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Cilostazol use is associated with FIM cognitive improvement during convalescent rehabilitation in patients with ischemic stroke: a retrospective study

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ABSTRACT

Cilostazol is a phosphodiesterase III-inhibiting antiplatelet agent that is often used to prevent stroke and peripheral artery disease, and its administration has shown significant improvements for cognitive impairment. We investigate the potential of cilostazol for reducing or restoring cognitive decline during convalescent rehabilitation in patients with non-cardioembolic ischemic stroke. The study sample included 371 consecutive patients with lacunar (n = 44) and atherothrombosis (n = 327) subtypes of non-cardioembolic ischemic stroke (224 men and 147 women; mean age, 72.9 ± 8.1 years) who were required for inpatient convalescent rehabilitation. Their medical records were retrospectively surveyed to identify those who had received cilostazol (n = 101). Patients were grouped based on cilostazol condition, and Functional Independence Measure (FIM) scores (total and motor or cognitive subtest scores) were assessed both at admission and discharge. The gain and efficiency in FIM cognitive scores from admission to discharge were significantly higher in patients who received cilostazol than those who did not ($p = 0.047$ and $p = 0.035$, respectively); we found no significant differences in other clinical factors or scores. Multiple linear regression analysis confirmed that cilostazol was a significant factor in FIM cognitive scores at discharge ($\beta = 0.041$, $B = 0.682$, $p = 0.045$); the two tested dosages were not significantly different (100 mg/day, n = 43; 200 mg/day, n = 58). Cilostazol can potentially improve cognitive function during convalescent rehabilitation of patients with non-cardioembolic ischemic stroke, although another research must be needed to confirm this potential.

Keywords: Cilostazol, ischemic stroke, FIM cognitive, convalescent rehabilitation

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INTRODUCTION

Antiplatelet drugs have been shown to protect patients with occlusive non-cardiogenic ischemic stroke and transient ischemic attacks from further episodes.[1,2] The antiplatelet therapy for ischemic stroke prevention includes aspirin, clopidogrel, prasugrel and dipyridamole (prasugrel and dipyridamole are not approved for use in patients with ischemic stroke in Japan) alone or in combination.[3,4] Cilostazol is an antiplatelet agent approved worldwide for the treatment of intermittent claudication with peripheral artery disease, and for the prevention of non-cardiogenic ischemic stroke in some Asian countries including Japan[5-7]; it is also recommended for use in the Japanese stroke treatment guidelines.[8] Cilostazol acts as a direct and indirect antiplatelet agent by inhibiting platelet activation in response to various stimuli, and by improving overall vascular endothelial function.[6,9] In addition to an antiplatelet effect[10] due to the cyclic guanosine monophosphate (cGMP)-mediated inhibition of phosphodiesterase activity, cilostazol is also reported to have pleiotropic and vasodilatory effects.11 Interestingly, cilostazol has been shown to decrease β-amyloid (Aβ) accumulation and protect patients from Aβ-induced cognitive deficits.[12,13]

In Japan, patients with acute ischemic stroke who cannot be discharged from an acute care hospital to a preclinical circumstance need convalescent rehabilitation of the impairments both in cognitive and motor function. Convalescent rehabilitation units for post-acute stroke ("Kaifukuki" in the Japanese language) were introduced by the Japanese National Insurance System in 2000, and transfers to this type of unit are compulsory for continuous in-hospital rehabilitation.[14] However, the relationship between the outcomes of convalescent rehabilitation with ischemic stroke and the use of antiplatelet drugs remains unclear.

Previous studies have shown that the administration of cilostazol in patients with cognitive impairment results in significantly reduced cognitive decline.[15-18] In this study, we retrospectively investigated the effects of cilostazol on convalescent rehabilitation outcomes in patients with non-cardioembolic ischemic stroke.

PATIENTS AND METHODS

The methodology in this study was generally described in our previous study,[19] which was added with the increased number of patients and the objective of cilostazol effectiveness for ischemic stroke rehabilitation.

Patients

The patients with ischemic stroke were enrolled who had been hospitalized for convalescent rehabilitation at the Kami-iida rehabilitation hospital between January 2008 and December 2014 consecutively. A total of 371 patients (224 men, 147 women; mean age, 72.9 ± 8.1 years) who fulfilled the following inclusion criteria: (1) no premature discharge due to changes in their condition or other reasons; (2) complete independence in the activities of daily living (ADL) (at a level such that the patient is capable of living alone) before the present ischemic stroke, on the basis of scores on both the modified Rankin Scale (score of 0)[20] and the Barthel Index (score of 100)[21]; (3) no diagnosis of dementia, including Alzheimer's disease or mild cognitive impairment, prior to the present ischemic stroke; (4) right-hand dominant; and (5) diagnosed with ischemic stroke on the basis of intracranial magnetic resonance imaging/angiography (MRI/MRA). The average length from the onset of the ischemic stroke to the transfer to our hospital, as the period at the 29 acute care hospitals, was 31.4 ± 10.4 days. The average daily rehabilitation time at our convalescent hospital was 110.0 ± 10.1 min/day. The total Functional Independence

