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Effect of Cilostazol on Cerebral Vasospasm and Outcome in Patients with Aneurysmal Subarachnoid Hemorrhage: A Randomized, Double-Blind, Placebo-Controlled Trial

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Key Words
Subarachnoid hemorrhage · Cerebral vasospasm · Antiplatelet agents · Cerebral aneurysm · Delayed neuronal damage caused by spasm · Randomized controlled trial

Abstract
Background: Several clinical studies have indicated the efficacy of cilostazol, a selective inhibitor of phosphodiesterase 3, in preventing cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH). They were not double-blinded trial resulting in disunited results on assessment of end points among the studies. The randomized, double-blind, placebo-controlled study was performed to assess the effectiveness of cilostazol on cerebral vasospasm. ***Methods:*** Patients with aneurysmal SAH admitted within 24 h after the ictus who met the following criteria were enrolled in this study: SAH on CT scan was diffuse thick, diffuse thin, or local thick, Hunt and Hess score was less than 4, administration of cilostazol or placebo could be started within 48 h of SAH. Patients were randomly allocated to placebo or cilostazol after repair of a ruptured saccular aneurysm by aneurysmal neck clipping or endovascular coiling, and the administration of cilostazol or placebo was continued up to 14 days after initiation of treatment. The primary end point was the occurrence of symptomatic vasospasm (sVS), and secondary end points were angiographic vasospasm (aVS) evaluated on digital subtraction angiography, vasospasm-related new cerebral infarction evaluated on CT scan or MRI, and clinical outcome at 3 months of SAH as assessed by Glasgow Outcome Scale, in which poor outcome was defined as severe disability, vegetative state, and death. All end points were evaluated with blinded assessment. ***Results:*** One hundred forty eight patients were randomly allocated to the cilostazol group (n = 74) or the control group (n = 74). The occurrence of sVS was significantly lower in the cilostazol group than in the control group (10.8 vs. 24.3%, p = 0.031), and multiple logistic analysis showed that cilostazol use was an independent factor reducing sVS (OR 0.293, 95% CI 0.099–0.568, p = 0.027). The incidence of aVS and vasospasm-related cerebral infarction were not significantly different between the groups. Poor outcome was significantly lower in the cilostazol group than in the control group (5.4 vs. 17.6%, p = 0.011), and multiple logistic analyses demonstrated that cilostazol use was an independent factor that reduced the incidence of poor outcome (OR 0.221, 95% CI 0.054–0.903, p = 0.035). Severe adverse events due to cilostazol administration did not occur during the study period. ***Conclusions:*** Cilostazol administration is effective in preventing sVS and improving outcomes without severe adverse events. A larger-scale study including more cases was necessary to confirm this efficacy of cilostazol.

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Introduction

Subarachnoid hemorrhage (SAH) caused by the rupture of cerebral aneurysms is a life-threatening disease [1, 2]. One of the most important causes of mortality and morbidity therefrom is cerebral vasospasm causing delayed cerebral ischemia (DCI). DCI had been considered to be caused by persistent luminal narrowing of the major cerebral arteries. However, recent investigations have indicated that other factors, such as microcirculatory disturbance [3], early brain injury [4], and cortical spreading depression [5], are also related to the pathogenesis of DCI. The pathogenesis of DCI due to cerebral vasospasm is therefore complicated and has not yet been fully clarified. This is background to the fact that excellent treatment for the prevention of DCI due to cerebral vasospasm has not been established, although many drugs and treatments have been tried until now [6].

Recently, cilostazol, a selective inhibitor of phosphodiesterase 3 (PDE3), has been reported as an efficacious drug for the prevention of cerebral vasospasm in experimental studies [7–9]. Cilostazol is widely used throughout the world for arteriosclerosis obliterans, the intermittent claudication, or the prevention of a second ischemic stroke [10, 11]. In addition to an anti-platelet and vasodilating effect, several experimental studies have proven that cilostazol has pleiotropic effects that can have inhibitory potential against cerebral vasospasm, such as inhibition of reactive oxygen species (ROS) [12], inhibition of apoptosis [13], anti-inflammation [8], anti-lipid peroxidation [9], and induction of nitric oxide (NO) synthesis [14].

