REVIEW ARTICLE

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Meditation for Alzheimer's Disease: Systematic Review and Meta-Analysis

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Objectives: Interest in the use of complementary and alternative treatments to treat dementia. Meditation is used to treat various symptoms of physical and psychological diseases. Some studies suggest that meditation might have positive effects on cognitive functions, especially attention, in the elderly. However, how meditation affects Alzheimer's disease (AD) patients remains unclear. In this review, we assessed the effectiveness of practicing meditation in combination with standard care in AD.
Methods: We searched the CCRCT, MEDLINE, EMBASE, AMED and CINAHL databases on 30 May 2017. We included randomized controlled trials (RCTs) that used meditation in adult patients diagnosed with AD. We allocated patients to a meditation combined with standard care or a standard care-only group.
Results: The two RCTs met the inclusion criteria. A total of 98 patients were included in the meditation with standard care and standard care-only groups in this review. All meditation programs in the included trials were based on practicing mindfulness. The results of our meta-analysis indicatedthat adjunctive mindfulness meditation programs exerted favourable but non-significant effects on cognitive function on the Mini Mental State Examination (MMSE) (MD=4.68, 95% CI -0.11 to 9.46; Z=1.92, p=0.06). Only one study assessed depression, anxiety, quality of life and stress. No adverse events related to meditation were reported in the included studies.
Conclusions: Insufficient data iscurrently available to determine the effectiveness of practicing meditation on patients diagnosed with AD. Hence, further RCTs with high methodological quality and larger sample sizes are needed to effectively estimate the effects of meditation on AD.

Key Words: Meditation, Mindfulness, Alzheimer's disease, Dementia.

I. INTRODUCTION

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disease characterized by cognitive decline, neuropsychiatric symptoms, and problematic behaviours that interferes with daily living activities[1,2]. In addition, AD is the most prevalent neurodegenerative disease, affecting more than 36 million people worldwide[3]. The number of people with AD is expected to increase to 66 million in 2030[3] and 135 million in 2050[4] because AD is strongly related to age, and the age of the world's population is increasing[5].

The neuropathological features of AD are known to be related to the overproduction and accumulation of β-amyloid peptide in the tissues. This peptide has a pronounced neurotoxic effect on cholinergic neurons. However, the aetiology of AD is not yet clear. Thus, no effective therapy for AD has previously been proposed.

Among the various treatments that are currently applied in AD, medications are the primary mode of treatment[6]. Medications currently used to treat AD are categorized into two classes, cholinesterase inhibitors (ChEIs) (e.g., donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate receptor antagonist (e.g., memantine). These medications have been shown to slow the rate of cognitive decline for periods of up to one year, but they do not modify the course of the disease[7].

In addition to pharmacological approaches to AD, a number of non-pharmacological methods have also been proposed because they are associated with fewer risks and adverse effects[8]. The important effects of non-pharmacological interventions postpone the institutionalization of patients and reduce the burden on caregivers[9]. Non-pharmacological approaches include cognitive training or stimulation, behavioural interventions aimed at improving skills during activities of daily living (ADL), movement therapy (exercise), art therapy and music therapy[1,10]. One kind of nonpharmacological intervention in AD involves the use of various meditation techniques.

Meditation originated in ancient eastern traditions and is a mind-body practice used in complementary and alternative medicine[11]. Meditation is defined as a self-regulatory technique focused on maintaining one's attention to achieve spiritual development, inner peace, concentration and positive emotions[12]. Meditative techniques vary in several ways[13]. Popular meditative techniques include mindfulness-based stress reduction, Zen meditation, transcendental meditation and Kirtan Kirya. In addition, these techniques involve either focused attention or an open-monitoring process[14]. Therefore, meditation is considered a cognitive-stimulating activity and a potential strategy for preventing AD[15].