Measure (FIM) score (including FIM motor and FIM cognitive subtest scores)[22] was assessed in all patients both at admission and discharge. The efficiency values[23] for total, motor, and cognitive FIM scores were also calculated. The prescription for the choice of antiplatelet drugs and their doses with aspirin, clopidogrel, and cilostazol were decided by the physicians in the 29 acute care hospitals, and were not changed during our hospital.

The ethics committee from the Kami-iida Rehabilitation Hospital approved this study, which was performed in accordance with the Declaration of Helsinki.

Ischemic stroke subtype evaluation

We used the National Institute of Neurological Disorders and Stroke (NINDS)-III classification system[24] to classify to strokes into lacunar infarction (LI), atherothrombosis (AT), and cardiogenic embolism (CE) subtypes. Such classification was performed in order to include only cases with clearly evident causes, defined as follows: (1) LI: Ischemic stroke of the deep brain, basal ganglia, or brain stem, ≤15 mm on MRI[25]; (2) AT: Ischemic stroke based on a cortical atherosclerotic lesion or caused by an atherosclerotic lesion extending into multiple perforating branches (>15 mm), including artery-to-artery embolism (A-to-A) (n = 80) in which an atherosclerotic lesion in the proximal artery is confirmed to be the source of embolism on a carotid artery echogram or intracranial MRA[26]; and (3) CE: Cerebral embolism resulting from a thrombus in the heart due to atrial fibrillation or other heart diseases. Furthermore, cases of embolism in which A-to-A and CE could not be distinguished, or in which the source of embolism was unknown, were classified as undetermined embolism (UN).[27] Ischemic stroke due to specific mechanisms such as vasculitis or postoperative ischemia was classified as "other."[28] We excluded the CE, UN, and other stroke groups from the study.

The disease subtype was diagnosed with blood tests, carotid artery and cardiac echograms, electrocardiograms, intracranial MRI/MRA findings, and any other relevant data. The use of medication to treat hypertension, diabetes mellitus, and hyperlipidemia was also analyzed.

MRI/MRA assessments

All patients in this study were checked with intracranial MRI/MRA findings. White matter lesions were classified on admission by the Fazekas criteria for periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) on T2-weighted or fluid-attenuated inversion recovery MR images (Figure 1). PVH was graded from 0 to 3 as follows: Grade 0, none or rim only; grade 1, localized lesion depicted in pencil-thin lining or caps; grade 2, irregular hyperintensity, a smooth halo; and grade 3, lesion spreading into the deep white matter and periventricular region.[27] The DWMH was also graded from 0 to 3 as follows: Grade 0, none; grade 1, punctate hyperintensity; grade 2, punctate hyperintensity with fusion tendency; and grade 3, large fused punctate hyperintensity.[29] For the MRA, the presence of ≥50% stenosis or occlusion in the intracranial trunk arteries in the visible range was considered "stenosis positive."[27]

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD). The chi-square test was used to analyze multigroup qualitative variables, while the Mann-Whitney U test was used to analyze quantitative variables. Results with p values less than 0.05 were considered statistically significant. Stepwise multiple regression analysis was performed to characterize the relationships between (A) the total FIM score at admission and discharge, (B) the FIM motor score at admission and discharge, and (C) the FIM cognitive score at admission and discharge. The dependent variables used included the total FIM score, FIM cognitive score, and FIM motor score at discharge. The independent variables used included the (a) total FIM score, FIM

