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Effects of cilostazol on cognition and regional cerebral blood flow in patients with Alzheimer's disease and cerebrovascular disease: A pilot study

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Aim: It remains unknown whether antiplatelet agents have a preventive effect on cognitive decline in patients with Alzheimer's disease (AD). We investigated the effects of cilostazol, an antiplatelet agent and cyclic adenosine monophosphate phosphodiesterase 3 inhibitor, on cognition and regional cerebral blood flow (rCBF) in elderly patients with AD and cerebrovascular disease (CVD).

Methods: A total of 20 patients with AD and CVD were randomly assigned to a cilostazol group ($n = 11$, 100 mg daily) or control group ($n = 9$, aspirin 100 mg or clopidogrel 50 mg–75 mg daily) for 6 months.

Results: The cilostazol group did not show any statistically significant changes in cognitive function test scores, whereas the control group showed statistically significant cognitive decline on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (Japanese version), Revised Wechsler Memory Scale (logical memory-I) and Trail Making Test-A. Analysis of covariance of treatment effect revealed that the cilostazol group showed increased rCBF in the right anterior cingulate lobe compared with baseline, whereas the control group showed decreased rCBF in the left middle temporal gyrus compared with baseline.

Conclusion: These findings suggest that cilostazol might have a preventive effect on cognitive decline in patients with AD and CVD. **Geriatr Gerontol Int 2013; 13: 90–97.**

Keywords: Alzheimer's disease, cerebral blood flow, cerebrovascular disease, cilostazol, cognition.

Introduction

Vascular risk factors, such as hypertension, diabetes and hypercholesterolemia, are related to an increased risk of Alzheimer's disease (AD).[1,2] Furthermore, some studies have shown that vascular risk factors play a role in the progression of AD.[3–7] In recent years, AD and vascular pathology have been considered the major pathological correlates of cognitive decline in elderly people, and most patients have mixed disease.[8] Several studies have shown that cerebrovascular disease (CVD) is associated with the progression of AD.[9,10] The Nun Study showed that CVD might play an important role in determining the presence and severity of the clinical symptoms of AD.[9]

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Cilostazol is a unique antiplatelet agent. Previous studies have suggested that cilostazol has pleiotropic effects including increased cerebral blood flow (CBF), protection of the endothelia and an upregulated phosphorylation of cyclic adenosine monophosphate pathway response element-binding (CREB) protein.[11]

In a pilot follow-up study, Arai *et al.* reported that a combination therapy of donepezil and cilostazol, when given to 10 patients with moderate AD, maintained improvement or stability on the Mini-Mental State Examination (MMSE) over a 7.6-month period.[12] However, it was an open trial in which the MMSE was the only assessment of cognitive function.

We designed a randomized controlled trial using a set of neuropsychological tests and regional CBF (rCBF) assessment to determine whether cilostazol has beneficial effects in elderly patients with AD and CVD.

We compared the effects of cilostazol with those of aspirin or clopidogrel (control) on cognitive function and rCBF in patients with AD and CVD. We chose aspirin or clopidogrel as control, as both drugs are the most widely used antiplatelet agents. To the best of our

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knowledge, there are currently no reports showing that both drugs have additional benefits on cognition or rCBF in patients with AD.

Methods

Participants

We enrolled 20 patients with possible AD (a Clinical Dementia Rating[13] of 1–2) and confirmed CVD lesions from the Memory Clinic of Tokyo Medical University Hospital, Tokyo, Japan. Patients with AD met the clinical criteria for AD established by the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.[14] However, none of the patients in the current study met the criteria for vascular dementia as defined by the National Institute of Neurological Disorders and Stroke or the Association Internationale pour la Recherche et l' Enseignement en Neurosciences.[15] This was because the CVD lesions in the 20 enrolled patients comprised lacunar infarctions in the deep gray or white matter, or hyperintense lesions in the white matter, and we classified these as grade 1 or grade 2 according to the scale of Fazekas *et al*.[16] All patients had mild to moderate AD, showing scores of 12–27 on the MMSE at baseline. All patients had been treated with donepezil (a cholinesterase inhibitor) for more than 6 months at a dose of 5 mg/day before participation in the current study.

