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Effects of cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a multicenter prospective, randomized, open-label blinded end point trial

Clinical article

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Object. Cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH) is a major cause of subsequent morbidity and mortality. Cilostazol, a selective inhibitor of phosphodiesterase 3, may attenuate cerebral vasospasm because of its antiplatelet and vasodilatory effects. A multicenter prospective randomized trial was conducted to investigate the effect of cilostazol on cerebral vasospasm.

Methods. Patients admitted with SAH caused by a ruptured anterior circulation aneurysm who were in Hunt and Kosnik Grades I to IV and were treated by clipping within 72 hours of SAH onset were enrolled at 7 neurosurgical sites in Japan. These patients were assigned to one of 2 groups: the usual therapy group (control group) or the add-on 100 mg cilostazol twice daily group (cilostazol group). The group assignments were done by a computer-generated randomization sequence. The primary study end point was the onset of symptomatic vasospasm. Secondary end points were the onset of angiographic vasospasm and new cerebral infarctions related to cerebral vasospasm, clinical outcome as assessed by the modified Rankin scale, and length of hospitalization. All end points were assessed for the intention-to-treat population.

Results. Between November 2009 and December 2010, 114 patients with SAH were treated by clipping within 72 hours from the onset of SAH and were screened. Five patients were excluded because no consent was given. Thus, 109 patients were randomly assigned to the cilostazol group (n = 54) or the control group (n = 55). Symptomatic vasospasm occurred in 13% (n = 7) of the cilostazol group and in 40% (n = 22) of the control group (p = 0.0021, Fisher exact test). The incidence of angiographic vasospasm was significantly lower in the cilostazol group than in the control group (50% vs 77%; p = 0.0055, Fisher exact test). Multiple logistic analyses demonstrated that nonuse of cilostazol is an independent factor for symptomatic and angiographic vasospasm. The incidence of new cerebral infarctions was also significantly lower in the cilostazol group than in the control group (11% vs 29%; p = 0.0304, Fisher exact test). Clinical outcomes at 1, 3, and 6 months after SAH in the cilostazol group were better than those in the control group, although a significant difference was not shown. There was also no significant difference in the length of hospitalization between the groups. No severe adverse event occurred during the study period.

Conclusions. Oral administration of cilostazol is effective in preventing cerebral vasospasm with a low risk of severe adverse events. Clinical trial registration no. UMIN000004347, University Hospital Medical Information Network Clinical Trials Registry.
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Key Words • **cilostazol** • **subarachnoid hemorrhage** • **cerebral vasospasm** • **surgical outcome** • **vascular disorders**

Cerebral vasospasm remains one of the most serious complications in patients with aneurysmal SAH, and the resulting ischemic brain damage can cause poor outcomes. An international cooperative study reported that 39% of morbidity after aneurysmal SAH was caused by cerebral vasospasm.[21] Angiographic

Abbreviations used in this paper: CTA = CT angiography; DSA = digital subtraction angiography; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage.

vasospasm was initially confirmed by cerebral angiography in the early 1950s,[6] and the distribution and severity of cerebral vasospasm are well known to correlate with those of subarachnoid clots.[10,39] Vasoconstriction promoters derived from subarachnoid clots may cause imbalance of vasodilation and vasoconstriction, resulting in cerebral vasospasm.

Removal of subarachnoid clots is known to be effective in preventing the occurrence of cerebral vasospasm. Intraoperative bolus injection of tissue-type plasminogen activator into the cisterns appeared to be effective,[9] but a randomized study failed to confirm any preventive effect against cerebral vasospasm.[8] Postoperative cisternal irrigation and drainage using tissue-type plasminogen activator or urokinase has also been described,[22,23,32] but the procedure is cumbersome and carries the risk of infection. In addition to medical treatments, such as calcium antagonist,[1,30] Rho kinase inhibitor,[34] and triple-H therapy,[28] endovascular treatments including angioplasty[7] and intraarterial drug administration[25,33,41] have been reported to be effective in improving cerebral vasospasm. However, angioplasty can be used only in major arteries and cannot be performed for distal arteries because of the risk of arterial dissection.[7] The effect of intraarterial infusion of agents, such as papaverine[33] and nimodipine,[25] is temporary, and the procedure needs to be repeated to maintain the efficacy. Consequently, although the incidence of cerebral vasospasm has been gradually reduced by such treatments, the risk of symptomatic and angiographic vasospasm reportedly remains as high as 20%–50%[3,8,38,43] and 30% to nearly 80%, respectively.[1,8,43,46] The detailed mechanism and pathogenesis of cerebral vasospasm have not been fully elucidated, and cerebral vasospasm is not yet completely preventable by any treatment modalities.

Cilostazol is a platelet aggregation inhibitor used for the treatment of symptomatic intermittent claudication associated with peripheral arterial disease or for the prevention of recurrent cerebral infarction, except that caused by cardiogenic embolism. Cilostazol does not increase the occurrence of cerebral hemorrhage[13,35] and selectively inhibits phosphodiesterase 3, resulting in an increase in intracellular cyclic adenosine monophosphate.[20] Phosphodiesterase 3 is an isoform strongly expressed in platelets and vascular smooth muscle cells, and thus cilostazol has effects on the vascular wall as well as platelets.[16,20] Cilostazol has a vasodilatory effect on the cerebral arteries in healthy individuals,[2] and it inhibits cerebral vasospasm after SAH in animal models.[19,48] Furthermore, cilostazol was shown to attenuate cerebral vasospasm in a retrospective clinical study.[50]

The present multicenter prospective randomized trial investigated the safety and effectiveness of cilostazol administration for the prevention of cerebral vasospasm following aneurysmal SAH.