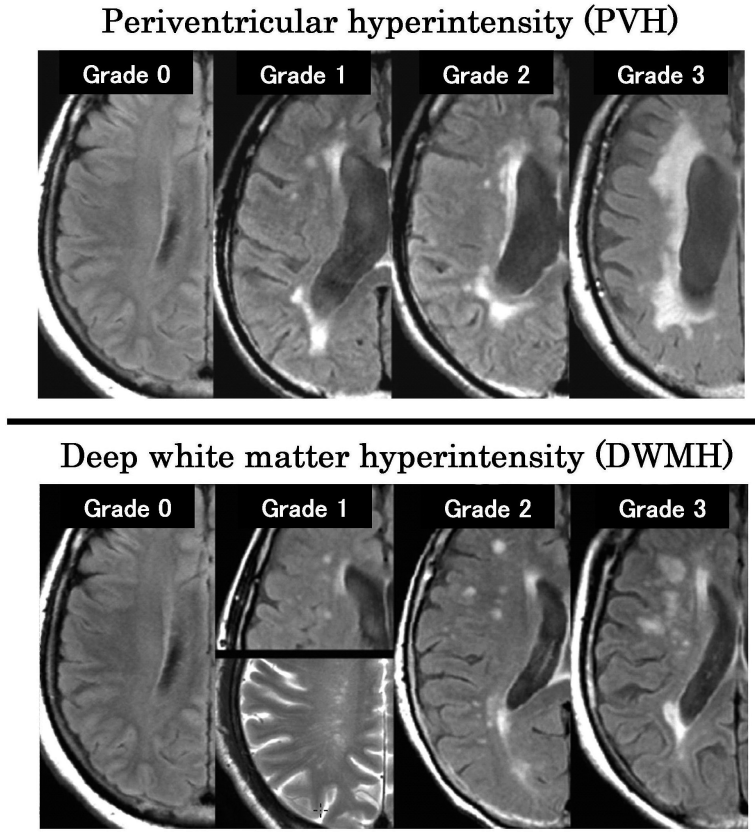

Fig. 1 PVH and DWMH grading of magnetic resonance images
PVH and DWMH grading was performed according to the Fazekas scale using axial T2-weighted or fluid-attenuated inversion recovery images.
PVH: paraventricular hyperintensity, DWMH: deep white matter hyperintensity.

cognitive score, and FIM motor score at admission; use of various medications including those for (b) hypertension, (c) diabetes mellitus, and (d) hyperlipidemia; (e) age; (f) sex; (g) history of stroke; (h) history of heart disease; (i) history of tobacco use; (j) lateralization of the ischemic stroke lesion (right or left side); (k) whether the lesion was unilateral or bilateral; (l) PVH grade; (m) DWMH grade; and (n) presence of stenosis ≥50% or occlusion on MRA; and (o) average daily rehabilitation time. History of stroke did not include the current ischemic stroke. This history was decided by the interviews from each patient or his/her family, and was not diagnosed based on information from previous attending doctors. However, we established strict criteria that all patients with a positive history of stroke had complete independence in ADL before the current ischemic stroke. Additional independent variables for all subjects included the use of the following antiplatelet drugs: (p) aspirin (100 mg/day; enteric-coated tablet), (q) clopidogrel (75 mg/day), and (r) cilostazol (100 mg/day, n = 43; 200 mg/day, n = 58) (Figure 2A).[8] Thus, for the cilostazol-treated group (n=101), we used (s) the two dosages of cilostazol (100 mg/day or 200 mg/day) as the independent variables in place of cilostazol usage (variable r above) in additional multiple regression analyses (Figure 2B). The usage and dosages of these antiplatelet drugs were determined by the attending doctor at the acute stage, and not changed