A total of 20 patients with AD and CVD were randomly assigned to either a cilostazol group ($n = 11$, 100 mg daily) or a control group ($n = 9$, aspirin 100 mg or clopidogrel 50 mg–75 mg daily) for 6 months. Randomization was carried out using the envelope method as follows. We prepared 40 envelopes and placed them in one folder. Of these 40 envelopes, 20 envelopes contained cards on which was written "control group" and the other 20 envelopes contained cards on which was written "cilostazol group". We randomly selected one envelope for each patient.

No participants were taking any medication known to affect cognition or behavior, such as neuroleptics, benzodiazepines or antidepressants, during the study. Participants were excluded if they showed any evidence of other neurological or psychiatric disorders sufficient to cause memory impairment including depression or anxiety disorder as indicated by a score of more than 5 on the Geriatric Depression Scale-15.[17] Participants were also excluded if they had clinically significant medical problems including cancer within the preceding 3 years, chronic renal or heart failure, severe pulmonary disease or poorly controlled diabetes. Patients underwent detailed general physical, neurological and psychiatric examinations, extensive laboratory tests and brain computed tomography (CT) or magnetic resonance imaging (MRI), and single-photon emission CT (SPECT) to exclude other potential causes of dementia.

Ethical considerations

Written informed consent was obtained from all participants and from the legal representative of the participants with AD. The present study was approved by the Ethics Committee of Tokyo Medical University.

Study protocol

The present study was a prospective randomized, open-label parallel design. Participants were randomly assigned to receive cilostazol or a control drug (aspirin or clopidogrel) for 6 months**.** The doses of cilostazol, aspirin and clopidogrel were 100 mg/day, 100 mg/day and 50–75 mg/day, respectively. We administered the MMSE,[18] Alzheimer's Disease Assessment Scale-cognitive subscale Japanese version (ADAS-Jcog),[19] Wechsler Memory Scale-Revised (WMS-R) logical memory-I,[20] and Trail Making Test A (TMT-A)[21] at baseline and at 6 months after treatment. All tests were administered by an experienced psychometrist who was blinded to the clinical data.

Regional cerebral blood flow study

All participants underwent SPECT studies at baseline and at 6 months after treatment to measure rCBF deficits. However, the SPECT data of one participant in the cilostazol group and those of two participants in the control group were excluded from analysis, because the intervals between cognitive assessment and rCBF evaluation were more than 2 months. SPECT studies after an intravenous injection of 222 MBq of N-isopropyl-p-[123I] iodoamphetamine were carried out using a triple-head rotating gamma camera (Prism 3000 XP; Philips Medical Systems, Cleveland, OH, USA) with a fan-beam collimator permitting a spatial resolution of 6.8 mm full width at half maximum. Three-dimensional stereotactic surface projections (3D-SSP) created with the Neurological Statistical Image Analysis Software (Neurostat [Dr. Minoshima, University of Washington, Seattle, WA, USA]) developed by Minoshima *et al*.[22] was used to evaluate the spatial distribution of abnormal CBF. Each image set was realigned to the bicommissure stereotactic coordinate system.[23] Each brain image was anatomically standardized to match a standard atlas brain while preserving rCBF activity. Subsequently, maximum cortical activity was extracted to adjacent predefined surface pixels on a pixel-by-pixel basis using 3D-SSP.[22] Data sets were normalized to the mean cortical activity. To quantify rCBF deficits, the normalized brain activity of each patient was compared with that of

Table 1 Demographic features of patients in the cilostazol and control groups

	Cilostazol group	Control group
n	11	9 (aspirin [*n* = 5], clopidogrel [*n* = 4])
Age (years)	79.7 ± 4.6	78.8 ± 7.3
Sex (men/women)	3/8	1/8
Duration of donepezil use (months)	14.8 ± 10.0	15.9 ± 7.1
Education (years)	11.1 ± 4.1	11.9 ± 2.7
Hypertension	55%	78%
Diabetes	27%	22%
Hyperlipidemia	18%	22%

28 normal controls (12 men and 16 women, mean age 75.1 ± 6.4 years) using pixel-by-pixel z-score analysis: ([normal mean] – [individual value] / normal SD. A positive z-score represents reduced rCBF in the patient relative to the normal control mean.

