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Improving Medication Adherence in Isolated Patients With Cognitive Impairment Using Automated Telephone Reminders

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ABSTRACT

Background and Purpose: Medication adherence is essential for effective medical treatment. However, it is challenging for cognitively impaired patients. We investigated whether an automated telephone reminder service improves medication adherence and reduces the decline of cognitive function in isolated patients with cognitive impairment.

Methods: This was a single-center, randomized clinical trial. We enrolled mild cognitive impairment (MCI) or Alzheimer's disease (AD) patients who lived alone or with a cognitively impaired spouse. We provided an automated telephone reminder service for taking medication to the intervention group for 6 months. The control group was provided with general guidelines for taking the medication every month. The participants underwent neuropsychological assessment at the beginning and end of the study. Statistical significance was tested using nonparametric Wilcoxon rank sum and Wilcoxon matched-pairs signed-rank tests.

Results: Thirty participants were allocated randomly to groups, and data for 29 participants were analyzed. The mean age was 79.6 (standard deviation, 6.0) years and 79.3% of the participants were female. There was no significant difference in medication adherence between the 2 groups. However, a subgroup analysis among participants with more than 70% response rates showed better medication adherence compared to the control group (intervention: 94.6%; control: 90.2%, p=0.0478). There was no significant difference in the change in cognitive function between the 2 groups.

Conclusions: If a patient's compliance is good, telephone reminders might be effective in improving medication adherence. It is necessary to develop reminder tools that can improve compliance for cognitively impaired patients.

Keywords: Alzheimer Disease; Medication Adherence; Reminder Systems; Telemedicine

INTRODUCTION

Medication adherence is vital for effective treatment. Unfortunately, medication non-adherence is a common and consequential phenomenon that not only affects patients but also healthcare systems. Barriers to medication adherence are related to individual patient characteristics, socio-economic status, and the healthcare team. Lack of knowledge on disease characteristics or treatment, low educational level, and rural location lead to poor compliance. Furthermore, persistence rates of patient care are lower in primary care than in tertiary care.[1,2]

The elderly often exhibit low medication adherence, ranging from 26%–84%.[3] Especially, older persons with Alzheimer's disease (AD) are at a higher risk for medication non-adherence because of their memory impairments. Previous studies reported that 40%–60% of AD patients showed poor medication adherence[4,5] which is mainly attributed to cognitive impairments and lack of caregiver support.[6]

A previous intervention study assessed the efficacy of telehealth home video monitoring to improve medication adherence in 14 patients with mild dementia, and reported 81% adherence in the video-monitored group compared to 66% among controls who were given only general guidelines.[7] However, telehealth home video monitoring requires significant human resources and is difficult to apply in rural areas as many residents lack internet services or have difficulties using new technologies.

Hongcheon Dementia Center is in a rural area whose majority of patients are over 70 years old, with many living alone or with a spouse who is also cognitively impaired. These factors place patients at risk of non-adherence. Therefore, we investigated whether an automated telephone reminder service would improve medication adherence and whether the reminder service would improve cognitive function in these patients.

METHODS

Study design and participants

This was a single-center, randomized trial that was conducted from March 2019 to February 2020, at Hongcheon Dementia Center in South Korea. We enrolled patients aged 65 and older who were diagnosed with mild cognitive impairment (MCI) or AD, were taking medication, and lived alone or with a cognitively impaired spouse. MCI was defined according to Peterson's criteria.[8] AD dementia diagnosis was confirmed when patients met the diagnostic criteria for probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[9] After diagnosis, we assessed patients using the Clinical Dementia Rating (CDR) scale and included patients with a CDR of 0.5 or more in the study sample. We excluded patients with a history of traumatic brain injury, cortical stroke, seizure, brain surgery, or current systemic medical disease that could affect cognition. We determined that the participant's spouses were cognitively impaired if they had a history of MCI or probable AD diagnosis.