Methods

Study Design

This multicenter prospective, randomized, open-label blinded end point trial was performed with the cooperation of 7 neurosurgical institutions in Japan. Given the risk of recurrent SAH,[24] most patients with SAH caused by a ruptured anterior circulation aneurysm had been treated by clip treatment rather than endovascular treatment at all participating neurosurgical institutions prior to the start of this study. Patients with SAH caused by a ruptured posterior circulation aneurysm are known to be less likely to develop symptomatic vasospasm[17] and were excluded from this study to avoid bias. Therefore, this study included patients admitted to the hospital with SAH caused by a ruptured anterior circulation aneurysm with Hunt and Kosnik grades of I–IV,[18] who were treated by clipping within 72 hours after the onset of SAH. Subarachnoid hemorrhage was diagnosed by CT scanning. Exclusion criteria were nonaneurysmal SAH, untreatable severe SAH in Hunt and Kosnik Grade V, endovascular treatment, allergy to cilostazol, pregnancy, known bleeding diatheses, hemorrhagic complications such as gastrointestinal bleeding, and severe concomitant diseases such as congestive heart failure.

This study was done in accordance with ethics principles originating from the Declaration of Helsinki and in compliance with ethical guidelines for clinical research. The study protocol was evaluated and approved by the ethics committees of all participating institutions, and all patients or close relatives gave written informed consent. This trial is registered with University Hospital Medical Information Network Clinical Trials Registry (no. UMIN000004347).

Randomization and Treatment Protocol

Patients were randomly assigned to one of the following 2 groups: the cilostazol group, which received cilostazol (Otsuka Pharmaceutical Co.) orally or through a nasogastric tube, and the control group, which did not receive cilostazol. Patients were assigned to the groups according to a computer-generated randomization sequence at the central office of the present study located at the University of Yamanashi. The computerized allocation was strictly controlled by a person who was independent from study personnel, investigators, and the attending physicians.

After confirming the absence of postoperative intracranial hemorrhage on CT the day after surgery, cilostazol 100 mg twice daily was given for 14 days in the treatment group. Cilostazol administration was started by 96 hours after the onset of SAH and by 48 hours after surgery. Postoperatively, the conventional postoperative treatments adopted by each institution were continued in both groups. Basically, a normal circulating blood volume was maintained and hypovolemia was avoided, and 30 mg fasudil hydrochloride 3 times per day daily (Asahi Kasei Pharma Corp.), which is a widely used vasodilator that causes Rho-kinase inhibition[34] and is recommended under the Japanese guidelines for the management of aneurysmal SAH,[36,37] was administered for 2 weeks. Nimodipine, a calcium-channel blocker indicated to reduce poor outcome related to aneurysmal SAH,[1] was not administered because it has not been approved yet in Japan. Administration of other antiplatelet agents, such as aspirin, ticlopidine hydrochloride, clopidogrel sulfate, sodium ozagrel, beraprost sodium, limaprost alfadex,

sarpogrelate hydrochloride, and ethyl icosapentate, was prohibited during the study period.

Radiological and Clinical Evaluations

Patient demographics, medical history, family history, coexisting disorders, and precritical mRS score[31] were recorded on admission. Subarachnoid hemorrhage was diagnosed using CT scanning, and the severity was assessed by Hunt and Kosnik grade. The amount and distribution of clot demonstrated on the initial CT scan was evaluated by the Fisher CT grade, and Hounsfield unit values were measured in the basal cistern and in the bilateral sylvian fissures. A ruptured aneurysm was confirmed by DSA or CTA.

Either DSA or CTA was performed between 7 and 10 days after the onset of SAH to assess angiographic vasospasm. Computed tomography angiography was performed using a multidetector system at every institution. The timing of scanning and threshold intensity were kept constant to maintain data reliability, and maximum intensity projection images and multiplanar reconstruction images were obtained to minimize variations as far as possible at each institution. Angiographic vasospasm was defined as arterial narrowing not attributable to atherosclerosis, catheter-induced vasospasm, or vessel hypoplasia.[12] The degree of angiographic vasospasm was calculated as the ratio of the narrowed vessel diameter on the follow-up images to the initial diameter. In each patient, the smallest diameters of 10 arterial segments of the bilateral distal ICAs, M_1 and M_2 segments of the MCA, and A_1 and A_2 segments of the anterior cerebral artery were measured. The severity of angiographic vasospasm was categorized as follows: none or mild, 0%–25% decrease in vessel diameter on the follow-up images; moderate, 25%–50% decrease; and severe, greater than 50% decrease (Fig. 1), according to former studies.[5,27,45] The most affected segment was used to determine the severity of angiographic vasospasm, and moderate or severe categories were defined as the occurrence of angiographic vasospasm. The distribution of angiographic vasospasm of each patient was further classified as follows: local, localized to one side; and diffuse bilateral vasospasm.

