-up MMSE measurements. The coefficient associated with the indicator variable was −3.76 (t (df = 9) = −5.869), meaning that $MMSE_{improved}$ achieved 3.76 units of MMSE improvement over time. Table 8 summarizes the age, sex, follow-up period, diagnosis, and detailed treatment history of the 8 MCI patients whose MMSE scores did not worsen.

4. Discussion

In this study, we demonstrated our integrative practice of combining CM and KM to treat dementia and cognitive dysfunction, and we suggested potential ways to improve cognitive dysfunction among a subset of patients who were receiving these integrative medical services at our clinic.

CAM has been institutionalized in the medical system in a variety of ways and to varying degrees depending on the health care system involved as well as other factors. With this paper, we addressed the operation of particular medical clinics for dementia and cognitive disorder where the Western and Korean
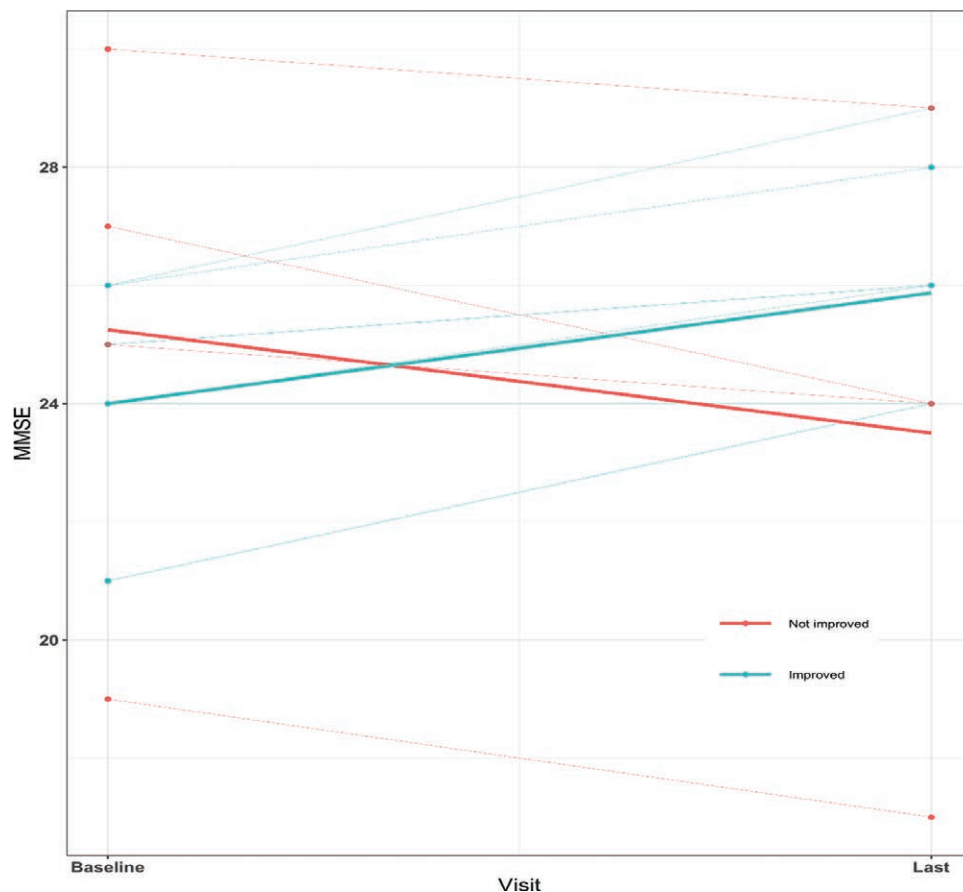
Figure 2. Changes in MMSE from baseline to the last visit for those showing improvement and no improvement. Changes in MMSE from the first visit to the last visit of the MMSE-improved group and the MMSE-worsened group were visualized. The MMSE-improved group is marked in blue, and the MMSE-worsened group is marked in red. MMSE = Mini-Mental State Examination.

(*hanui*) doctors integrate the common practices of each. In contrast to our clinic, most facilities specialize in only one or the other type.

Cooperation between Western and Oriental medical practices involves doctors sharing patients' medical information and consulting with each other. In 2016, the Korean government established a pilot program called Cooperative Medical Care between WM and KM; the purpose of the project was to prepare a basis for providing Western medicine and Korean consultation services in an integrative practice and to evaluate the effectiveness of integrating the 2 practices as well as the feasibility of applying health insurance to such practices. The cooperative project took place in 3 phases: phase 1, data collection to understand the status of cooperation; phase 2, securing the validity of the fee system and the effectiveness of cooperation, and phase 3, preparing a plan for managing cooperation standards, and the project is now in phase 3. The most frequent diseases among the patients in this 2-stage collaborative pilot project, in descending order, were facial nerve palsy, intervertebral disc disorder, and cerebral infarction.[26] Naturally, dementia is one of this project's target diseases.