Standard protocol approvals and patient consent

The Institutional Review Board at Kangwon National University Hospital approved the trial and all subsequent amendments (KNUH-2019-02-005). The study was conducted

following the Korea Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients or legally acceptable representatives before enrollment.

Randomization and protocol

Eligible patients were randomly assigned in a 1:1 ratio to receive additional automated telephone reminders to take medication or only general guidelines for taking medication. The allocator prepared a concealed, computer-generated, 1:1 randomization list using permuted blocks (random block sizes of 2 or 4), that were not accessible to the lead researcher who enrolled participants.

Participants visited the Hongcheon Dementia Center every month for 6 months. We provided patients in the intervention group with an automated telephone reminder service for taking medication for 6 months. We offered the control group general guidelines for taking medication when visiting the Hongcheon Dementia Center during monthly follow-ups. AD patients were taking cognitive function medications (donepezil or rivastigmine patch) while MCI patients were taking low-dose donepezil. Cognitive function medications were separately prescribed to the participants. The interventions applied to the medications taken once a day. We collected monthly medication adherence and response rates for the telephone reminder service from the intervention group. Due to the pandemic, there were some cases where the caregivers visited the clinic instead of the patient. In these situations, the researcher called the participants and let them check the number of remaining pills to assess adherence. If it was difficult for the participants to report, the researcher asked the caregiver to check the number of the remaining drugs.

Telephone-based reminder service

The free telephone reminder service was provided by Eisai to help patients remember to take dementia medications. The telephone-based reminder service was offered using home telephones. When patients or caregivers set alarms, patients receive reminder calls at the desired times. When they answer the phone, they hear a recorded voice reminding them to take their medication. If the participants did not take the call for more than 3 days, a researcher who did not participate in the data analysis contacted them and confirmed whether or not they could continue participating in the study. Eisai provided the reminder service only and did not play any other role in this study.

Measurements

The participants underwent a detailed neuropsychological assessment at the beginning of the study and 6 months later. We determined cognitive status and evaluated cognitive function using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD).[10] CERAD standards are accepted for clinical, neuropsychological, and neuropathologic diagnosis of AD[11] and are a translation of the original English version of the CERAD clinical battery.[10]

Outcomes

The primary outcome was the difference in mean monthly medication adherence between the 2 groups. Medication adherence was defined as follows.

$$\text{Medication Adherence} = \frac{The\ Number\ of\ Taken\ Medications}{The\ Number\ of\ Prescribed\ Medications} \times 100$$

The secondary outcome measure was the difference in the degree of change in cognitive function between groups. We compared the z-score for each CERAD clinical battery item between the 2 groups.

Statistical analyses

We compared demographic characteristics between the groups using *t*-tests for continuous variables and χ^2 tests for categorical variables. The significance of the difference in mean medication adherence between the groups was evaluated using nonparametric Wilcoxon rank sum tests. We also compared differences in cognitive function between the 2 groups using Wilcoxon matched-pairs signed-rank tests. Statistical analysis was performed with Stata software, version 15 (StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics of the participants

Thirty participants were allocated randomly to the intervention (n=15) and control (n=15) groups. One withdrew consent. Finally, 29 participants (15 in the intervention group and 14 in the control group) were analyzed (**Fig. 1**). The mean age was 79.6 (standard deviation [SD], 6.0) years, 79.3% were female, and the mean education duration was 3.4 (SD, 4.5) years. The mean baseline Mini-Mental State Examination (MMSE) score was 19.5 (SD, 4.6). Among the participants, 34.5% were living alone while 58.6% lived with a cognitively impaired spouse. Of the 29 participants, 20.7% were diagnosed with MCI and 79.3% had dementia. There were no significant differences in demographics between the 2 groups (**Table 1**). We further analyzed the demographic characteristics of reminder group by dividing them into 2 groups with an answering rate less than 70% and more than 70%. We found there was difference of years of education and baseline MMSE, and the lower answering rate group had higher education and baseline MMSE compared to the reminder group (education, *p*=0.033; MMSE, *p*=0.008). Other than that, there was no difference of demographic characteristics (**Supplementary Table 1**).