Recently, interest in the mechanisms underlying the effects of meditation on cognitive function has increased. However, this research remains unresolved and in its infancy. Some studies aimed at understanding the effects of meditation on cognitive function have used morphometric neuroimaging techniques, such as MRI, to examine potential structural changes in the brain. Others have used electroencephalography (EEG), event-related potentials (ERPs), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to explore characteristics related to functional connectiveness in the brain. In MRI studies, researchers have found that both grey matter[16,17] and white matter[18] structures associated with learning and behaviour are changed in AD. In addition, one systematic review reported that eight brain regions were consistently altered by the practice of meditation[19]. These included areas involved in meta-awareness (frontopolar cortex/BA 10), exteroceptive and interoceptive body awareness (sensory cortices and the insula), memory consoli-

dation and reconsolidation (hippocampus), self and emotional regulation (anterior and mid-cingulate and orbitofrontal cortex), and intra- and interhemispheric communication (superior longitudinal fasciculus and corpus callosum)[19]. When alpha power was assessed by EEG, it was found to be higher during meditation than in a resting state and was associated with memory[20], imagination[21] and attention to internal stimuli[22]. Additionally, the results of a study that used ERP suggested that meditation enhanced the speed of attention[23].

The effects of meditation on cognitive functions have been reported to include improvements in attention[24], working memory[25], introspection[26,27] and perceptual discrimination[28]. In clinical studies performed in the elderly, meditation-practicing groups performed significantly better during attentional tasks than did the control groups[29-31]. Moreover, meditation can influence risk factors for AD, such as hypertension[32], hypercholesterolemia[33,34] and cerebral blood flow[35-37]. Thus, meditation could be a potential tool for combating and preventing AD[38].

The results of these studies suggest that meditation has positive effects on cognitive functions. However, no systematic review has explored the effects of meditation on AD. In this paper, we used a systematic review to evaluate the effectiveness of meditation in patients with AD.

II. METHODS

1. Eligibility criteria

1) Study

We included only randomized controlled trials (RCTs) that reported the effects of meditation on patients with AD. Abstract publications in which the full text did not include sufficient information and trials published before 2000 were excluded.

2) Participants

Participants in the included studies were required to have a diagnosis of AD or AD-type dementia based on the diagnostic criteria of the International Classification of Diseases-10 (ICD-10) (WHO 1993), the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV (APA 1994), or probable AD or possible AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer' Disease and Related Disorders Association (NINCDS-ADRDA). We included AD patients older than 18 years old and all severities of AD.

Patients with other non-AD types of dementia (e.g., Lewy body disease (DLB), frontotemporal lobar degeneration (frontotemporal dementia), traumatic brain injury (head trauma), prion disease (e.g., Creutzfeldt-Jakob's disease (CJD)), Parkinson's disease, Huntington's disease, Pick's disease, Wernicke's encephalopathy, Binswanger's disease, Korsakoff Syndrome, normal pressure hydrocephalus, and substance/medication use) were excluded. Patients with delirium and elderly patients with normal cognitive levels were also excluded.

3) Interventions

We included any form of meditation that was performed in addition to standard care.

4) Control

Acceptable control interventions were placebo or standard care.

5) Outcome measures

The included studies were required to assess at least one reliable and validated instrument of cognition, activities of daily living (ADLs), behavioural problems, or mood in dementia.

(1) Primary outcomes

① Cognition (global or single domain (e.g., attention, orientation, memory, fluency, language skills (speech content and fluency) and visuospatial perception)).

② Activities of daily living

③ Mood (e.g., depression and anxiety)

④ Behavioural problems (e.g., agitation)

(2) Secondary outcomes

① Adverse effects

② Quality of life

③ Caregiver burden or distress

2. Search strategy

Five databases, including the Cochrane Central Register of Controlled Trials (CCRCT), MEDLINE, EMBASE, Allied and Complementary Medicine Database (AMED) and Cumulative Index of Nursing and Allied Health (CINAHL) databases, were searched through May 30, 2017. To reduce language bias, we applied no language restriction. We searched using terms related to meditation (including a Mesh search performed using 'Meditation', 'Mind-Body Therapies' 'breathing exercises' and 'Mindfulness' and a keyword search performed using 'meditation', 'breathing exercise', 'mindfulness-base' and 'vipassana') and terms related to dementia and AD (including a Mesh search performed using 'Dementia' 'Alzheimer Disease', 'Cognition Disorders' and 'Amnesia' and a keyword search performed using 'dement*', 'Alzheimer*', 'AD', 'cognit* impair*', 'cognit* declin*', 'cognit* deficit*', 'cognit* disturb*', 'cognit* defect*' and 'memory impairment').