Computed tomography scanning or MRI was scheduled for assessment of new cerebral infarctions at 4 time points after surgery (the next day, 7 ± 2 days, 14 ± 2 days, and 1 month after surgery). Low-density areas on CT or signal changes on MRI performed the day after surgery were defined as procedure-related infarctions or brain damage, and ischemic lesions demonstrated by follow-up CT scanning or MRI were interpreted as new cerebral infarctions caused by cerebral vasospasm, regardless of any association with symptoms. The locations of the new cerebral infarctions were classified into 2 categories: territories of the parent artery of the ruptured aneurysm and other territories.

All patients were kept under close observation, and clinical symptoms of cerebral vasospasm were evaluated for 14 days. Symptomatic vasospasm was defined as development of a new focal or global neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale,[42] which was not explained by initial hemorrhage, rebleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI and angiographic vasospasm on DSA or CTA.[11,12,14] Clinical outcomes were evaluated using the mRS at 1, 3, and 6 months after surgery, with outcomes divided into mRS scores of 0–2 and 3–6, and the total duration of hospitalization was also recorded.

The primary end point was the onset of symptomatic vasospasm. Secondary end points were the onset of angiographic vasospasm, new cerebral infarctions related to cerebral vasospasm, clinical outcomes, and length of hospitalization. All end points were assessed for the intention-to-treat population. All radiological and clinical assessments were done based on clinical chart and hard copy films provided by each institution by 2 physicians on the evaluation committee who had no information regarding the allocation, independently from the attending physicians.

Adverse events of cilostazol were evaluated from the start of administration to 3 days after discontinuation; the effect of cilostazol has been reported to resolve within 96 hours after discontinuing medication.[49] All adverse events occurring during the period were recorded. The rates of hemorrhagic and cardiac events were especially analyzed to assess drug safety.

Statistical Analysis

Sample size estimation was calculated according to

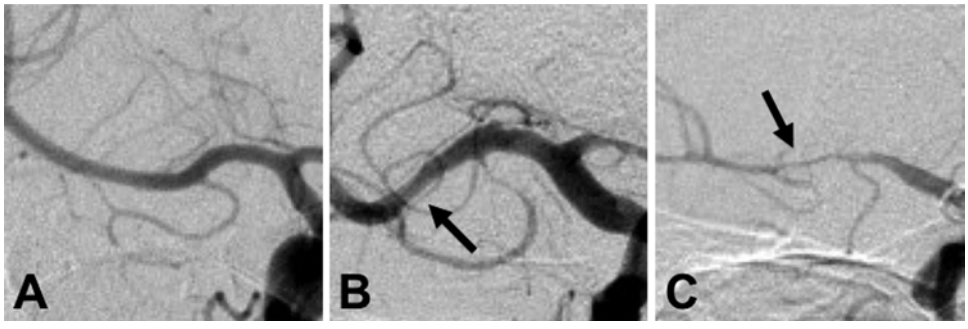

Fig. 1. Examples of severity of angiographic vasospasm involving the right M_1 segment as follows: none or mild, 0–25% decrease in vessel diameter compared with the initial diameter **(A)**, moderate, 25–50% decrease **(B)**, and severe, > 50% decrease **(C)**. The *arrows* indicate the most affected portion used to determine the individual severity of angiographic vasospasm.

the study of Yoshimoto et al.,[50] which was reported from a single neurological institute and was the only study available at the time of study design. In that study, 37.5% of the control group and 19.2% of the cilostazol group had symptomatic vasospasm. Based on these values, the required sample size for a 2-tailed test with a 5% significance level and 80% power was 44 patients for each study group. Assuming a dropout of 10%, the required sample size was 50 for each study group. Intergroup differences were measured using the Student t-test, Wilcoxon rank sum test, Pearson chi-square test, or Fisher exact probability test. A 2-sided probability value < 0.05 was considered as significant. Clinical factors affecting symptomatic and angiographic vasospasm was assessed using multiple logistic regression analysis after confirming apparent influential factors by univariate analysis.

Results

Patient Characteristics

Between November 2009 and December 2010, 114 patients with SAH were treated by clipping within 72 hours of the onset of SAH and were screened. Informed consent was not obtained from 5 patients. Finally, 109 patients were randomly assigned to the cilostazol group (n = 54) or the control group (n = 55). No protocol violation was found in the population (Fig. 2). No significant difference in the demographic and background data of the patients, including age, sex, medical history, severity of SAH, and location of aneurysm, was found between the groups (Table 1). The drugs used and external CSF drainage after clipping were similar in both groups. Intravenous fasudil hydrochloride was administered in all patients in both groups.

Study End Points

The primary and secondary end points are shown in Table 2. Symptomatic vasospasm occurred at a lower incidence in the cilostazol group (7 [13.0%]) than in the control group (22 [40.0%]; p = 0.0021). The incidence of symptomatic vasospasm was significantly different between the cilostazol and control groups even after stratification by Hunt and Kosnik grades as Grades I/II and III/IV (Table 3). Factors apparently relating to the occurrence of symptomatic vasospasm were Hunt and Kosnik grade, nonuse of cilostazol, and external CSF drainage. Multiple logistic analyses demonstrated that nonuse of cilostazol and external CSF drainage were independent factors for symptomatic vasospasm (Table 4).