Under regulations in Korea stemming from the concept of exclusive pluralism, hospitals can only provide either WM or KM services in their registered specialty areas, and patients can only receive care under both types through bidirectional referrals from a physician in one practice to care from the other. That is, the current service model in Korea does not allow for an effective and patient-centered bidirectional pathway. Indeed, after extensive searching, we found nearly no other service offerings like DUIH-DUIOMH. Our clinic is unique because we

provide both CM and KM medical services in the same space, so that patients and caregivers have simultaneous access to both types of services. This convenience can in turn engender more, and more positive, relationships and improved patient communication.

Moreover, our typical patient encounters exceed 30 minutes, allowing adequate time to attentively listen to the patient's concern and evaluate the complexities of their problems. Having such additional time carved out for patient visits is a crucial element of the integrative medicine care model.[36] Our clinic practices patient-centered care and appears from our evidence to be meeting our patients' needs and is especially satisfactory given the critical shortage within academic institutions of available space for integrative medicine clinics.[37] There are also many issues involved in establishing integrative medicine programs (IMPs) within academic health centers.[21] Operating such programs is complicated by decisions regarding organizational settings, the populations to be treated, the research roles, and administrative and financial issues. The consensus on how best to organize IMPs did not increase the number of US academic health centers that joined the Academic Consortium for Integrative Medicine and Health.[21] A detailed business plan and road map for IMPs within academic medical hospitals are beyond the scope of this paper. However, we identified from published examinations of delivering TEAM care to dementia patients[14,26,30] that our clinic had the most patients at 58 patients. Further, the fact that our clinic has been operating for more than 5 years strongly suggests that our efforts have been successful operation.

According to the WHO, an integrative system is established when traditional medicine exists within the national medical,

Table 7

Comparison of treatment response for patients with MCI (n = 12).

	MMSE, down (N = 4)	MMSE, up (N = 8)	P value*
Age, mean (SD)	70.5 (6.40)	68.5 (7.84)	.733
Male/female	1/3	3/5	1.000
Baseline MMSE (n = 4/8, total 12)			
Mean (SD)	25.25 (4.65)	24 (2.00)	.439
Breakdown			
>26	2 (50%)	0	1.000
20–26	1 (25%)	8 (100%)	
0–19	1 (25%)	0	
CDR (n = 4/6, total 10)			
0 (normal)	0	1 (16.66%)	.400
0.5 (uncertain)	3 (75%)	5 (83.33%)	
1 (mild)	1 (25%)	0	
GDS (n = 4/6, total 10)			
2 and 3 (mild cognitive impairment)	3 (75%)	6 (100%)	.286
4 (mild dementia)	1 (25%)	0	
SNSB (n = 4/6, total 10)			
Attention	50.31	39.35	
Language	21.04	44.95	.286
Visuospatial function	19.54	23.29	1.000
Memory	18.83	6.28	.556
Frontal/executive function	38.18	35.97	1.000
K-IADL (mean) (n = 4/6, total 10)	0.27	0.21	.341
ApoE ε4−/ApoE ε4+ (n = 4/5, total 9)	2/2	5/0	.167
Change in MMSE (baseline − last follow-up), mean (SD)	1.75 (0.96)	-1.88 (1.13)	.008**
Length of follow-up	30 (15)	31 (13)	.808

ApoE = Apolipoprotein E, CDR = Clinical Dementia Rating, GDS = Global Deterioration Scale, K-IADL = K-instrumental activities of daily living, MCI = mild cognitive impairment, MMSE = Mini Mental State Examination, SD = standard deviation, SNSB = Seoul Neuropsychologic Screening Battery.

*P values for continuous and categorical variables were computed using a Wilcoxon rank sum test and Fisher exact test, respectively.