There have been 3 clinical studies investigating the efficacy of cilostazol on the prevention of cerebral vasospasm; 2 were randomized controlled trials [15, 16] and one was controlled clinical trial [17]. However, the results among the studies have not necessarily been consistent. Several factors may be responsible for this: basic management of SAH, such as the use of fasudil hydrochloride, sodium ozagrel, calcium channel blockers, and/or statin were not standardized between the groups [15]; cilostazol-administration was initiated over a relatively prolonged period of time: 96 h after SAH16 or its timing was not clearly defined [15, 17]; end-point assessment was not performed by double-blind evaluation, therefore not completely excluding assessment bias.

The aim of this study was to investigate the efficacy of cilostazol on cerebral vasospasm under a more strict protocol and uniform SAH management; cilostazol administration was initiated within 48 h after SAH following the aneurysm repair; the other management protocols for SAH including the use of agents were strictly standardized; and all end points were evaluated with double-blinded assessment.

Methods

Study Design

This study was an investigator-indicated, multicenter, prospective, randomized controlled trial with blinded outcome assessment, performed at 3 neurosurgical institutions in Aomori prefecture, Japan, between August 2010 and December 2013. This study was performed in accordance with ethics principles originating from the Declaration of Helsinki and in compliance with ethical guidelines for clinical research. The study protocol received Ethics Committee approval from all of the participating centers. All participants or their legal representatives provided written, informed consent. This trial is registered with the University Hospital Medical Information Network Clinical Trials Registry (No. UMIN000014402).

Study Population

Eligible patients were 20–80 years with aneurysmal SAH, admitted within 24 h after the ictus, and for whom oral administration of placebo or cilostazol could be started within 48 h after the onset of SAH following repair of a ruptured saccular aneurysm by aneurysmal neck clipping or endovascular coiling. The other inclusion criteria were as follows: SAH should be diffuse (long axis ≥20 mm) or localized (long axis <20 mm) thick (short axis ≥4 mm) subarachnoid clot on CT scan performed within 24 h of SAH; clinical grade evaluated by Hunt and Hess grade was grades 1–4 before clipping or coiling. Exclusion criteria were as follows: (1) prior cerebral damage from past history of stroke or traumatic brain injury confirmed by CT scan; (2) postoperative neurological deficit having arisen due to clipping or coiling procedure; (3) major neurological deficits due to accompanying intracerebral clot; (4) current use of anti-platelet and/or anticoagulant agent; (5) pre-existing major hepatic, renal, pulmonary or cardiac disease; (6) pregnancy.

Randomization

Participants were randomized into one of the following 2 groups: the cilostazol group, which received cilostazol orally or through a nasogastric tube, and the control group, which received placebo instead of cilostazol. The study drug assignments were kept in sealed envelopes that were opened by site study investigators who were not involved in patient care. Both the patients and the assessors were blinded to group allocation.

After the absence of postoperative intracranial hemorrhage was confirmed on CT scan performed 6–12 h after operating, the administration of placebo or 100 mg of cilostazol was started twice per day and continued for 14 days.

Standard of Care

Postoperative treatments were standardized and continued for 14 days in both groups in all institutions. A normovolemia, normal circulating blood volume, was maintained, and 30 mg of fasudil hydrochloride, which has a vasodilatory effect due to

Rho-kinase inhibition and is recommended under the Japanese guidelines for the management of aneurysmal SAH, was administered intravenously 3 times per day, daily [18]. Administration of other antiplatelet agents was prohibited during the study period.

The standardized rescue therapy was initiated when symptomatic vasospasm (sVS) was diagnosed as described later. This included induced hypertension and endovascular infusion of vasodilator, followed by balloon dilation if adequate vasodilation could not be achieved by vasodilator infusion.