Postoperative DSA was performed in nearly half of the patients in both groups, and no significant difference was shown in diagnostic modalities between the groups. The occurrence of angiographic vasospasm was significantly lower in the cilostazol group (50.0% [27 patients]) than in the control group (76.4% [42 patients]; p = 0.0055). There was a significant difference between groups in Hunt and Kosnik Grades I and II, but not in Hunt and Kosnik Grades III and IV. The severity of angiographic vasospasm for each patient was also significantly lower in the cilostazol group than in the control group (p = 0.0048). The occurrence of none or mild, moderate, and severe angiographic vasospasm was 50.0% (n = 27), 31.5% (n = 17), and 18.5% (n = 10), respectively, in the cilostazol group, and 23.6% (n = 13), 32.7% (n = 18), and 43.6% (n = 24), respectively, in the control group. Figure 3 shows the severity of angiographic vasospasm in each segment, which was significantly lower in the cilostazol group than in the control group (p < 0.05) except for the left A_2 and M_1 segments. The distribution of angiographic vasospasm was significantly different (p = 0.0156), and the diffuse

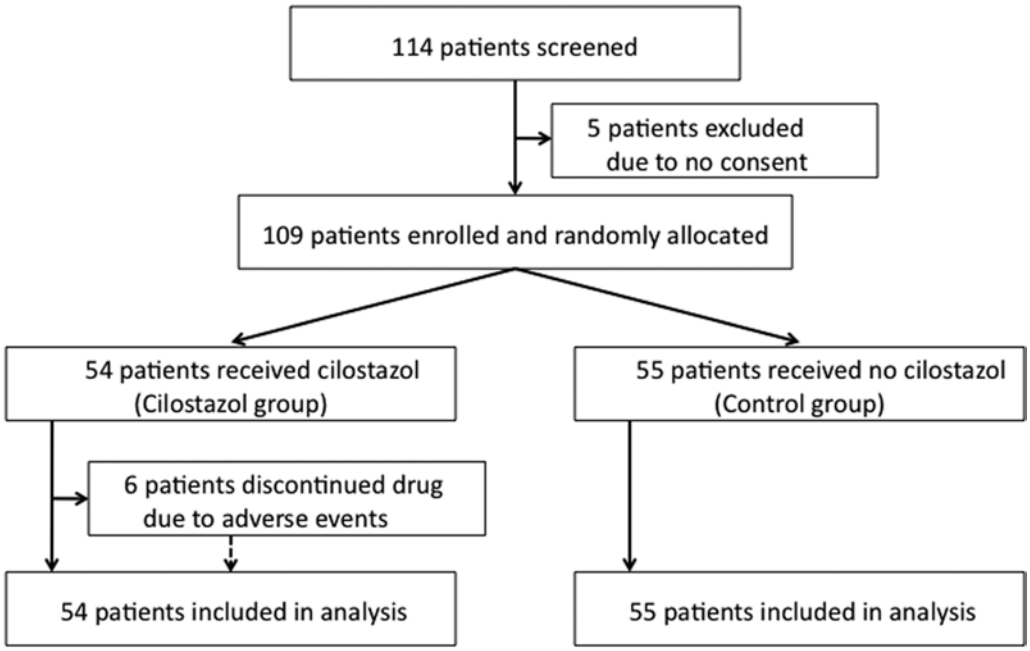

Fig. 2. Diagram showing the patient group assignments.

TABLE 1: Clinical and radiological characteristics of patients in the cilostazol and control groups*

Characteristic	Value†		p Value‡
	Cilostazol	Control	
no. of patients	54	55	
mean age (yrs)	60.0 ± 12.5	61.3 ± 12.7	0.5835
female sex	35 (64.8)	33 (60.0)	0.6936
hypertension	25 (46.3)	27 (49.1)	0.8487
diabetes mellitus	8 (14.8)	8 (14.5)	1.0000
dyslipidemia	16 (29.6)	13 (23.6)	0.5211
current smoker	15 (27.8)	23 (41.8)	0.1600
coronary artery disease	0 (0.0)	1 (1.8)	1.0000
stroke	3 (5.6)	3 (5.5)	1.0000
peripheral artery disease	0 (0.0)	0 (0.0)	
mRS score before onset of SAH			1.0000
0	53 (98.1)	53 (96.4)	
1	1 (1.9)	2 (3.6)	
H & K grade on admission			0.8736
I	3 (5.6)	3 (5.5)	
II	23 (42.6)	20 (36.4)	
III	20 (37.0)	21 (38.2)	
IV	8 (14.8)	11 (20.0)	
Fisher CT grade			0.2314
2	8 (14.8)	3 (5.5)	
3	37 (68.5)	44 (80.0)	
4	9 (16.7)	8 (14.5)	
mean Hounsfield unit			
basal cistern	54.8 ± 10.3	54.2 ± 11.3	0.9045
rt sylvian fissure	56.9 ± 10.7	54.5 ± 11.9	0.2696
lt sylvian fissure	53.6 ± 12.5	53.2 ± 11.5	0.7121
aneurysm location			0.1653
ACA	22 (40.7)	20 (36.4)	
ICA	12 (22.2)	21 (38.2)	
MCA	20 (37.0)	14 (25.5)	
drugs used after clipping			
calcium-channel blockers (except nimodipine)	2 (3.7)	2 (3.6)	1.0000
intravenous fasudil hydrochloride	54 (100)	55 (100)	
intraarterial infusion of fasudil hydrochloride	6 (11.1)	13 (23.6)	0.1287
external CSF drainage	29 (53.7)	29 (52.7)	1.0000