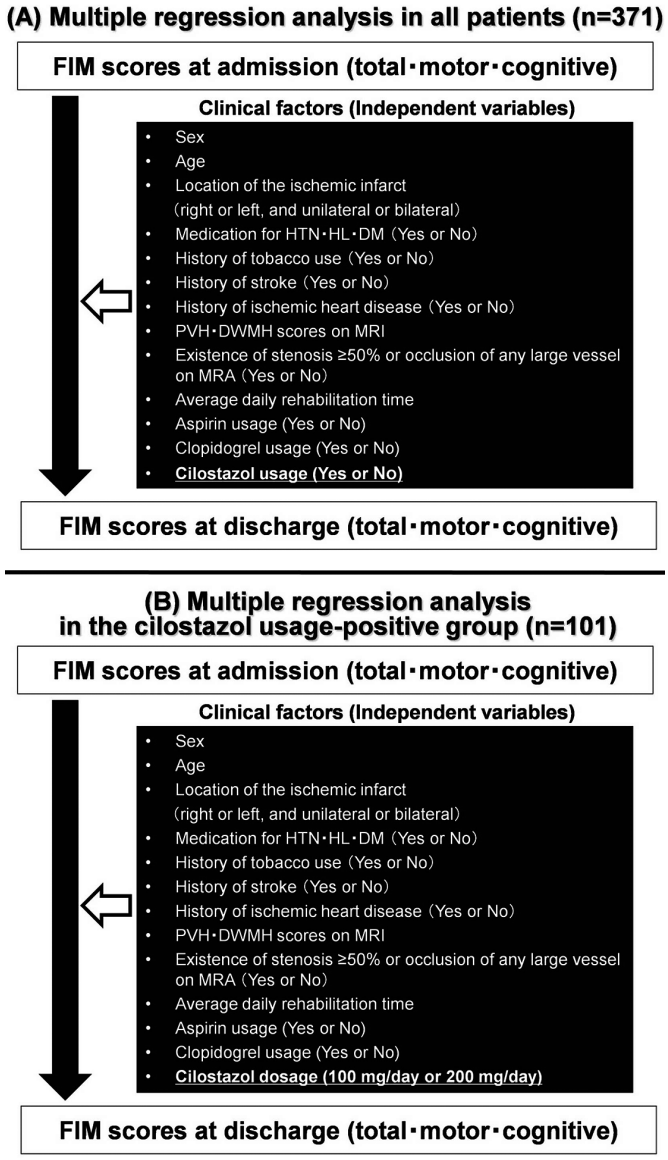

Fig. 2 Stepwise multiple regression analysis

Fig. 2A: Use of antiplatelet drugs. The stepwise multiple regression models included independent variables such as the usage of antiplatelet drugs, namely aspirin, clopidogrel, and cilostazol.

Fig. 2B: Dosage of cilostazol. The stepwise multiple regression models included independent variables such as the usage of antiplatelet drugs, namely aspirin, clopidogrel, and cilostazol (the use of cilostazol was subdivided on the basis of the dosage used: low (100 mg/day) or high (200 mg/day)).

FIM, functional independence measure; HTN, hypertension; HL, hyperlipidemia; DM, diabetes mellitus; PVH, paraventricular hyperintensity; DWMH, deep white matter hyperintensity; MRA, magnetic resonance angiography.

during the course of convalescent rehabilitation.

Multiple linear regression analysis using a stepwise approach was used to develop direct prediction formulae of functional recovery as a rehabilitation outcome using patient variables,

although this technique may have led to an increase in the number of Type I errors. The statistical analyses were performed with SPSS Statistics software (version 20.0J, SPSS IBM Japan Inc., Tokyo, Japan).

RESULTS

The demographic characteristics of the study participants are summarized in Table 1. The average FIM cognitive score gain from admission to discharge in the cilostazol-treated group was significantly higher than that in the cilostazol-untreated group (1.83 ± 2.27 and 1.06 ± 2.00, respectively; $p = 0.047$), and the average FIM cognitive efficiency in the cilostazol-treated group was also significantly higher than that in the cilostazol-untreated group (0.026 ± 0.031 and 0.015 ± 0.029, respectively; $p = 0.035$), although there were no significant differences in the three FIM scores between groups at admission or at discharge. Just over half of the cilostazol-untreated patient group was taking clopidogrel or aspirin, and these rates were significantly higher than those of cilostazol-treated patient group ($p < 0.0001$ and $p = 0.023$, respectively). The percentage of patients with a previous history of heart disease in the cilostazol-untreated group was significantly higher than that in the cilostazol-treated group ($p = 0.022$). We found no significant differences in the other characteristics or clinical data between the two groups. Table 2 describes the characteristics of patients in the low-dose cilostazol (100 mg/day) and high-dose cilostazol (200 mg/day) groups; the latter group had significantly higher rates of dual antiplatelet therapy ($p = 0.0013$) and aspirin usage ($p = 0.0064$) compared to the former. We found no statically significant differences in the other characteristics, clinical data, or outcomes between the two groups.

Next, we examined how their rehabilitation outcomes at discharge were affected by the clinical factors. Various assessments carried out, including prescribed medications for diabetes mellitus, hypertension, and hyperlipidemia; age; sex; focus site (right or left side, unilateral or bilateral); histories of tobacco use, stroke, and heart disease; PVH and DWMH grades; presence of ≥50% stenosis or occlusion on MRA; average daily rehabilitation time; and prescribed medication for aspirin, clopidogrel, and cilostazol, were used as independent variables. Stepwise multiple regression analysis revealed the relationships between these factors and all ischemic stroke subtypes combined, in addition to the relationships between these factors and each disease subtype separately. In terms of the total FIM score at discharge as a measure of the rehabilitation outcome, increases in the PVH grade and total FIM score at admission were significantly associated with the worsening of the rehabilitation outcome in all 371 patients. In terms of each disease subtype separately, previous history of stroke was significantly associated with the worsening of the rehabilitation outcome in the AT group. In terms of the FIM motor scores at admission and discharge, increases in the PVH grade were significantly associated with the decline of the rehabilitation outcomes in the total patient group, as well as in the AT group alone. In terms of the FIM-cognition scores at admission and discharge, the age and use of hypertension medication were significantly associated with the worsening of the rehabilitation outcome; however, cilostazol use was significantly associated with cognitive improvements in the outcomes in all the patients. When each disease subtype was considered separately, age was significantly associated with the worsening of the rehabilitation outcome in the AT group (Table 3).