**P value < .01.

educational, and compensation system as an independent and official medical provider. Traditional medicine exists all over the world, but in many countries, it does not have independent status. In East Asian countries such as China, Taiwan, and Korea, integrative systems have secured meaningful institutional positions.[26] Given this, we reviewed studies conducted in East Asian countries on cooperative care dementia clinics. First, in a 2018 retrospective analysis of such a clinic in Korea, the authors only noted collaboration but identified no indicators of actual positive effects from collaborative treatment; the authors' study duration was also only 2 years, and they gave an insufficient explanation of the basis for their Oriental medicine treatment.[30] Authors of a retrospective analysis conducted in China in 2017 only included patients with Alzheimer disease and did not describe the nature and operation of the collaboration they reported on.[14] In contrast, in a 2015 Taiwan cohort study, 43.3% of dementia patients were receiving CAM treatment,[38] and some scholars determined that cooperative treatment can decrease medical costs.[39] However, it is difficult to find reports of actual cooperative dementia clinics operating in Taiwan.

CM entails a full diagnostic workup and treatment process, whereas KM practitioners tend to rely on HRV. This suggests the utility of supporting diagnostic tools for dementia, given the finding of a positive relationship between autonomic dysfunctions and onset cognitive impairment. HRV testing has clinical utility, particularly as a preventive measure to minimize the risk of developing a cognitive impairment.[40] We can expand our study to demonstrate the role of HRV as a prognostic or preventive biomarker in an integrative approach. Similarly, combining CM and KM should enable interpreting apolipoprotein E4.

To better understand and define how KM is incorporated in the CM delivered to our patients, it is important to delineate how the process works. For example, adding herbal medicine (H) to conventional therapy (CT)—which includes treatment with donepezil and/or memantine—has demonstrated a superior effect in stabilizing cognitive function compared with conventional therapy alone.[14]

The results of this study showed significant improvement among patients with mild cognitive dysfunction (24-month MSSE CT + H: −0.06 vs CT: −2.66 decrease). This beneficial effect was dominant and time dependent for at least 12 months. A recent study has demonstrated the potential effect of KM in improving cognition among patients with mild cognitive impairment. However, only patients were considered in this case series, and the follow-up duration was 24 weeks from intervention.[41] Similarly, all of our patients who showed no worsening of cognitive function had mild cognitive dysfunction at baseline. Because we aimed to review real clinical integrative practice, our patient follow-up intervals were inconsistent, ranging from 13 to 55 months. Research has increasingly emphasized the importance of treating dementia at an early stage.[42] For instance, MCI often converts to normal cognition with an increase of 15% to 20% within one or 2, and this change is greater with clinical parameters such as non-amnestic and less severe MCI without the apoE E4 allele.[43] In our findings, 67% of patients with MCI who were available to complete a follow-up MMSE (8/12) showed no worsening of their MMSE scores. Among them, 63% (5/8) of patients were amnestic and with multiple domain subtypes, while none of the patients listed in Table 8 had the apoE E4 allele. A high proportion of MCI patients with amnesic and multiple domains in our findings did not show disease progression, suggesting that our integrative approach might be effective for a particular subset of patients, specifically, those having mild cognitive dysfunctions at an early stage. All 8 MCI patients who did not have worsening MMSE scores received integrative CM-KM treatment. The KM treatment course included the administration of herbal medicine, acupuncture, and moxibustion. There were no significant differences in baseline MMSE or length of follow-up among the 4 patients with worsening MMSE scores compared to the 8 patients without worsening MMSE scores. However, the average period from the onset of symptoms to the first outpatient visit was relatively long, with an average period of 1153 days. Further, compliance with KM treatment was relatively low, as patients who did not receive all herbal, acupuncture, and moxibustion treatments were included. The factors described above may be potential explanations for the worsening MMSE scores. Because herbal medicine is a mixture of a variety of materials, we need to list the detailed KM prescriptions data we administer at our clinic. A number of researchers have examined the herbal medicines our patients take (Supplementary File 1, Supplemental Digital Content, http://links.lww.com/MD/H142), and our herbal mixtures appear to have multiple targets to regulate neurogenesis,[44] they are not recommended for routine practice. The main motivation of our clinic was the Korean government's health policy encouraging the integration of CM and KM as well as the engagement of individual physicians with mutual trust.

This study has some limitations. First, although we demonstrated bidirectional clinical collaboration between 2 institutions, integrative medical care for dementia operates under a variety of methods and with differing study populations; therefore, ours should not be considered the only effective model. Second, we reviewed retrospective data and thus could not perform a schematic evaluation that included cost-effectiveness and adverse effects from the interaction of herbal mixtures. Although our data showed a subset of patients whose memory function had not worsened during our study period

Table 8

Lists of patients with MCI who demonstrated not worsening MMSE score (n = 8).