To show rCBF alterations, two-sample Student's *t*-test values were calculated on a pixel-by-pixel basis between controls and each group at initial SPECT, and then transformed to z-values by a probability integral transformation. Furthermore, to assess rCBF changes, differences between SPECT data at baseline and after 6 months were compared in each group. To measure rCBF reduction, the mean z-score for each patient was calculated using the stereotactic extraction estimation method.[24] The mean z-scores for each gyrus of the frontal, parietal, temporal, occipital and limbic lobes of the right and left hemispheres were automatically measured (average z-value of the coordinates, with a z-value that exceeds 0 of the threshold value). Each mean value for a patient was compared with the corresponding mean values of the 28 control participants on a region-by-region basis and the magnitude of CBF reduction was expressed as a z-score.

Statistical analysis

Values were expressed as means ± SD. Statistical analysis was carried out using paired t-tests, the Mann–Whitney *U*-test and the Wilcoxon signed-rank test. The treatment effect, based on mean z-scores for cerebral subregions at 6 months, was estimated using analysis of covariance. The measurement of z-scores obtained at 6 months was used as the outcome variable, treatment assignment was assigned as the main effect, and the baseline measurement of z-scores was used as a covariate. A *P*-value of less than 0.05 was considered to show a statistically significant difference.

Results

Within the two groups (cilostazol and control), there were no significant differences in age, sex, education or duration of donepezil use (Table 1). The occurrence rates of comorbidities, such as diabetes, hyperlipidemia, or hypertension, were not statistically significantly different between these two groups. All diabetic patients in the cilostazol and control groups were treated with sulfonylureas, and all patients with hyperlipidemia and hypertension were treated with statins and antihypertensive drugs, respectively. The plasma glucose, total cholesterol and blood pressure levels of all patients were successfully controlled. There were no patients with new incidence of CVD in either the cilostazol or control group during the study.

At baseline, no significant differences in neuropsychological performance on the MMSE, ADAS-Jcog, TMT-A or WMS-R logical memory-I-tests were found between the two groups. Furthermore, the cilostazol group did not show any significant changes in score on the MMSE, ADAS-J cog, TMT-A or WMS-R logical memory-1-tests between baseline and after 6 months. However, the control group showed a significant cognitive decline on the ADAS-Jcog, TMT-A and WMS-R logical memory-I test scores between baseline and after 6 months (Table 2).

Table 3 shows the mean z-scores of the cerebral subregions at baseline and after 6 months in both groups. Figure 1a and b shows a relative decrease in rCBF in the cilostazol and control patients compared with the normal elderly patients at baseline. Both groups showed significant decreases in rCBF in the parietotemporal region and posterior cingulate, which are considered characteristic features of AD. Although the cilostazol group showed significantly higher z-scores than the control group in the paracentral gyrus, there were no

Table 2 Changes in neuropsychological test scores between baseline and after 6 months

	Cilostazol group ($n = 11$)	Control group ($n = 9$)
MMSE		
Baseline	20.8 ± 5.3	20.6 ± 4.2
After 6 months	21.2 ± 5.2	20.1 ± 4.9
ADAS-Jcog		
Baseline	19.2 ± 8.9	17.8 ± 6.8
After 6 months	20.3 ± 10.5	20.1 ± 8.3*
WMS-R (logical memory-I)		
Baseline	4.6 ± 4.0	7.3 ± 5.2
After 6 months	5.6 ± 4.7	4.2 ± 3.5*
TMT-A		
Baseline	87.6 ± 41.7	65.3 ± 21.0
After 6 months	78.6 ± 39.5	85.1 ± 22.5*

*$P < 0.05$ compared with score at baseline. ADAS-Jcog, Alzheimer's Disease Assessment Scale-cognitive subscale (Japanese version); MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test-A; WMS-R, Wechsler Memory Scale-Revised.

significant differences in z-scores in any other regions between the two groups.

The cilostazol group showed a significant increase in rCBF in the right anterior cingulate lobe, but showed a significant decrease in rCBF only in the right postcentral gyrus. However, the control group showed a significant increase in rCBF in the right postcentral gyrus, but a significant decrease in rCBF in the left middle temporal gyrus. Figure 2a and b shows the rCBF changes from baseline to 6 months in both groups.