Table 1 Patient characteristics according to cilostazol usage

	All	Cilostazol usage		*p* value
		Positive	Negative	
Number	371	101	270	–
Sex: Male/Female	224 / 147	66 / 35	158 / 112	0.23
Age (years)	72.9 ± 8.1	73.1 ± 7.9	72.8 ± 8.2	0.86
Lacunar Infarction	11.9%	12.9%	11.5%	0.71
Atherothrombosis	88.1%	87.1%	88.5%	0.71
Hospital stay (days)	79.7 ± 26.7	79.9 ± 28.4	79.6 ± 26.1	0.92
Average daily rehabilitation time (minute)	110.0 ± 10.1	109.5 ± 11.8	110.2 ± 9.5	0.62
Hypertension	63.9%	66.3%	67.4%	0.85
Diabetes mellitus	28.8%	36.6%	33.0%	0.51
Hyperlipidemia	36.1%	42.6%	40.7%	0.75
Right-lateralized	44.2%	43.6%	44.4%	0.88
Left-lateralized	49.9%	48.5%	50.4%	0.75
Bilateral	5.9%	7.9%	5.2%	0.33
History of tobacco use	38.7%	42.5%	36.2%	0.27
History of stroke	23.7%	26.7%	20.7%	0.22
History of heart disease	8.4%	3.0%	10.4%	0.022†
MRI-PVH	1.34 ± 0.79	1.56 ± 0.95	1.40 ± 0.76	0.14
MRI-DWMH	1.43 ± 0.77	1.63 ± 0.86	1.49 ± 0.70	0.15
MRA stenosis ≥50% or occlusion (+)	41.2%	38.6%	42.2%	0.76
Cilostazol usage (+)	27.5%	100%	0%	< 0.0001†
Aspirin usage (+)	51.2%	41.6%	54.8%	0.023†
Clopidogrel usage (+)	40.7%	18.9%	56.7%	< 0.0001†
Total FIM score at admission	78.61 ± 20.92	76.78 ± 22.78	79.29 ± 20.26	0.70
Total FIM score at discharge	95.89 ± 20.31	93.68 ± 21.57	96.71 ± 19.82	0.49
Total FIM score gain	17.28 ± 9.31	16.90 ± 8.97	17.42 ± 9.42	0.40
Total FIM score efficiency	0.17 ± 0.11	0.17 ± 0.12	0.17 ± 0.11	0.83
Total FIM score effectiveness	0.32 ± 0.18	0.31 ± 0.17	0.32 ± 0.19	0.63
FIM motor score at admission	52.98 ± 16.46	51.84 ± 17.80	53.41 ± 15.95	0.49
FIM motor score at discharge	68.99 ± 15.59	66.91 ± 16.63	69.77 ± 15.21	0.22
FIM motor score gain	16.01 ± 8.54	15.07 ± 8.42	16.36 ± 8.54	0.30
FIM motor score efficiency	0.23 ± 0.12	0.21 ± 0.17	0.23 ± 0.12	0.42
FIM cognitive score at admission	26.63 ± 6.39	24.94 ± 6.55	25.88 ± 6.32	0.32
FIM cognitive score at discharge	26.89 ± 5.94	26.77 ± 6.04	26.94 ± 5.90	0.84
FIM cognitive score gain	1.27 ± 2.09	1.83 ± 2.27	1.06 ± 2.00	0.047††
FIM cognitive score efficiency	0.018 ± 0.029	0.026 ± 0.031	0.015 ± 0.029	0.035††

Data shown as mean ± standard deviation (SD) or as the percentage of cases in the group. LI: lacunar infarction; AT: atherothrombosis; Right, Left, Bilateral: infarction on the right, left, or both sides, respectively; PVH: periventricular hyperintensity; DWMH: deep white matter hyperintensity; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; FIM: Functional Independence Measure; NS: not significant; †Chi-square test, ††Mann-Whitney U test.