Age, sex	Number of visits/follow up duration	Diagnosis	CM	KM	Treatment, durations	
					Before	After (follow up interval)
81, F	CM: 432015/11/11–2020/4/28KM: 692017/6/8–2019/5/28IMC: 142017/6/8–2019/1/3	MCI, amnestic, multiple domain	Tianeptine sodium2016/1/19–2020/4/28Vortioxetine2018/2/22–2020/4/28Exelon patch2016/6/21–2017/9	Hyungbangjihwang-tang 2017/6/20–2019/2/2Woohwangchengsimwon2017/7/18–2018/5/17AcupunctureMoxibustion	2017/06/08K-MMSE 21, GDS 3, GDpS 9, K-IADL 0/4 (score 0)	2019/3/5 (21 mo f/u) K-MMSE 22, CDR 1, GDpS 9 K-IADL 7/9 (score 0.77) 2020/02/06 (32 mo f/u) K-MMSE 24, CDR 1, GDpS 9, K-IADL 3/11 (score 0.27)
70, M	CM: 272011/12/30–2020/1/13KM: 92016/5/26–2016/11/24IMC: 72016/5/26–2016/10/13	MCI, amnestic, multiple domain	Donepezil2016/6/23–2020/1/13	Gagam-sohabhwangwon 2016/6/2–2016/9/17Gongjindan2016/7/4WoohwangchengsimwonCupping Therapy	2016/6/22K-MMSE 24, GDS 3, K-IADL 2/8 (score 0.25)	2017/9/19 (15 mo f/u) K-MMSE 24, GDS 3, GDpS3, K-IADL 2/10 (score 0.2) 2018/9/17 (27 mo f/u) K-MMSE 25, CDR 0.5, GDS 4, GDpS1, K-IADL 6/10 (score 0.6) 2019/9/16 (39 mo f/u) K-MMSE 26, CDR 1, GDS 4, GDpS1, K-IADL 6/10 (score 0.6)
60, M	CM: 152016/4/15–2019/6/13KM: 182015/10/22–2018/7/19IMC: 122015/10/22–2018/7/19	MCI, amnestic, multiple domain	Donepezil2016/4/16–2018/7/19	Chengsimyeonja-tang2016/4/9–2016/5/26Gagam-sohabhwangwon2016/6/28–2018/6/14Acupuncture-Moxibustion	2016/04/16K-MMSE 24, GDS 3, SGDpS 8/15	2018/06/14 (26 mo f/u) K-MMSE 24, CDR 0.5, GDpS 4, K-IADL 2/8 (score 0.25)
69, M	CM: 242018/5/31–2020/5/7KM 222018/5/31–2020/5/7IMC 212018/5/31–2020/5/7	MCI, amnestic, single domain	Acetyl-l-carnitine 2018/6/14–2020/5/7Lacosamide2018/7/3–2020/5/7Levetiracetam 2018/6/8–2020/5/7	Gagam-sohabhwangwon 2018/6/9–2020/5/7Chengsimyeonja-tang2018/10/18–2018/11/22AcupunctureMoxibustion	2018/09/10K-MMSE 25, CDR 0.5, GDS 3, GDpS 1 K-IADL 4/9 (score 0.44)	2020/02/20 (17 mo f/u) K-MMSE 26, CDR 0.5, GDS 3, GDpS 1, K-IADL 5/9 (score 0.55)
65, F	CM: 102015/11/12–2017/1/4KM: 42015/11/12–2015/11/23IMC: 22015/11/12–2015/12/15	MCI, amnestic, single domain	Donepezil2015/11/19–2017/1/14Acetyl-l-carnitine2015/11/19–2017/1/14Escitalopram2015/11/19–2017/1/14	Gagam-sohabhwangwon2015/11/19–2015/12/23Bojungikgi-tang2015/12/15AcupunctureMoxibustionCupping therapy	2015/11/13K-MMSE 25, K-IADL 1/11 (score 0.09), GDS 3	2017/1/4 (14 mo f/u) K-MMSE 26, GDS 3, GDpS 4, K-IADL 2/10 (score 0.2)
78, F	CM: 242016/12/15–2020/3/12KM: 72016/12/15–2017/9/7IMC: 52016/12/15–2017/8/17	MCI, amnestic, multiple domain	Donepezil2017/1/12–2017/9/7Levetiracetam2017/1/13–2020/3/12Nortriptyline2017/9/7–2019/9/9	Gagam-sohabhwangwon2017/7/27–2017/9/7AcupunctureMoxibustionCupping therapy	2016/12/30K-MMSE 26, K-IADL 2/9 (score 0.22), GDS 3	2018/4/19 (16 mo f/u) K-MMSE 26, CDR 0.5/1.5, GDpS 0, K-IADL 1/10 (score 0.1) 2019/6/5 (29 mo f/u) K-MMSE 26, CDR 1, GDS 3, GDpS 1, K-IADL 4/10 (score 0.4) 2020/1/6 (36 mo f/u) K-MMSE 28, CDR 1, GDS 3, GDpS 3, K-IADL 2/9 (score 0.22)
66, F	CM 462015/10/29–2020/6/2KM: 1720115/10/29–2017/1/20IMC:22015/10/29–2017/1/16	MCI, amnestic, multiple domain	Donepezil2015/11/26–2016/11/13Acetyl-l-carnitine2015/11/26Rivastigmine2016/2/17–2017/5/24Escitalopram2015/11/26	Gagam-sohabhwangwon 2015/12/1AcupunctureMoxibustion	2015/11/16K-MMSE 21, K-IADL 1/10 (score 0.1) GDS 3	2018/7/4 (32 mo f/u) K-MMSE 24, GDS 3, GDpS 12019/6/25 (43 mo f/u) K-MMSE 25, CDR 1, GDS 3, GDpS 1, K-IADL 4/10 (score 0.4) 2020/6/2 (55 mo f/u) K-MMSE 24, CDR 1, GDS 3, GDpS 1, K-IADL 4/10 (score 0.4)
59, F	CM: 182015/7/16–2017/12/13KM: 92015/7/16–2015/9/25IMC:22015/7/16–2015/9/15	MCI, amnestic, single domain	Lamotrigine2015/7/30–2017/12/13Acetyl-l-carnitine2015/12/12/13Clonazepam2016/5/19–2017/12/13	Hyungbangjihwang-tang (2015/7/30–2015/10/12) AcupunctureMoxibustion	2015/07/21K-MMSE 26 K-IADL 1/10 (score 0.1) GDS 3	2016/8/10 (13 mo f/u) K-MMSE 28, GDS 3, GDpS 3, K-IADL 3/10 (score 0.3) 2017/12/13 (29 mo f/u) K-MMSE 29, GDS 3, GDpS 4, K-IADL 4/9 (score 0.44)