Discussion

We set out to determine whether cilostazol has beneficial effects on cognition and rCBF in elderly patients with AD and CVD. In the present results, the cilostazol group did not show deterioration in scores on any of the detailed neuropsychological tests after 6 months, whereas the control group showed a significant cognitive decline between baseline and after 6 months. The cilostazol group showed a significant increase in rCBF in the right anterior cingulate lobe, whereas the control group showed a significant decrease in rCBF in the left middle temporal gyrus, consistent with a deterioration in cognitive function. In the present study, although statistically significant only in the right anterior cingulate gyrus, increased CBF induced by cilostazol was observed in many brain regions, including the inferior frontal gyrus, left middle frontal gyrus, left medial frontal gyrus, angular gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, thalamus, anterior cingulate gyrus and left posterior cingulate gyrus.

Cilostazol is an antiplatelet drug and cyclic adenosine monophosphate phosphodiesterase 3 inhibitor. Previous studies have shown that cilostazol has pleiotropic effects, including increased CBF, protection of the endothelia and the upregulated phosphorylation of CREB.[11]

Furthermore, some investigators have suggested an underlying mechanism by which cilostazol protects against cognitive decline.[25–29] A possible mechanism for this is increased CBF and the subsequent prevention of demyelination or microinfarction of the cerebral white matter, not as yet depicted by neuroimaging studies, which might be associated with the progression of AD.[26,30]

A previous study has shown that cilostazol is effective in improving CBF and P300 latency in patients with chronic-stage cerebral infarction.[25] The current results show that another possible mechanism is the direct action of cilostazol on AD pathology. In a rat model, cognitive impairment with chronic cerebral hypoperfusion was effectively improved through the upregulated phosphorylation of CREB.[26] The concurrent administration of cilostazol with donepezil effectively improved cognitive dysfunction with increased neuroprotection by the activation of phosphorylated CREB after cerebral hypoperfusion in rats.[27] In contrast, the downregulation of the CREB function has been found in AD brains.[28] Furthermore, an amyloid-beta (Aβ) peptide was reported to suppress CREB phosphorylation in cultured cortical and hippocampal neurons,[29] and it is known that oxidase stress is associated with impairment of cognitive function in AD.[31] Cilostazol ameliorates the memory deficits induced by the Aβ peptide in mice, and

Table 3 Mean z-scores of the single-photon emission computed tomography study for cerebral subregions at baseline and after 6 months for each group