* ACA = anterior cerebral artery (including the anterior communicating artery); H & K = Hunt and Kosnik.
† Mean values are presented as the mean ± SD. All other values are the number of patients (%).
‡ Calculated using the Student t-test, the Wilcoxon rank-sum test, the Pearson chi-square test, or the Fisher exact probability test.

type was more common in the control group. In patients with symptomatic vasospasm, severe angiographic vasospasm and diffuse type of angiographic vasospasm were more common (Table 5). Despite detection of none or

TABLE 2: Primary and secondary end points in the cilostazol and control groups

Parameter	Value*		p Value†
	Cilostazol	Control	
no. of patients	54	55	
no. w/ symptomatic vasospasm	7 (13.0)	22 (40.0)	0.0021
diagnostic modality of angiographic vasospasm			1.0000
DSA	26 (48.1)	26 (47.3)	
CTA	28 (51.9)	29 (52.7)	
no. w/ angiographic vasospasm	27 (50.0)	42 (76.4)	0.0055
severity of vasospasm			0.0048
none or mild	27 (50.0)	13 (23.6)	
moderate	17 (31.5)	18 (32.7)	
severe	10 (18.5)	24 (43.6)	
distribution			0.0156
local	13/27 (48.1)	8/42 (19.0)	
diffuse	14/27 (51.9)	34/42 (81.0)	
cerebral infarction			
diagnostic modality of cerebral infarction			0.2159
CT	42 (77.8)	48 (87.3)	
MRI	12 (22.2)	7 (12.7)	
infarction or brain damage in total	11 (20.4)	21 (38.2)	0.0579
new infarction caused by cerebral vasospasm	6 (11.1)	16 (29.1)	0.0304
location			1.0000
parent artery territories	3/6 (50.0)	8/16 (50.0)	
other territories	3/6 (50.0)	8/16 (50.0)	
mRS score 0–2 postop			
1	39 (72.2)	33 (60.0)	0.2257
3	47 (87.0)	40 (72.7)	0.0938
6	48 (88.9)	41 (74.5)	0.0818
mean hospital stay (days)	74.8 ± 68.9	88.4 ± 76.8	0.3305

* Mean values are presented as the mean ± SD. All other values are the number of patients (%).
† Calculated using the Fisher exact probability test or the Pearson chi-square test.

only mild angiographic vasospasm, 2 patients in the cilostazol group and 1 patient in the control group presented with symptomatic vasospasm. Apparent clinical factors associated with the occurrence of angiographic vasospasm were smoking, Hunt and Kosnik grade, nonuse of cilostazol, and external CSF drainage. Multiple logistic analyses demonstrated that nonuse of cilostazol was the only factor affecting angiographic vasospasm (Table 6). Computed tomography was performed in almost all patients in both groups, and no significant difference was shown in diagnostic modalities between the groups. The occurrence of new cerebral infarctions was significantly lower in the cilostazol group (11.1% [6 patients]) than in the control group (29.1% [16 patients]; p = 0.0304). New

TABLE 3: Stratified analysis by Hunt and Kosnik grade of symptomatic and angiographic vasospasm in the cilostazol and control groups

Parameter	No. of Patients (%)		p Value*
	Cilostazol	Control	
H & K Grade I & II	26	23	
symptomatic vasospasm	0 (0.0)	5 (21.7)	0.0176
angiographic vasospasm	9 (34.6)	17 (73.9)	0.0096
H & K Grade III & IV	28	32	
symptomatic vasospasm	7 (25.0)	17 (53.1)	0.0358
angiographic vasospasm	18 (64.3)	25 (78.1)	0.2644

* Calculated using the Fisher exact probability test.

cerebral infarctions occurred equally in the parent artery territory and other territories in both groups. Clinical outcomes using the mRS at 1, 3, and 6 months after SAH are shown in Fig. 4. Although no statistically significant difference was found, the cilostazol group tended to have better outcomes than the control group. There was no difference in the mortality rate between the groups. In the cilostazol group, one patient died of severe pneumonia on Day 21, and another patient died of a dissecting aneurysm of the aorta on Day 28 after the onset of SAH. In the control group, one patient died of a dissecting aneurysm of the aorta on Day 11, and another died of a new infarction caused by severe cerebral vasospasm on Day 10 after the onset of SAH. No significant difference regarding the hospitalization period was found between the groups.