Effect of reminder service on medication adherence

The mean response rate to the reminder service in the intervention group was 51.3%. Six participants' response rate to the reminder service was greater than 70%, with a mean response rate of 86.6%.
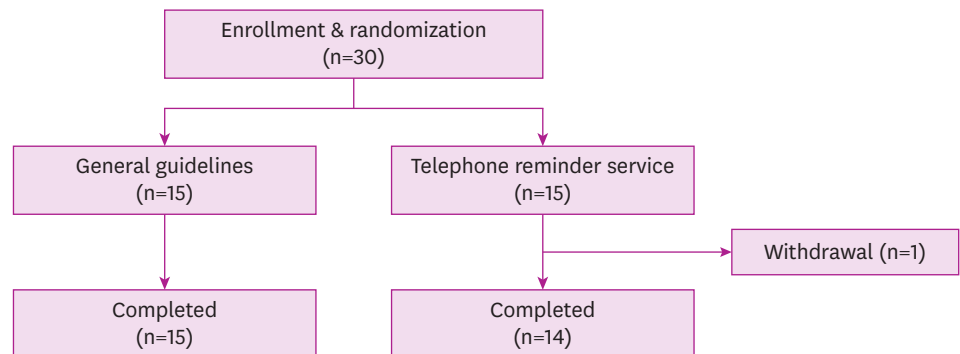

Fig. 1. Study flow diagram.

Table 1. Demographic characteristics of the participants

Characteristics	Total			Answering rate ≥70%		
	Control (n=14)	Reminder (n=15)	p	Control (n=14)	Reminder (n=6)	p
Age	78.7±2.0	80.3±1.2	0.492	78.7±2.0	82.7±1.5	0.125
Sex, female	11 (78.6)	12 (80.0)	0.924	11 (78.69)	5 (83.3)	0.060
Education	2.9±0.8	3.9±1.4	0.523	2.9±0.8	0.7±0.5	0.036
Baseline MMSE	19.5±1.3	19.5±1.1	0.985	19.5±13.4	16.2±1.2	0.086
Diagnosis			0.924			1.513
MCI	3 (21.4)	3 (20.0)		3 (21.4)	0 (0.0)	
Probable AD	11 (78.6)	12 (80.0)		11 (78.6)	6 (100.0)	
Family type			0.363			2.483
Alone	5 (35.7)	7 (46.7)		5 (35.7)	3 (50.0)	
With spouse	9 (64.3)	8 (53.3)		9 (64.3)	3 (50.0)	
Answering rate		51.3 (60.2)			86.6 (19)	

Values are expressed as mean ± standard deviation or number (percent).
AD, Alzheimer's dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Table 2. Medication adherence in groups and subgroups

Characteristics	Total			Answering rate >70%		
	Control (n=14)	Reminder (n=15)	p	Control (n=14)	Reminder (n=6)	p
Adherence	90.2 (6.0)	92.6 (12.1)	0.295	90.2 (6.0)	94.6 (4.3)	0.048

Values are expressed as median (interquartile range).

Table 3. Cognitive function changes in groups

Characteristics	Reminder (n=12)			Control (n=9)		
	Initial	Follow-up	p	Initial	Follow-up	p
MMSE	16.5 (4)	17 (2.5)	0.257	19 (6)	19 (3)	1.000
Word fluency_z	−1.0 (1.9)	−1.1 (1.4)	0.273	−0.9 (1.0)	−0.9 (1.4)	0.214
Naming_z	−1.2 (1.1)	−1.4 (2.0)	0.353	−0.9 (1.3)	−0.7 (1.6)	0.429
Verbal memory delayed recall_z	−2.0 (0.5)	−1.8 (0.6)	0.161	−1.7 (0.5)	−2.1 (0.9)	0.671
Visual memory delayed recall_z	−1.2 (0)	−0.7 (1.0)	0.317	−1.2 (1.7)	−1.5 (0.5)	0.934
Visuospatial	0.1 (0.6)	−0.4 (2.9)	0.317	0.1 (2.5)	−0.4 (2.2)	0.491
Stroop color reading_z	−1.4 (2.5)	−1.8 (2.9)	0.095	−1.2 (2.2)	−0.1 (1.6)	0.553

Values are expressed as median (interquartile range).
MMSE: Mini-Mental State Examination, z: z-score.