3. Study selection and data extraction

Two of the review authors (GE and SH) independently screened the titles and abstracts of the reports identified using the above criteria. In cases of disagreement, we obtained the full-text publication. If no consensus was reached, we asked a third review author (IC). The flow chart shown in Fig. 1 represents the process by which studies were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[39]. If the data were incomplete, we tried to contact the main author via electronic mail to ask for specific details related to the research data.

4. Risk of bias

Two of the review authors (GE and SH) independently assessed the risk of bias of all included trials according to the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[40]. We resolved any disagreement by discussion or by involving the third reviewer (IC). This risk of bias tool examines sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessors), incomplete outcome data, selective outcome reporting and other sources of bias. Each domain was assessed and classified as having either a low or high risk of bias or unclear in cases where the details reported in the study were insufficient to assess the risk. We used the Cochrane 'Risk of Bias' tool in RevMan 5.3[41].

5. Statistical analysis

We used Revman 5.3 software for the data analysis. For binary outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). We calculated continuous outcomes as standardized mean differences (SMDs) or mean differences (MD) with 95% CIs. The heterogeneity of the included trials was determined using the I^2 statistic. An I^2 value more than 50% was considered to indicate statistical heterogeneity, while a value less than 50% was considered to indicate homogeneity. A random effects model was utilized for the meta-analysis because there were so many differences among the interventions. Publication bias would have been comprehensively as-

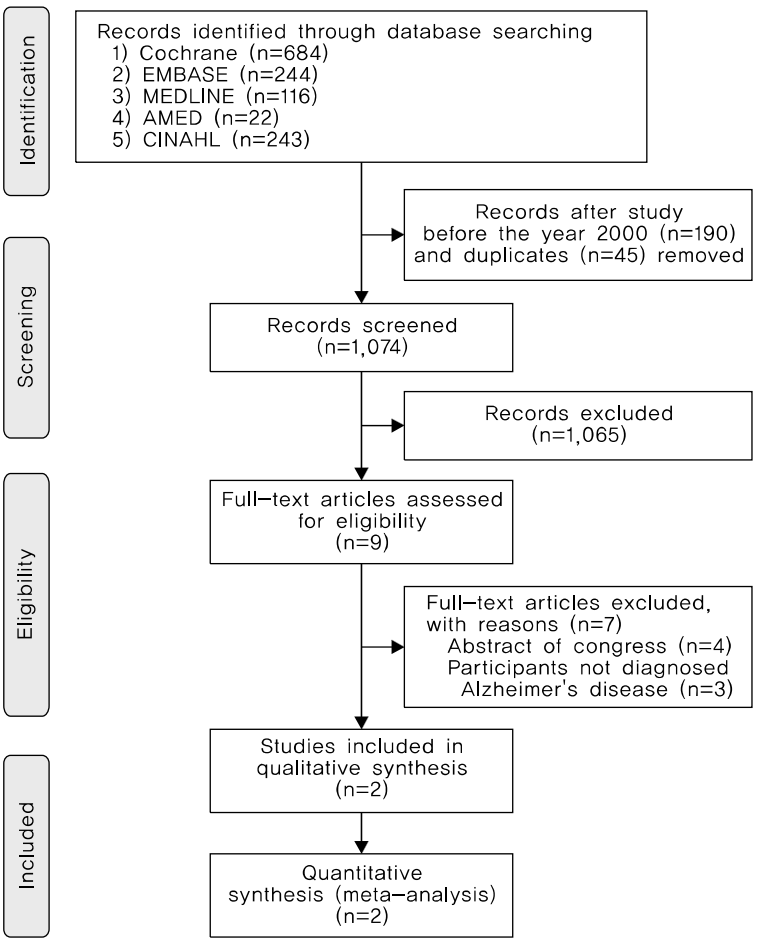

Fig. 1. Study flow diagra.

sessed using a funnel plot analysis in Revman 5.3 software if sufficient trials (≥10 trials) had been included.