Adverse Events

The adverse events of cilostazol during the follow-up period are shown in Table 7. Hemorrhagic events occurred in 3 patients in the cilostazol group (1 gastrointestinal hemorrhage, 1 epidural hematoma, and 1 intracerebral hemorrhage). These 3 patients did not receive further cilostazol and could be managed without additional surgical treatment. Hemorrhagic events occurred in 2 patients in the control group (2 gastrointestinal hemorrhages). Cardiac events occurred in 3 patients in the cilostazol group (sinus tachycardia in 1 and paroxysmal atrial fibrillation in 2). All patients improved after discontinuing cilostazol. Sinus tachycardia and hypotension occurred in 1 patient each in the control group. Other adverse events specified to cilostazol were not identified. The number of adverse events in both groups was equal. Additionally, no blood abnormalities were detected in the cilostazol group.

Discussion

In this study, cilostazol effectively reduced the incidence of symptomatic and angiographic vasospasm as proven in univariate and multivariate analyses. Based on the multiple logistic analyses, use of cilostazol reduced symptomatic vasospasm to 17% and angiographic vasospasm to 30%, and cilostazol was the only common factor that reduced symptomatic and angiographic vasospasm. Use of external CSF drainage was another factor

TABLE 4: Factors affecting symptomatic vasospasm*

Factor	Parameter Estimate	Standard Error	p Value	OR
age (≥60 yrs)	0.081	0.265	0.7603	1.18
H & K Grade I or II	−0.515	0.315	0.1021	0.36
cilostazol†	−0.899	0.278	0.0012	0.17
external CSF drainage†	1.017	0.333	0.0023	7.62

* Based on results of multiple logistic analyses.
† Identified as related factors.

associated with symptomatic vasospasm, and this may be because the procedure might have been performed in patients with massive hemorrhage. The other findings of this study were that cilostazol reduced the incidence of new cerebral infarctions; cilostazol tended to improve the clinical outcome for patients with aneurysmal SAH, although no significant difference was shown; and cilostazol did not cause serious adverse events during the acute stage of aneurysmal SAH.

The effects of cilostazol are basically mediated by inhibition of phosphodiesterase 3 in smooth muscle cells and platelets, leading to relaxation of intact smooth muscle cells and inhibition of platelet aggregation. Cilostazol caused dilation of the MCA without adverse effects on cerebral blood flow and blood pressure compared with placebo in healthy individuals.[2] Cilostazol attenuated cerebral vasospasm in animal models of SAH, which was confirmed by radiographic evaluation.[19,48] Additionally, cilostazol has effects on vascular endothelial cells to prevent endothelial damage.[16,48] Oxyhemoglobin derived from subarachnoid clots is cytotoxic and leads to apoptosis of endothelial cells in vitro and in vivo.[26,48] Endothelial damage causes coagulation and microthrombosis following platelet adhesion to endothelial cells. Microthrombosis is reported to be one of the important factors in the occurrence of delayed cerebral ischemia after aneurysmal SAH.[44] The present findings that the incidence of symptomatic and angiographic vasospasm and new cerebral infarctions were significantly lower in the cilostazol group may be supported by these reports.

Various agents are effective for the prevention of cerebral vasospasm. Oral nimodipine, a calcium-channel blocker used worldwide, reduces the relative incidences of cerebral infarction by 34% and poor outcome by 40%,[30] but the effects are probably caused by the direct neuroprotective properties rather than any vasodilatory effect.[1] Nimodipine was not used in this study because it is not an approved drug in Japan, and other calcium-channel blockers were used in a minority of patients in both groups only for controlling blood pressure. Intravenous fasudil hydrochloride reduces the relative incidence of symptomatic vasospasm by 30% and angiographic vasospasm by 38%, and consequently improves clinical outcome.[34] Therefore, administration of fasudil hydrochloride was allowed in this study, and consequently, all patients received intravenous fasudil hydrochloride. Intraarterial infusion of fasudil hydrochloride also prevents cerebral vasospasm, although the effect is temporary.[41]