There was no difference in medication adherence between the 2 groups when including all the participants (intervention group 92.6%; control group 90.2%, p=0.295). However, after subgroup analysis, participants with response rates greater than 70% showed significantly higher mean medication adherence compared to the control group (intervention group 94.6%; control group 90.2%, p=0.048) (**Table 2**).

Effect of reminder service on cognitive decline

In the reminder service group, 12 of the 15 participants underwent neuropsychological assessment after the intervention while 9 of the 14 participants in the control group were tested. Among the 6 participants in the intervention group with response rates of 70% or more, 4 underwent neuropsychological assessment. There were no significant differences in cognitive function scores between the 2 groups when all the participants were included (**Table 3**). Further, in the subgroup analysis, participants with response rates of more than 70% did not show any significant difference in cognitive function changes compared to the control group (**Table 4**).

Table 4. Cognitive function changes in subgroups (answering rate >70%)

Characteristics	Reminder (n=4)			Control (n=9)		
	Initial	Follow-up	p	Initial	Follow-up	p
MMSE	16.5 (4)	17 (2.5)	0.257	19 (6)	19 (3)	1.000
Word fluency_z	−1.0 (1.9)	−1.1 (1.4)	0.273	−0.9 (1.0)	−0.9 (1.4)	0.214
Naming_z	−1.2 (1.1)	−1.4 (2.0)	0.353	−0.9 (1.3)	−0.7 (1.6)	0.429
Verbal memory delayed recall_z	−2.0 (0.5)	−1.8 (0.6)	0.162	−1.7 (0.5)	−2.1 (0.9)	0.671
Visual memory delayed recall_z	−1.2 (0)	−0.7 (1.0)	0.317	−1.2 (1.7)	−1.5 (0.5)	0.934
Visuospatial	0.1 (0.6)	−0.4 (2.9)	0.317	0.1 (2.5)	−0.4 (2.2)	0.491
Stroop color reading_z	−1.4 (2.5)	−1.8 (2.9)	0.095	−1.2 (2.2)	−0.1 (1.6)	0.553

Values are expressed as median (interquartile range).
MMSE: Mini-Mental State Examination, z: z-score.

DISCUSSION

In this study, we examined whether automated telephone reminder service improves medication adherence and reduces decline in cognitive function. There was no difference in medication adherence between the 2 groups across all participants. However, participants with a good response rate to the reminder service exhibited higher medication adherence compared to the control group. Regardless of the response rate, there was no difference in cognitive change in both groups.

Although we could not find significant differences in medication adherence and cognitive function between the groups there could be the possibility of improvement with the alarm service when considering the results among good responders. Notably, when applying alarm service, maintaining compliance to the alarm service was important and it was affected by the alarm methods. Previously, few intervention trials have been conducted to improve medication adherence in cognitively impaired patients. The results of these studies varied according to the method applied. Studies using methods that rely on the participant's own memory function did not show any benefits[6,12] while a study using a video system for MCI and AD patients showed improvement in medication adherence in the intervention group (81%) compared to the telephone reminder only and control groups (66%).[7] Although video methods have strengths, they are time- and labor-consuming.[7] Another study among 18 patients with CDR scores of 0.5 or 1 using an automatic pill dispenser with a reminder system also observed improved medication adherence (from 16.7% to 50%), with participants with greater than 80% medication adherence.[13,14] However, for elderly individuals, using electrical devices might be difficult, and this method requires consistent caregiver monitoring, which is not available for isolated patients.