III. RESULTS

1. Literature search

The database searches located a total of 1309 articles. After those published before 2000 and duplicates were removed, 1074 studies remained. After the titles and abstracts were screened, the full-texts of 9 articles were independently examined by two of the review authors (GE and SH). Following this review and discussion, 7 trials were excluded as follows: 4 were only abstract publications[42-45], and 3 did not include participants diagnosed with AD[46-48]. Eventually, two trials[49,50] were found to meet the inclusion criteria. A diagram demonstrating the study flow is shown in Fig. 1.

2. Study characteristics

The characteristics of the included studies are listed in Table 1. The two studies[49,50] included in this review consisted of 199 participants aged 61~95 years old who were randomly assigned to one of the groups. The included participants were diagnosed with probable AD according to the NINCDS-ARDA criteria in the one study[49], while in the other study[50],

Table 1. Characteristics of the Included Studies

Study	Country	Design	Sample (I/C)	Age	Setting	Intervention	Duration	Frequency	Outcome
Quintana et al. (2016)	Spain	4 arm (donepezil, donepezil with MBAS, donepezil with CST, donepezil with PMR)	42/43	65～85	Community setting	MBAS	2 yrs	Three times per week for 90 min	MMSE CAMCOG Subitems of CAMCOG (Orientation, Global language, expression, global memory, recent memory, remote memory, learning, attention, praxis, calculation, abstract thinking, and perception)
Clarke et al. (2016)	UK	2 arm (Treatment as usual group, Treatment as usual plus MI)	20/11	61～95	Institutional setting	MI	5 weeks	Two times per week for 60 min	MMSE CSDD RAID QoLAD PSS-13

I: intervention group (meditation with standard care), C: control group (standard care), MBAS: mindfulness-based Alzheimer's stimulation, CST: cognitive stimulation therapy, PMR: progressive muscle relaxation, MI: mindfulness intervention, MMSE: Mini Mental State Examination, CAMCOG: Cambridge Cognitive Examination, CSDD: Cornell Scale for Depression in Dementia, RAID: Rating Anxiety in Dementia Scale, QoLAD: Quality of Life Alzheimer's Disease scale, PSS-13: The Perceived Stress Scale.

dementia patients older than 60 years old were diagnosed in accordance with the DSM-IV criteria. However, the exclusion criteria included patients with a history of brain lesions or major head trauma. Thus, these participants would grossly meet a diagnosis of AD. The one study[50] was designed with two groups, standard care (n=11) and standard care with mindfulness meditation (n=20). The other study[49] was a four-armed RCT. One group of patients used a meditative technique consisting of a mindfulness-based meditation program. Among the four groups, we selected two groups, including a donepezil medication as standard care group (n=43) and a mindfulness-based meditation program combined with donepezil as meditation with standard care group (n=42). Because 2 patients died and 16 patients declined to complete the outcome measures, a total of 101 patients were eligible for analysis throughout the follow up period. The meditation programs described in the included studies were based on mindfulness meditation. The program in one of the studies included a variety of techniques involved in mindfulness meditation, such as mindful breathing, body scanning, mindful movement, mindful listening, seeing, smelling and touch[50]. The program used in the other study[49] was composed of temporal and spatial orientation, yoga exercise in a chair, attention-to-breathing exercise, body scanning, the Kirtan Kriya technique, and multi-sensorial stimulation exercises. These programs lasted for 60～90 mins and were run two to three times per week. The duration of the intervention varied from 5 weeks to 2 years.

3. Risk of bias of the included studies

The risk of bias of the included studies is shown in Fig. 2 and Fig. 3.

1) Allocation

One study[50] described the generation of random sequences. However, in the other study[49], the risk of bias for random sequence generation was judged to be high because they assigned the participants according to the sequence. One study[50] that did not mention allocation concealment was judged to have an unclear risk of bias. In the other study[49], allocation concealment was judged to be low because only the main researcher knew which group the participants were assigned to.

2) Blinding

Because two of the studies were performed using single blinding, we judged the risk of blinding of participants and personnel bias to be high. However, blinding during outcome assessment was judged to be low in all of the included studies because the assessors were not aware of the treatment allocation.