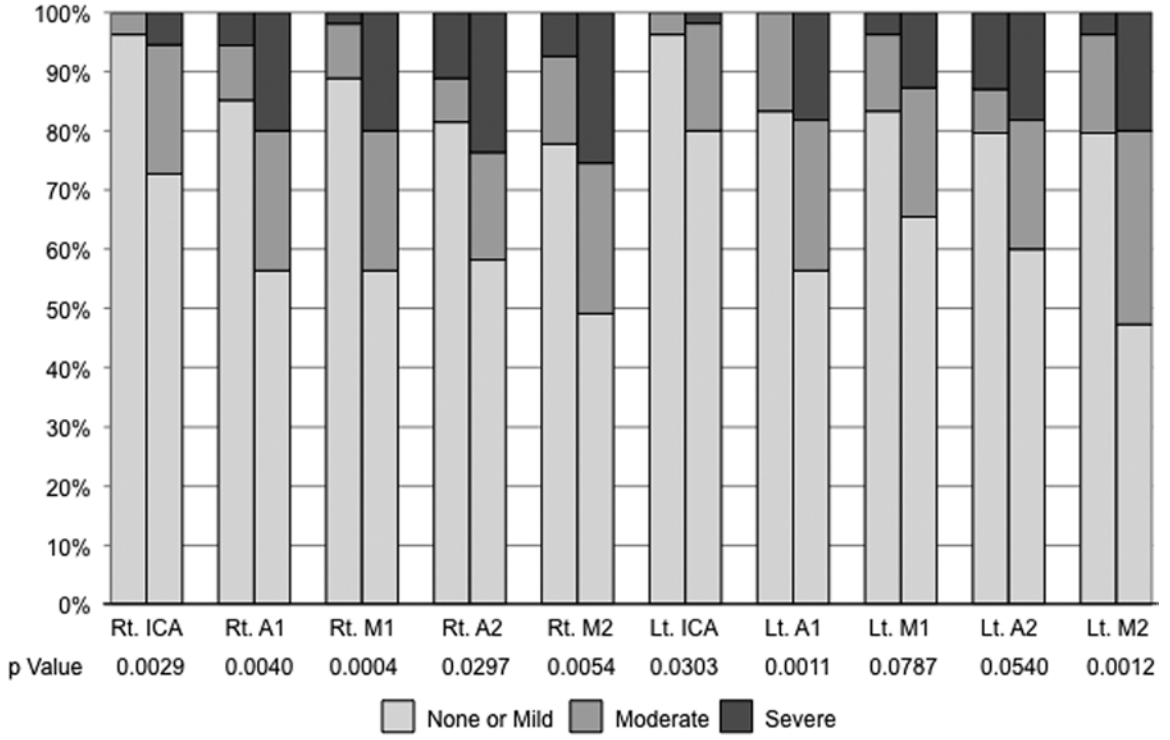

Fig. 3. Severity of angiographic vasospasm in each segment. In the pairings, the *bars* on the left indicate the cilostazol group and the *bars* on the right indicate the control group. The p values were calculated using the Pearson chi-square test.

Patients undergoing this procedure were more often in the control group than in the cilostazol group but with no significant difference, suggesting that severe cerebral vasospasm requiring this procedure occurred more often in the control group.

The present clinical randomized trial indicated that cilostazol is effective for the prevention of symptomatic and angiographic vasospasm and cerebral infarctions in patients with SAH caused by ruptured anterior circulation aneurysms treated by clipping for the first time. Symptomatic and angiographic vasospasm occurs in 20%–50% and 30% to nearly 80% of patients with aneurysmal SAH, respectively.[1,3,8,38,43,46] Incidence of symptomatic and angiographic vasospasm in the control group of the present study appeared to be relatively higher than that of the former studies. However, the difference might be derived from the study design and treatment protocol. In some previous studies in which cerebral vasospasm was evaluated in the same way as the present study, symptomatic and angiographic vasospasm were seen in 33%–46%[11,14] and 62%–71% of patients, respectively.[5,27,45] The results of the present study are consistent with these reports. The present study failed to prove any significant difference in clinical outcome between groups, possibly because the clinical outcome is affected by not only cerebral vasospasm but also by other factors, such as initial brain damage, surgical complications, or systemic complications. The sample of the present study is small; a larger number of patients is required to prove the significant effects of

TABLE 5: The severity and distribution of angiographic vasospasm in patients with symptomatic vasospasm in the cilostazol and control groups

Parameter	No. of Patients (%)		p Value*
	Cilostazol	Control	
no. w/ symptomatic vasospasm	7	22	
severity of angiographic vasospasm			0.0924
none or mild	2 (28.6)	1 (4.5)	
moderate	2 (28.6)	3 (13.6)	
severe	3 (42.8)	18 (81.8)	
distribution of angiographic vasospasm			1.0000
local	1 (14.3)	3 (13.6)	
diffuse	4 (57.1)	18 (81.8)	

* Calculated using the Pearson chi-square test.

TABLE 6: Factors affecting angiographic vasospasm*

Factor	Parameter Estimate	Standard Error	p Value	OR
age (≥60 yrs)	−0.126	0.237	0.5948	0.78
smoking	0.294	0.259	0.2577	1.80
H & K Grade I or II	−0.176	0.246	0.4733	0.70
cilostazol†	−0.604	0.223	0.0067	0.30
external CSF drainage	0.377	0.247	0.1262	2.13

* Based on results of multiple logistic analyses.
† Identified as related factor.