Table 2 Characteristics of patients taking cilostazol by doasge

Cilostazol dosage	100 mg/day	200 mg/day	*p* value
Number	43	58	–
Sex: Male/Female	24 / 19	42 / 16	0.083
Age (years)	73.7 ± 7.8	72.8 ± 8.1	0.62
Lacunar Infarction	11.6%	13.8%	0.75
Atherothrombosis	88.4%	86.2%	0.48
Hospital stay (days)	79.5 ± 24.9	80.2 ± 31.1	0.92
Average daily rehabilitation time (minute)	108.2 ± 11.1	110.4 ± 12.3	0.49
Hypertension	62.8%	69.0%	0.52
Diabetes mellitus	32.6%	39.7%	0.46
Hyperlipidemia	32.6%	50.0%	0.08
Right-lateralized	41.9%	44.8%	0.77
Left-lateralized	46.5%	50.0%	0.73
Bilateral	11.6%	5.2%	0.24
History of tobacco use	34.9%	48.3%	0.18
History of stroke	27.9%	25.9%	0.82
History of heart disease	4.7%	1.7%	0.39
MRI-PVH	1.51 ± 0.94	1.60 ± 0.94	0.67
MRI-DWMH	1.65 ± 0.85	1.62 ± 0.87	0.88
MRA stenosis ≥50% or occlusion (+)	48.8%	31.0%	0.069
Cilostazol single administration	25.6%	50.0%	0.0013†
Aspirin usage (+)	55.8%	31.0%	0.0064†
Clopidogrel usage (+)	14.0%	20.7%	0.58
Total FIM score at admission	71.58 ± 23.34	80.64 ± 19.67	0.24
Total FIM score at discharge	88.67 ± 23.01	97.40 ± 19.44	0.15
Total FIM score gain	17.09 ± 8.68	16.75 ± 8.32	0.79
Total FIM score efficiency	0.16 ± 0.10	0.19 ± 0.14	0.41
FIM motor score at admission	47.84 ± 18.17	54.81 ± 16.98	0.10
FIM motor score at discharge	63.35 ± 17.17	69.55 ± 15.99	0.15
FIM motor score gain	15.51 ± 8.43	14.74 ± 8.41	0.75
FIM motor score efficiency	0.22 ± 0.13	0.21 ± 0.11	0.76
FIM cognitive score at admission	23.74 ± 7.66	25.83 ± 5.69	0.19
FIM cognitive score at discharge	25.33 ± 6.89	27.84 ± 5.16	0.10
FIM cognitive score gain	1.58 ± 2.35	2.02 ± 2.20	0.50
FIM cognitive score efficiency	0.023 ± 0.031	0.029 ± 0.031	0.56

Data shown as mean ± standard deviation (SD) or as the percentage of cases in the group. Right, Left, Bilateral: infarction on the right, left, or both sides, respectively; PVH: periventricular hyperintensity; DWMH: deep white matter hyperintensity; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; FIM: Functional Independence Measure; NS: not significant; †Chi-square test, ††Mann-Whitney U test

Table 3 Multiple linear regression analysis of rehabilitation outcomes (FIM score at discharge) and clinical factors related to cilostazol usage

(A) Total FIM score

Disease type	Clinical Factors	β	B	*p* value	R^2
All (n = 371)	Total FIM score at admission	+ 0.914	+ 0.863	< 0.001	0.869
	PVH score	– 0.065	– 1.674	0.001	
LI (n = 41)	Total FIM score at admission	+ 0.929	+ 0.882	< 0.001	0.860
AT (n = 327)	Total FIM score at admission	+ 0.908	+ 0.857	< 0.001	0.872
	PVH score	– 0.067	– 1.173	0.002	
	History of stroke - positive	– 0.042	– 2.298	0.040	

(B) FIM motor score

Disease type	Clinical Factors	β	B	*p* value	R^2
All (n = 371)	FIM motor score at admission	+ 0.837	+ 0.817	< 0.001	0.691
	PVH score	– 0.078	– 1.662	0.008	
LI (n = 41)	FIM motor score at admission	+ 0.903	+ 0.901	< 0.001	0.816
AT (n = 327)	FIM motor score at admission	+ 0.804	+ 0.832	< 0.001	0.677
	PVH score	– 0.078	– 1.692	0.017	

(C) FIM cognitive score

Disease type	Clinical Factors	β	B	*p* value	R^2
All (n = 371)	FIM cognitive score at admission	+ 0.902	+ 0.844	< 0.001	0.844
	Age	– 0.071	– 0.005	0.001	
	Hypertension positive	– 0.059	– 0.622	0.005	
	Cilostazol usage: positive	+ 0.041	+ 0.682	0.045	
LI (n = 41)	FIM cognitive score at admission	+ 0.948	+ 0.935	< 0.001	0.892
AT (n = 327)	FIM cognitive score at admission	+ 0.894	+ 0.832	< 0.001	0.839
	Age	– 0.075	– 0.052	0.002	

AT: atherothrombosis, DWMH: deep white matter hyperintensity, FIM: Functional Independence Measure, LI: lacunar infarction, MRA: magnetic resonance angiography, PVH: periventricular hyperintensity, β: standardized regression coefficient, B: unstandardized coefficient, R^2: coefficient of determination.