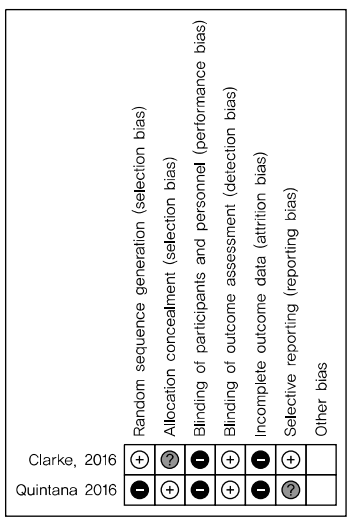

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for the included study.

3) Incomplete outcome data

Though two studies reported the reasons for and numbers of drop-outs, we strictly judged the risk of incomplete outcome data to be high because included studies used 'as treated' analyses only. Additionally, the drop-out rates were higher in the control arms.

4) Selective reporting

We could not obtain the protocol for two of the studies. One study[50] reported their stated outcomes, which included measurements of cognitive function, mood, quality of life and stress. This study was therefore judged to have a low risk of bias. However, the other study was judged to have an unclear risk of bias because the study assessed only cognition.

5) Other potential sources of bias

No information was provided, and we therefore judged the risk of other potential biases to be unclear.

4. Effects of interventions

The trials included in this review investigated the

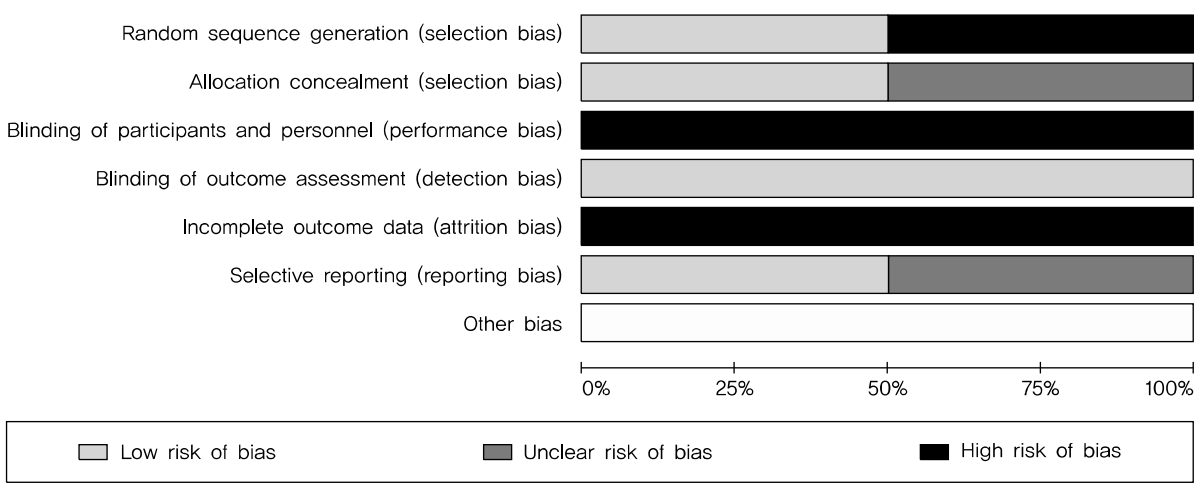

Fig. 3. Risk of bias graph.

effects of mindfulness-based meditation on the cognitive functions of patients who were diagnosed with AD.

1) Cognitive assessment

In the two included studies, the Mini Mental State Examination (MMSE) was used to assess cognitive function. The total score in the group treated with a combination of meditation and standard care was 4.68 points higher than in the group treated with only standard care, but this difference was not statistically significant (MD 4.68, 95% CI -0.11 to 9.46). The I^2 value (I^2=72%) indicated that there was considerable statistical heterogeneity between the studies (Fig. 4).