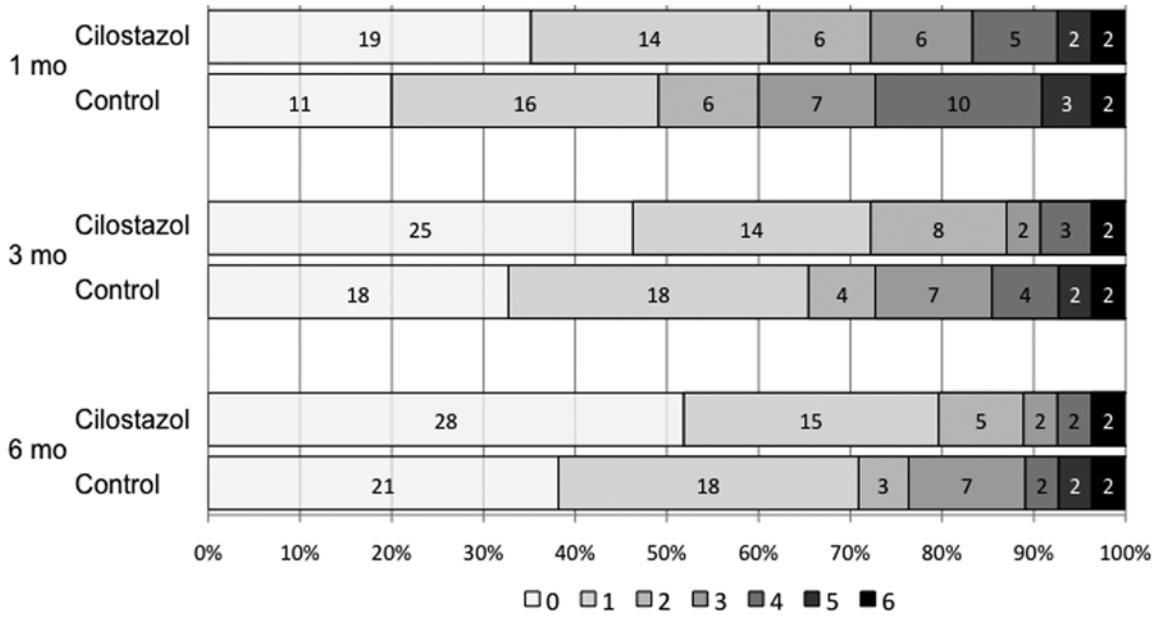

Fig. 4. Graph showing the number of patients in each mRS group evaluated 1, 3, and 6 months after surgery. Numbers in the key below the graph represent mRS scores.

cilostazol administration on clinical outcome. In contrast, a previous study reported that cilostazol improved clinical outcome at discharge after SAH, but it had no preventive effect on symptomatic vasospasm and cerebral infarction.[40] This discrepancy may be due to differences in the study design. The effects of cilostazol may not be different from others, such as intravenous nicardipine[14,15] and clazosentan, which have shown reduction in cerebral vasospasm without improvement in outcome.[43]

Cilostazol administration is a simple and safe treatment, which can be added to any conventional treatments without an increase in adverse events. The reason that hemorrhagic complications did not increase in the cilostazol group may be related to the fact that cilostazol does not prolong bleeding time.[47] Although no significant difference in the occurrence of cardiac complications was found, it should be noted that patients with severe SAH with Hunt and Kosnik Grade V and congestive heart failure were excluded from this study. Other common side effects of cilostazol, such as headache, dizziness, or nausea, are generally found to occur after SAH; therefore, these symptoms were not regarded as specific side effects of cilostazol, and the true occurrence rate of these symptoms remains unknown.

TABLE 7: Occurrence of adverse events in the cilostazol and control groups

Adverse Event	No. of Patients	
	Cilostazol	Control
overall adverse events	6	4
hemorrhagic events	3	2
gastrointestinal hemorrhage	1	2
epidural hematoma	1	0
intracerebral hemorrhage	1	0
cardiac events	3	2
sinus tachycardia	1	1
paroxysmal atrial fibrillation	2	0
hypotension	0	1

There are some limitations in this study. One is the possibility that the use of CTA led to an underestimation of the incidence and severity of angiographic vasospasm. The gold standard is DSA, but the risk for procedure-related stroke cannot be eliminated, and this procedure is more costly than CTA. Computed tomography angiography has been widely used for evaluating intracranial vascular lesions and has recently been recommended to evaluate angiographic vasospasm based on the high accuracy and convenience.[4,27,29] However, CTA is considered to be inferior to DSA in revealing vasospasm in the peripheral arteries, and thus evaluation was limited to the large arteries in this study. The reason that 2 patients in the cilostazol group and 1 patient in the control group presented with symptomatic vasospasm despite detection of none or only mild angiographic vasospasm was likely due to angiographic vasospasm of the peripheral arteries or other mechanisms, such as microthrombosis.[44] Another limitation is the possibility that the use of CT led to an underestimation of the incidence of cerebral infarctions compared with MRI. Third, the enrollment was limited to patients with SAH caused by ruptured anterior circulation aneurysms in Hunt and Kosnik Grades I–IV treated by clipping to avoid bias of the treatment modality. Currently, the number of endovascular treatments for ruptured anterior circulation aneurysms has been increasing in all participating neurosurgical institutions as well as in the world. Therefore, additional evaluation of patients treated by coiling is necessary for general versatility. Finally, this study demonstrated that cilostazol may be safe

for the acute stage of SAH and effective for the prevention of cerebral vasospasm and for improvement in final outcome after surgical treatment for aneurysmal SAH. However, it should be noted that there are differences in the use of drugs for cerebral vasospasm, and therefore the results of the present study may not necessarily apply to patients in other parts of world. Furthermore, this study is an open-label trial without placebo, and therefore the attending physicians were not completely blind to treatment allocation. These preliminary findings need to be further explored by larger prospective randomized double-blind trials with placebo.

Conclusions

Cilostazol reduced the incidence of symptomatic and angiographic vasospasm and new cerebral infarctions related to cerebral vasospasm in this study. Oral administration of cilostazol is an effective treatment for cerebral vasospasm with a low risk of severe adverse events.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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