We used an automated reminder service using home telephone as an intervention method. This method has some strengths. First, it was easy to access. Our patient population lives in a rural area, and the participants lived alone or with a cognitively impaired spouse. Most of them did not use internet service or cell phones, but they all had telephones in their home. Therefore, the home telephone-based reminder service was provided. Second, it was easy to apply. The participants were cognitively impaired, and most had low education levels. Therefore, most would have difficulties using new and complicated electronic devices. The telephone was an adequate option as they were already familiar with and knew how to use the phones. Third, it was cost-effective. Compared to previous studies using video devices or automated pill dispensers[7,13] telephone reminders do not require patients to buy a new device and there was no need for human resources because the service sends voice recordings automatically. Fourth, this reminder system could also serve as a monitoring mechanism,

as it was apparent if a patient did not answer the reminder call for 3 days. Despite the many advantages of the telephone reminder service, there were some limitations. The overall intervention group showed a low response rate of 51.3% with this method. Most of the reasons for not answering the calls were related to misunderstanding the recorded voice and being out of the house at the time of the call. Such misunderstandings might reflect that the telephone reminder service was not interactive. To address this problem, we explained the reminder service to the participants at the beginning of the study and repeated it each time the researcher contacted the participants who did not answer the phone call for 3 days. However, despite repeated explanations, some participants could not remember the details of the explanation. Therefore, for cognitively impaired participants, introductions about how to use the system should be provided repeatedly and in various ways. The other disadvantage of telephone reminders is that they can only be received at home. This could be a problem for patients who are active and leave their homes frequently for daily living activities. Similarly, a previous study using a video system reported that 10% to 15% of non-response cases were due to being out of the house.[7] For patients who maintain active daily life, wearable devices or cellular phones could be a good alternative to home phone calls.

We did not expect a significant change in cognitive function decline to occur during the short study period (6 months). Due to the coronavirus disease 2019 pandemic, there were restrictions on research follow-up and monitoring. However, similar to our study results, a previous study conducted for more than 2 years found no differences in the rate of MMSE, GDS score, or neuropsychiatric symptoms between the intervention and control groups.[5] In another study, longitudinal cognitive function changes occurred in 4 patients who used a reminder device for 3 to 4.5 years when measuring MMSE as an outcome. There were no significant trends and it is difficult to draw conclusions due to the small study sample.[14]

Our study has the following limitations. First, the study sample was small and the number of subgroup participants was smaller. Therefore, the results should be carefully interpreted. However, the results of this study suggest the potential for a positive effect of an alarm service, and provide a basis for further larger studies. Second, there could be a selection bias in the participants. Medication compliance in our control group was 90.2%, which was much higher than in the previous studies (17%–42%).[2] Individuals with high medication adherence might have been more likely to actively participate in the study. In addition, we tried to enroll the participants who were not assisted by other caregivers when taking their medications, but the intervention of the other caregivers may not have been fully controlled. Third, there could be a possibility of an inaccurate pill count. There were some cases where the caregivers visited the clinic instead of the patient. In these situations, the researcher called the participants and let them check the number of the remaining pills to assess adherence. If the researcher determined that the participant was not able to report, the caregiver was asked to count the number of remaining drugs. In more than 90% of the visits, researchers checked the remaining drugs. Although every effort was made to ensure that the pill counting was as reliable as possible, the number of pills checked by the participant or caregiver may not have been accurate.

Despite its limitations, this study is meaningful in that it is the first study of isolated cognitively impaired elderly patients living alone or with couples with cognitive decline. Among such patients, if compliance is good, automatic telephone reminders might be effective in improving medication adherence. It is necessary to develop a reminder tool that can improve compliance for isolated AD patients. Future research studies with improved

methods conducted over more extended periods are warranted to confirm whether automated reminders reduce cognitive function decline.

ACKNOWLEDGEMENTS

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Demographic characteristics of the reminder group participants

Click here to view

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