Cerebral subregions	Cilostazol group (n = 10)				Control group (n = 7)			
	Left hemisphere		Right hemisphere		Left hemisphere		Right hemisphere	
	Baseline SPECT	SPECT after 6 months	Baseline SPECT	SPECT after 6 months	Baseline SPECT	SPECT after 6 months	Baseline SPECT	SPECT after 6 months
Frontal lobe								
Superior frontal gyrus	0.85 ± 0.50	0.88 ± 0.50	0.84 ± 0.46	0.85 ± 0.35	0.67 ± 0.33	0.81 ± 0.37	0.75 ± 0.21	0.73 ± 0.21
Middle frontal gyrus	1.17 ± 0.50	1.00 ± 0.43	1.00 ± 0.54	1.03 ± 0.55	0.83 ± 0.28	0.89 ± 0.56	0.98 ± 0.36	1.01 ± 0.48
Inferior frontal gyrus	1.31 ± 0.75	1.08 ± 0.44	1.07 ± 0.58	0.89 ± 0.51	0.84 ± 0.74	0.92 ± 0.47	0.69 ± 0.43	0.67 ± 0.23
Medial frontal gyrus	1.06 ± 0.38	0.96 ± 0.45	1.00 ± 0.44	1.03 ± 0.36	0.82 ± 0.42	1.16 ± 0.60	0.81 ± 0.39	0.95 ± 0.31
Orbital gyrus	1.21 ± 0.94	0.90 ± 0.75	0.77 ± 0.69	1.01 ± 1.11	0.84 ± 0.69	1.69 ± 1.25	0.75 ± 0.67	1.49 ± 0.99
Rectal gyrus	1.17 ± 0.90	1.24 ± 1.00	1.23 ± 0.37	1.08 ± 0.52	0.80 ± 0.56	1.14 ± 0.79	0.69 ± 0.70	0.97 ± 0.58
Paracentral lobule	0.72 ± 0.31	0.56 ± 0.50	0.56 ± 0.33	0.47 ± 0.34	0.32 ± 0.23	0.25 ± 0.27	0.41 ± 0.36	0.33 ± 0.29
Precentral gyrus	0.84 ± 0.71	0.73 ± 0.40	0.86 ± 0.82	0.87 ± 0.61	0.73 ± 0.32	0.87 ± 0.29	0.84 ± 0.41	0.82 ± 0.41
Subcallosal gyrus	0.77 ± 0.52	0.99 ± 1.15	0.78 ± 0.41	0.93 ± 0.45	0.70 ± 0.82	0.99 ± 0.57	0.61 ± 0.49	0.61 ± 0.51
Parietal lobe								
Superior parietal lobule	1.01 ± 1.08	1.03 ± 0.96	0.84 ± 0.39	0.65 ± 0.28	1.29 ± 0.50	1.85 ± 1.12	0.83 ± 0.47	1.01 ± 0.56
Inferior parietal lobule	1.43 ± 1.15	1.41 ± 1.23	1.21 ± 0.60	1.35 ± 0.49	1.11 ± 0.78	1.41 ± 0.71	1.32 ± 1.02	1.58 ± 0.99
Angular gyrus	1.32 ± 1.00	1.20 ± 1.11	1.19 ± 0.85	0.96 ± 0.76	0.82 ± 0.49	0.86 ± 0.49	0.82 ± 0.75	1.28 ± 1.10
Postcentral gyrus	0.86 ± 0.58	0.92 ± 0.59	0.75 ± 0.49	0.98 ± 0.71*	0.60 ± 0.22	0.86 ± 0.49	0.91 ± 0.43	0.66 ± 0.40#
Precuneus	0.92 ± 0.55	0.93 ± 0.74	0.69 ± 0.44	0.64 ± 0.46	1.15 ± 1.01	1.51 ± 1.07	0.60 ± 0.57	0.78 ± 0.50
Supramarginal gyrus	1.32 ± 1.08	1.33 ± 1.25	1.17 ± 0.98	1.05 ± 0.60	1.15 ± 0.36	1.10 ± 0.49	0.73 ± 0.73	1.08 ± 1.02
Temporal lobe								
Superior temporal gyrus	1.22 ± 0.67	1.08 ± 0.56	1.20 ± 0.58	0.99 ± 0.52	1.03 ± 0.41	1.16 ± 0.55	0.96 ± 0.27	0.93 ± 0.45
Middle temporal gyrus	1.33 ± 0.91	1.08 ± 0.79	1.22 ± 0.70	0.96 ± 0.72	1.05 ± 0.70	1.37 ± 0.69*	1.03 ± 0.40	0.97 ± 0.40
Inferior temporal gyrus	1.58 ± 0.90	1.36 ± 0.89	1.36 ± 1.05	1.15 ± 1.03	0.16 ± 0.21	0.27 ± 0.21	1.10 ± 0.57	1.10 ± 0.63
Transverse temporal gyrus	0.65 ± 0.83	0.66 ± 0.68	0.34 ± 0.47	0.50 ± 0.89	0.67 ± 0.62	0.66 ± 0.57	0.15 ± 0.38	0.24 ± 0.54
Occipital lobe								
Superior occipital gyrus	0.99 ± 1.60	0.79 ± 1.23	1.07 ± 1.24	0.73 ± 0.56	0.87 ± 0.44	0.69 ± 0.43	0.98 ± 1.45	0.89 ± 0.76
Middle occipital gyrus	1.38 ± 1.83	1.36 ± 1.43	1.03 ± 1.03	0.82 ± 1.07	0.67 ± 0.62	0.52 ± 0.58	1.03 ± 0.48	0.76 ± 0.62
Inferior occipital gyrus	0.89 ± 1.48	0.91 ± 1.57	0.86 ± 1.12	0.59 ± 0.73	0.52 ± 0.15	0.34 ± 0.32	0.83 ± 0.59	0.80 ± 1.30
Cuneus	0.75 ± 1.02	0.85 ± 0.84	0.40 ± 0.62	0.58 ± 0.60	1.44 ± 0.46	1.51 ± 0.64	0.70 ± 0.29	0.53 ± 0.39
Fusiform gyrus	1.44 ± 1.01	1.71 ± 1.22	1.11 ± 0.94	1.17 ± 0.85	0.67 ± 0.70	0.34 ± 0.39	1.18 ± 0.50	1.00 ± 0.70
Lingual gyrus	0.52 ± 0.77	0.87 ± 1.01	0.25 ± 0.31	0.44 ± 0.67	0.51 ± 0.23	0.55 ± 0.54	0.57 ± 0.45	0.64 ± 0.69
Limbic lobe								
Thalamus	1.02 ± 0.92	0.71 ± 0.75	0.67 ± 0.54	0.47 ± 0.27	0.92 ± 0.45	1.27 ± 0.41	0.44 ± 0.38	0.70 ± 0.39
Cingulate gyrus	1.23 ± 0.56	1.12 ± 0.50	1.09 ± 0.51	1.09 ± 0.42	1.36 ± 0.71	1.46 ± 0.68	0.94 ± 0.46	1.14 ± 0.34
Parahippocampal gyrus	1.27 ± 0.94	1.31 ± 0.90	1.10 ± 0.81	0.94 ± 0.56	1.18 ± 0.64	1.31 ± 0.57	1.37 ± 0.70	1.01 ± 0.65
Anterior cingulate	1.35 ± 0.66	1.21 ± 0.59	1.28 ± 0.56	1.11 ± 0.42#	1.08 ± 0.42	1.08 ± 0.49	1.01 ± 0.48	1.12 ± 0.48
Posterior cingulate	1.10 ± 0.56	0.88 ± 0.56	0.78 ± 0.43	0.80 ± 0.45	1.41 ± 0.65	1.57 ± 0.83	0.93 ± 0.80	1.16 ± 0.49
Uncus	1.48 ± 0.93	1.27 ± 1.12	1.15 ± 1.18	1.06 ± 0.92	1.41 ± 0.65	1.57 ± 0.83	1.10 ± 0.50	1.04 ± 0.61