Finally, a further stepwise multiple regression analysis was performed by changing the usage of cilostazol (positive or negative) to the dosage of cilostazol (low, 100 mg/day; or high, 200 mg/day) in the cilostazol-treated group (n = 101). The differences in cilostazol dosage had no significant effect on the three FIM scores as indicators of the rehabilitation outcome (Table 4).

In addition, we found a mild but significant correlation between age and PVH grade (r = 0.371, $p < 0.001$), and between age and DWMH grade (r = 0.351, $p < 0.001$), from the viewpoint of multicollinearity, consistent with our previous study.[19] However, in each stepwise multiple regression model, the variance inflation factor values of the PVH or DWMH were relatively low (< 1.1 in each analysis); thus, we used each independent variable factor as the PVH and

Table 4 Multiple linear regression analysis of rehabilitation outcomes (FIM score at discharge) and clinical factors related to cilostazol dosage

(A) Total FIM score

Disease type	Clinical Factors	β	B	*p* value	R^2
All (n = 101)	Total FIM score at admission	+ 0.948	+ 0.893	< 0.001	0.898
LI (n = 13)	Total FIM score at admission	+ 0.889	+ 0.866	< 0.001	0.771
AT (n = 88)	Total FIM score at admission	+ 0.925	+ 0.870	< 0.001	0.915
	PVH score	– 0.088	– 2.271	0.013	

(B) FIM motor score

Disease type	Clinical Factors	β	B	*p* value	R^2
All (n = 101)	FIM motor score at admission	+ 0.822	+ 0.835	< 0.001	0.739
	PVH score	– 0.124	– 2.442	0.022	
LI (n = 13)	FIM motor score at admission	+ 1.011	+ 1.155	< 0.001	0.806
AT (n = 88)	FIM motor score at admission	+ 0.820	+ 0.825	< 0.001	0.741
	PVH score	– 0.135	– 2.776	0.019	

(C) FIM cognitive score

Disease type	Clinical Factors	β	B	*p* value	R^2
All (n = 101)	FIM cognitive score at admission	+ 0.882	+ 0.832	< 0.001	0.857
	Age	– 0.117	– 0.091	0.006	
LI (n = 13)	FIM cognitive score at admission	+ 0.934	+ 1.060	< 0.001	0.973
AT (n = 88)	FIM cognitive score at admission	+ 0.833	+ 0.773	< 0.001	0.849
	Age	– 0.145	– 0.117	0.002	

AT: atherothrombosis, DWMH: deep white matter hyperintensity, FIM: Functional Independence Measure, LI: lacunar infarction, MRA: magnetic resonance angiography, PVH: periventricular hyperintensity, β: standardized regression coefficient, B: unstandardized coefficient, R^2: coefficient of determination.

DWMH grades directly in this study.

DISCUSSION

Recent experimental and clinical studies have shown that cilostazol has pleiotropic effects in addition to its antiplatelet action. For examples, cilostazol was reported to suppress cognitive decline in patients with mild Alzheimer's disease,[16,17] protect against cognitive impairment and white matter disintegration,[15] and improved cerebral blood flow and rehabilitation outcomes in patients following stroke.[18,30] Moreover, cilostazol has an endothelial protective effect and prevents blood-brain barrier disruption in the ischemic brain.[31,32] It protects the microvasculature in the ischemic brain by reducing matrix metalloproteinase-9 activity,[33,34] and has been shown to decrease Aβ accumulation and protect against Aβ-induced cognitive deficits.[35,36]

Our results revealed that several factors influence the outcome of convalescent rehabilitation

following non-cardioembolic (LI and AT subtypes) ischemic stroke. In particular, the outcome was seen to improve with cilostazol treatment, as demonstrated by a greater cognitive-FIM score increase over time with cilostazol treatment than without it according to the multiple linear regression analysis.

The most striking finding of this study was that cilostazol improved cognitive function in about 3 months during the course of the convalescent rehabilitation. However, previous studies of mild cognitive impairment and Alzheimer's disease have found that cilostazol can improve the cognitive decline over a period lasting several years.[16,17] We believe the result herein is valid despite the short time period analyzed, given that it has also been shown to increase cerebrovascular flow, decrease Aβ accumulation, and protect from Aβ-induced cognitive deficits in vitro in comparatively short periods of time.[35,36]

The differences in the dosage of cilostazol did not affect the rehabilitation outcomes in this study, although we acknowledge that the size of the cilostazol-treated group was comparatively small. Previous cardiovascular studies have shown that cilostazol was able to efficiently prevent cardiovascular events at either dosage used herein as 100 mg/day or 200 mg/day.[37] In addition, in an in vitro study, the dosage of cilostazol did not alter the decrease in Aβ accumulation.[36] Therefore, the findings from the above studies support our result that the dosage of cilostazol did not influence the rehabilitation outcomes. Nevertheless, there appeared to be a trend, though it was not statistically significant, toward an accelerated increase with the higher dose; thus, we cannot completely rule out a degree of dose-dependence.[38]