One study[50] reported total scores on the MMSE. The other study[49] assessed performance using the Cambridge Examination for Mental Disorders of the Elderly - Revised Version (CAMDEX-R), which is a standardized, structured interview used to diagnose common mental disorders in older patients, with a special focus on dementia[51,52]. It incorporates two scales, including the MMSE and Cambridge Cognitive Examination (CAMCOG), to evaluate cognitive functions in section B. The included study reported that the results for cognition (MMSE and the total score and subitems of the CAMCOG) divided the patients into two groups, including those with mild to moderate dementia (MMSE≥18) and those with moderate to severe dementia (MMSE≤17). Among the patients with mild to moderate AD, the degree of decline, according to MMSE and CAMCOG total scores, was significantly lower in the adjunctive meditation group than in the standard care group. Moreover, meditation addition to standard care was more effective than only standard care in patients with mild to moderate AD at improving subitems on the CAMCOG (e.g., global language, understanding, expression, global memory, recent memory, learning, praxis, calculation, abstract thinking and perception) except for orientation and remote memory. However, in moderate to severe AD patients, there were no significant differences in MMSE and CAMCOG scores or in subitems on the CAMCOG between two groups.

2) Mood, quality of life and stress

Only one study[50] assessed mood, quality of life and stress. The Cornell Scale for Depression in Dementia (CSDD)[53] and the Rating Anxiety in Dementia Scale (RAID)[54] were used to assess depression and anxiety. These scales are clinician-administered instruments used to interview persons with dementia and care staff. The quality of life Alzheimer's disease scale (QoLAD) was used to assess quality of life and is completed by dementia patients and their caregivers[55]. Stress was assessed using the perceived stress scale (PSS-13)[56], which has good reliability and validity in elderly patients with mild cognitive impairment but not dementia[57]. Quality of life was significantly higher in the meditation group than in the control group.

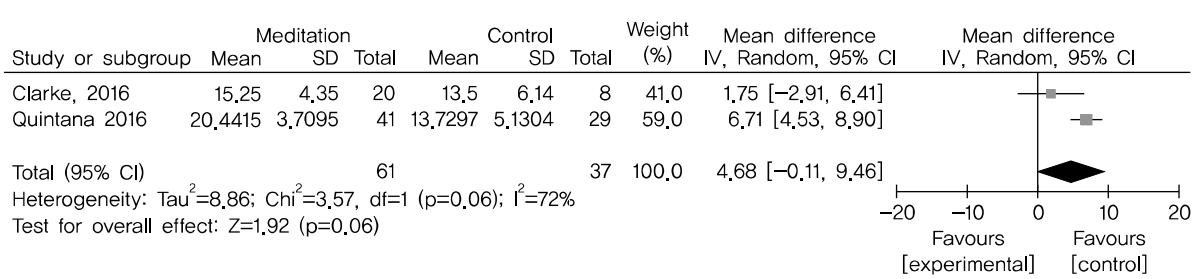

Fig. 4. Total Scores on the Mini Mental State Examination (MMSE).

However, there was no significant difference between the two groups in scales used to assess depression, anxiety and stress.

3) Adverse effects

Only one study[50] reported no adverse events. The other study[49] provided no detailed information regarding adverse events related to meditation.

IV. DISCUSSION

We identified two small trials that fulfilled our inclusion criteria, and we investigated the effects of meditation on the cognitive function of patients with AD. One hundred and ninety nine participants were randomly assigned to the groups in the included trials. We selected patients for two groups, including a standard care combined with meditation group and a standard care alone group. Thus, 116 patients of the 199 randomized patients were selected. In addition, total scores on the MMSE were available for 101 patients who were eligible for the meta-analysis. The results of the meta-analysis showed that there was no significant difference in total scores on the MMSE between the meditation group and control group in terms of overall effectiveness. One of the studies reported data related to depression, anxiety, quality of life and stress. Among these, only the quality of life was significantly different between the two groups. In addition, only one of the studies reported no adverse events. The overall quality of the included studies suggested the presence of considerable methodological problems because there was a high risk of selection bias, performance bias, attrition bias and imprecise results (too few participants). Therefore, these studies did not allow us to clearly evaluate the beneficial and harmful effects of meditation on AD.