Data are expressed as means ± SD.

*$P < 0.05$ increased z-values by analysis of covariance for effects of treatment, with baseline values as the covariate. #$P < 0.05$ decreased z-values by analysis of covariance for effects of treatment, with baseline values as the covariate. SPECT, single-photon emission computed tomography.

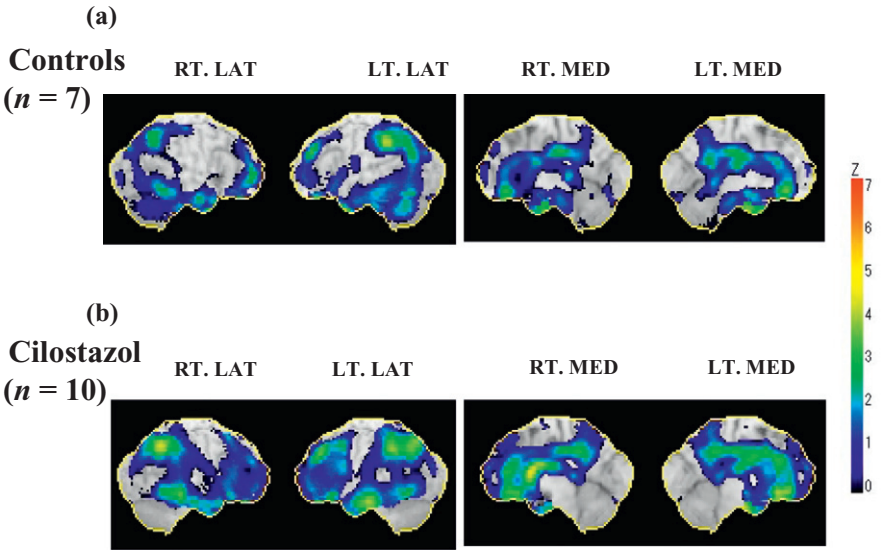

Figure 1 Three-dimensional views of decreased regional cerebral blood flow (rCBF) in the (a) control and (b) cilostazol groups compared with normal controls at baseline. Both groups showed a marked decrease in rCBF in the parietotemporal, posterior cingulate and frontal lobes. LT.LAT, left lateral; LT.MED, left medial; RT.LAT, right lateral; RT.MED, right medial.