CDR = Clinical Dementia Rating, CM = conventional medicine, GDS = Global Deterioration Scale, IMC = integrative medical clinic, K-IADL = K-instrumental activities of daily living, KM = Korean medicine, MCI = mild cognitive impairment, MMSE = Mini Mental State Examination.

(these data were presented at the 2021 Alzheimer's Association International Conference: Poster 52,545 Preventing Cognitive Decline in Older Adults with Mild Cognitive Impairment Using Integrated Traditional Korean and Western Treatments: Initial Results), it remains to be seen whether our integrative medical service genuinely results in clinical improvement among dementia patients. In a recent study on managing patients with acute stroke, patients who received integrative medicine with both CM and KM had lower all-risk mortality at both 3 and 12 months after discharge,[45] and we need to further examine whether we can achieve the same desirable results through applying integrative medical care to our patients with dementia and cognitive impairment. Specifically, we can target those with mild cognitive dysfunction or early dementia and prevent later deterioration.

Third, we only had a small sample for statistical analysis. Dementia and cognitive decline are among the most prevalent neurodegenerative diseases, but our KM-CM integrative clinic is only provided once per week, and there are certain limitations due to the dual medical system in South Korea. However, the present study is meaningful in that we outline a unique treatment system that shows initial but promising results. Future researchers should collect and analyze more patient data.

Finally, we did not conduct systematic and standardized genetic screening and dementia profiling in this study. For example, next-generation sequencing (NGS) technology is a promising technique for diagnosing and managing neurodegenerative diseases, including dementia[46] that can minimize the "diagnostic odyssey,"[47] and investigators have attempted to discover genes associated with disease in the field of dementia.[46] Studies based on NGS are also being attempted with Oriental medicine, and a recent report analyzed the biological information of the anti-asthma effect of *Descurainia sophia* seed extract using NGS.[48] Our diagnostic accuracy would likely improve with using NGS-based analysis in our follow-up studies.

5. Conclusions

This retrospective study showed that integrating CM and KM practices can positively affect cognitive function in patients with mild cognitive impairment, and it suggests the possibility of a patient-centered CM–KM collaboration model. However, further research is needed to demonstrate the effectiveness of integrative therapy models to address the present work's limitations of a retrospective study design and a small sample size. We suggest in this article the potential benefits of applying integrative medical services for treatment of dementia and cognitive dysfunction despite the differences in national health contexts. Further research examining several clinical outcomes, including cost-effectiveness and patient satisfaction, should follow.

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