In the present study, the total FIM score at discharge was correlated with the degree of PVH. When the total FIM score was subdivided into its motor and cognitive components, the PVH grade was found to correlate with the motor FIM score, but the DWMH grade was not correlated with any rehabilitation outcomes revealed by the FIM scores. In our previous study, the DWMH grade was associated with decreased cognitive rehabilitation outcomes in patients with ischemic stroke related to thrombosis identified as A-to-A and CE.[19] Indeed, when the A-to-A subtype (n = 80) was extracted from AT in the present study, it correlated with cognitive rehabilitation outcomes following stroke of this subtype ($\beta = -0.096$, $B = -0.875$, $p = 0.013$), in a manner unaffected by cilostazol. However, we could not use A-to-A and CE subtypes in the present study because (1) we focused on non-cardioembolic ischemic stroke (e.g. LI and AT) to investigate the effects of cilostazol, and (2) patients with the CE subtype do not require cilostazol for the prevention of ischemic stroke recurrence. Thus, in this present study, we did not categorize these ischemic stroke subtypes.

The degree of leukoaraiosis seen as PVH or DWMH on intracranial MRI does not necessarily reflect the pathological severity of the white matter lesions,[39] and it is difficult to predict the level of impairment in cognitive function from the extent of the white matter hyperintensity.[40] Moreover, the presence of leukoaraiosis alone does not necessarily lead to a decline in cognitive function in elderly individuals.[41] However, the progression of leukoaraiosis represented by increased PVH and DWMH grades has been associated with decreased cerebrovascular flow,[42] as well as decreased motor and cognitive function in nondisabled patients.[43] The portions of leukoaraiosis located in the subcortical region represent injury to the short association fibers that form the between- or within-lobe connections; such damage leads to impairments in cognitive function.[44,45] Furthermore, these small abnormalities in the subcortical region are more important to the development of vascular cognitive impairment, and various cardiovascular risk factors are also related.[46,47] These brain tissue changes of Alzheimer's disease with Aβ plaques and neurofibrillary pathology are found more often in patients with cerebrovascular disease than in those with no ischemic lesions. Consequently, a combination of Alzheimer-type pathological changes and these subcortical impairments can decline cognitive function.[48] Indeed, we hypothesize that cilostazol

might ameliorate both the decreased cerebrovascular flow and the increased Aβ accumulation in the above white matter abnormalities, as well as each of the current stroke lesions.

The occurrence rate of heart disease in the cilostazol-untreated group was significantly higher than that in the treated group. In addition, just over half of the group not taking cilostazol were instead taking clopidogrel. Cilostazol is contraindicated in patients with heart failure due to adverse cardiac-related events, especially tachycardia and palpitations,[49] and we believe that heart disease and clopidogrel use contribute to the noted adverse effects. Patients in the cilostazol-treated group (especially the low-dose subgroup) were frequently on combination therapies that included the use of other antiplatelet drugs, thereby increasing the risk of bleeding events.[50] Cilostazol use is associated with a lower risk of such events than the use of other antiplatelet drugs[5,6]; thus, we assumed that cilostazol had been the first choice for the combination therapies.

We should acknowledge some limitations to the present retrospective study. First, the sample size was small, and a large-scale, multicenter double-blind study will be needed to confirm our findings. Second, whether our observations were related to cilostazol treatment alone or to the combination of cilostazol and rehabilitation remains to be determined. Third, the premorbid ADL of the study participants was assessed only through medical history interviews; more accurate and comprehensive assessments with cognitive function scales like the Mini-Mental State Examination[51] or Montreal Cognitive Assessment (MOCA)[52] were not carried out. Fourth, we only examined the average daily rehabilitation times, and could not investigate the relationships between our outcomes and details of the rehabilitation types, such as speech, occupational, and physical therapies, for each patient. Fifth, other unknown factors not investigated in this study may have also contributed to our outcomes. Further investigations will be necessary to confirm and address these issues.

In conclusion, the relationship between cilostazol and the outcomes of convalescent rehabilitation in patients with ischemic stroke has been described in only one study,[29] to the best of our knowledge. We examined the effects of cilostazol in addition to those of factors that might influence rehabilitation outcomes in patients with ischemic stroke. Our findings suggest that cilostazol can improve cognitive function even during the convalescent rehabilitation stage within as little as 3 months, in a manner that may not be dose-dependent. Overall, our data indicate that cilostazol could be an effective drug for cognitive support or restoration in patients with ischemic stroke.

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CONFLICTS OF INTEREST

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