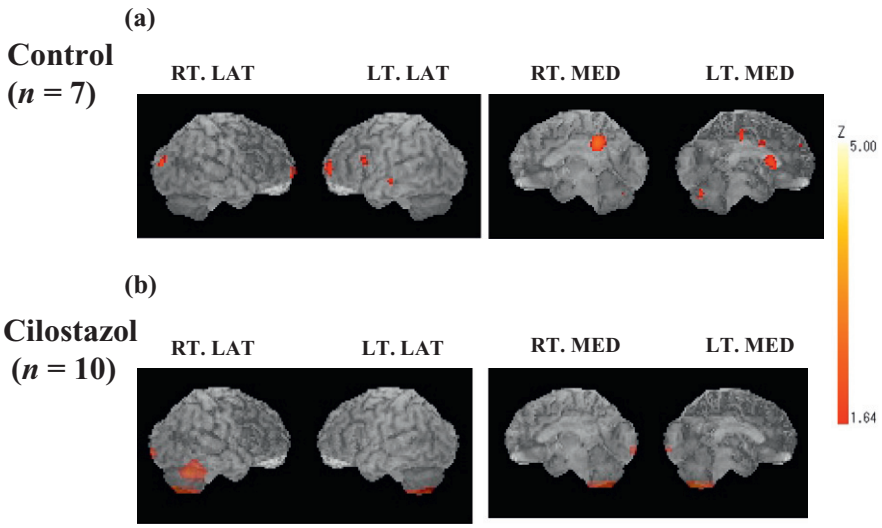

Figure 2 Statistical maps showing relative changes in regional cerebral blood flow (rCBF) on repeated single-photon emission computed tomography studies in the (a) control and (b) cilostazol groups. The cilostazol group showed a significant decrease in rCBF only in the right postcentral gyrus, whereas the control group showed a decrease in rCBF in the left middle temporal gyrus. The red scale shows a relative rCBF decrease. The color of the outer contour corresponds to a z-score of 1.64–5.00. LT.LAT, left lateral; LT.MED, left medial; RT.LAT, right lateral; RT.MED, right medial.

this might be attributable to the prevention of oxidative damage in the hippocampus, as measured in terms of the amount of peroxidized lipid.[32] These reports suggest a possible direct action of cilostazol on AD pathology by the activation of phosphorylated CREB, which is associated with increased CBF.

The present study had some limitations. First, the number of participants was small. Second, it remains uncertain whether a 6-month study period is sufficient for assessing the clinical efficacy of treatment in patients with AD and CVD. Nevertheless, we were able to assess rCBF changes and confirm the statistically significant efficacy of cilostazol. Although rCBF deficits in the cilostazol group at baseline were more marked than those in the control group, it must be considered that differences in rCBF at baseline can affect the results of cognitive decline. However, the cilostazol group did not show significant decreases in cognitive function test scores after 6 months of treatment, whereas the control group showed worse scores on the ADAS-cog, TMT-A and WMS-R logical memory-I tests.

Third, although the diagnosis of AD in the present study was not confirmed neuropathologically, brain MRI and SPECT were used as part of the diagnostic process. A reduction in rCBF in the parietotemporal association cortex on SPECT is recognized as a diagnostic pattern for AD, and SPECT studies provide a higher specificity for other types of dementia than clinical criteria alone.[33] All the patients in the present study showed characteristic features of rCBF patterns of AD on the baseline SPECT images.

In conclusion, cilostazol might be an additional treatment option for elderly patients with AD. The present findings showed that cilostazol has beneficial effects on

cognitive and rCBF deficits in elderly patients with AD and CVD. Although most AD patients are currently treated with a cholinesterase inhibitor or N-methyl-D-aspartic acid receptor antagonist, the present findings suggest another strategy for the prevention of AD progression. Further large-scale, double-blind, long-term studies will be required to confirm the clinical efficacy of cilostazol treatment on cognition and rCBF in patients with AD and CVD.

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Disclosure statement

All authors report that they have no conflicts of interest associated with this manuscript.

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