As far as we know, this systematic review is the first to provide an overview of what is currently known of the effects of meditation on adult patients with AD. Other recent systematic reviews have proposed that meditation might improve cognitive functions in normal elderly[12] and cancer[58] patients. Other trials that have included elderly with normal and declined cognition have reported results similar to those presented in reviews showing enhanced cognitive function and increased cerebral blood flow to the prefrontal and parietal lobe[36,59,60]. In neuroimaging studies of meditation, a number of changes were reported that might support the use of meditation to potentially promote memory, attention and other aspects of cognition. In particular, some studies reported that the thickness of the prefrontal cortex was increased[61-63] and structural connections, such as the projections of the commissural and association pathways, were stronger in meditators[64]. These results also imply that meditation could lead to neuroregeneration and have a compensatory effect that decreases the cortical thickness that has been associated with aging[12]. Moreover, mindfulness meditation which was used in all of the included trials is one of the more popular meditative techniques and has been very intensely researched. Practicing mindfulness is characterized by training in present-focused awareness without any judgement[65]. This practice begins by focusing the attention on breathing followed by a receptive state of open-monitoring[66]. Mindfulness has been applied to treat various psychosomatic or physical symptoms, such as chronic pain[67], cancer[68], migraine[69], depression[70], and substance abuse[71,72]. One review suggested that mindfulness meditation could enhance selective and executive attention in a focused attention state and increase long-term attention during a non-judgemental observation state[73]. Thus, in light of these previous reports, some of the effects of meditation, especially mindfulness-based meditation, on dementia can be predicted.

The results of the studies reviewed in this meta-

analysis show that groups in which a mindfulness based meditation program was combined with standard care had comparatively but not significantly higher total scores on the MMSE. However, one of the included studies reported that the total scores on the MMSE and CAMCOG and on the subitems of the CAMCOG were significantly higher in the meditation group in patients with mild to moderate AD. Therefore, it couldn't be concluded that adjunctive meditation with standard care might not have any benefit in delaying deterioration of cognitive function on AD.

This systematic review and meta-analysis may have several important limitations. First, despite the fact that we searched several databases for information related to dementia, only two small trials fulfilled the inclusion criteria, and the number of total participants was too small. Second, the methodological quality of the included trials was generally low. Third, evident heterogeneity was observed in the included studies. Differences in the setting to enrol the participants and in the duration of intervention may have potentially influenced the results of our study. Finally, although meditation originated in Asian cultures and is popular in India, trials performed in Asia and India are not usually accessible in electronic databases. Therefore, publication bias cannot be excluded.

Because only limited evidence is available to evaluate the effects of meditation on cognitive functions in AD patients, additional RCTs with high methodological quality, larger populations, and a variety of severities of AD are needed. The type of meditation and the frequency and duration with which it is performed should also be considered for identifying the optimal type of meditation for AD. And to make it possible to incorporate results of trial into future meta-analyses and permit subgroup analyses, it is advisable to include detailed descriptions of the meditation techniques and procedures used in each study.

Additionally, these studies should be conducted in a community setting and not only in an institutional setting to focus on patient-relevant outcomes, such as ADLs, depression, neuropsychiatric symptoms, quality of life and overall survival, as well as family caregiver outcomes in addition to cognitive function.

In addition, one of the studies included in this review suggested that no adverse events were attributed to participation in the meditation program. Therefore, forthcoming studies should reported the details related to adverse events, the reasons for study dropouts or withdrawals and the difficulties experienced in conducting the meditation program in patients in AD.

V. CONCLUSION

Following a search, we performed a systematic review and meta-analysis that suggested that combining meditation with standard care did not significantly delay the deterioration of cognitive function in AD when the meditation with standard care group was compared to the standard care only group. In addition, the quality of the included trials was low, and they included a small number of participants. Thus, with regard for the efficacy of combining meditation with standard care to treat patients with AD, no credible conclusions can be drawn at the current time. Additionally, all of the results presented here should be considered very cautiously, and it is clear that further well-designed RCTs are needed to determine the safety and efficacy of meditation in AD.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS' CONTRIBUTION

Lee GE, Kim SH, Jung IC and Kang HW designed the study, including its concept and protocol. Lee GE, Kim SH and Jung IC performed the literature search and data extraction and assessed the risk of bias. Lee GE and Kim SH analysed the data and wrote the manuscript. Lee GE, Jung IC and Kang HW revised the manuscript. All authors agreed with the final version of the manuscript.

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