Clinical Assessment and Radiology

Baseline digital subtraction cerebral angiography (DSA) was performed on admission within 24 h of SAH in all patients. In order to assess angiographic vasospasm (aVS), DSA was re-performed on day 9 ± 2 post-SAH. If patients showed signs of sVS, DSA was also performed at any time. CT scan was performed on admission within 24 h of SAH and 6–12 h after the aneurysm-securing procedure. A follow-up CT scan was performed 7 ± 2, 14 ± 2 days, 1, and 3 months after SAH, and whenever neurological worsening occurred.

The images were assessed by 2 independent, blinded reviewers at the central office. The degree of SAH was assessed using CT scan performed on admission within 24 h of SAH. A new cerebral infarction considered to be due to cerebral vasospasm was evaluated using follow-up CT scan. In order to assess aVS, the diameters of 10 arterial segments of proximal cerebral arteries, which were the bilateral distal internal cerebral arteries, M1 and M2 segments of the middle cerebral artery, and A1 and A2 segments of the anterior cerebral artery, were measured on DSA, and aVS was evaluated by calculating the ratio of the narrowed vessel diameter on the follow-up images to the initial diameter on the baseline images. The severity of aVS was categorized into none or mild, 0–25% decrease in arterial diameter on the follow-up images; moderate, 25–50% decrease; and severe, over 50% decrease [19]. The occurrences of each category of aVS were evaluated, and intergroup differences in 3 categories were compared: aVS; moderate and severe aVS; and severe aVS.

The occurrence of sVS was defined as the development of new, focal neurological signs, deterioration in level of consciousness of at least 2 points on the Glasgow Coma Scale, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening had been excluded [20]. This was assessed by 2 independent, blinded site-investigators. Clinical outcomes were evaluated using the Glasgow Outcome Scale (GOS) at 3 months after SAH. Favorable outcome was defined as good recovery and moderate disability; poor outcome was defined as severe disability (SD), vegetative state (VS), and death (D). This was directly assessed by 2 independent, blinded reviewers at the central office.

Efficacy and Safety

The primary efficacy end point was the onset of sVS. The secondary end points were the onset of aVS, new cerebral infarctions related to cerebral vasospasm, and clinical outcome. All end points were analyzed with the intention-to-treat principle.

Any adverse events occurring during the period from the start of administration to 3 days after study treatment discontinuation were recorded. Adverse events of specific interest were cardiac complications, hemorrhagic complications, and liver damage.

Statistics

Intergroup differences were measured using the Student t test, Mann–Whitney U test, Pearson chi-square test, or Fisher exact probability test. A 2-sided probability value <0.05 was considered significant. When cilostazol use significantly affected any end point by univariate analysis, multivariate analyses were performed using logistic regression by including possible confounding factors. The factors with p value <0.2 or the factors reported to have an influence on any end point were selected as the possible confounding factors.

Results

Patient Population

A flow diagram according to the Consolidated Standards of Reporting Trials guideline is shown in figure 1. Between August 2010 and December 2013, 257 patients with aneurysmal SAH were admitted within 24 h after the ictus. Of these cases, 148 met both the inclusion criteria and consented to participate in this study. These 148 cases were randomized to receive either cilostazol or placebo.

Cilostazol was discontinued in 2 cases in the cilostazol group; one was due to liver damage, and the other was due to recurrent aneurysm formation just near the clipped aneurysm that was found at the follow-up DSA performed on day 9, followed by clipping it on day 10. In the placebo group, placebo was discontinued in 1 case, which was due to gastric hemorrhage. However, end-points analyses could be performed in all cases.

The patient profiles are shown in table 1. There were no statistically significant differences in the patient profiles between the groups.

Efficacy Assessment of Study End Points

The results of each study end point are shown in table 2.

sVS occurred in 8 cases (10.8%) in the cilostazol group, which was statistically and significantly less than 18 cases (24.3%) in the control group (p = 0.031). As the rescue therapy performed when sVS occurred, induced hypertension and endovascular infusion of vasodilator were performed in all of 26 cases, and additional balloon dilatation was performed in 6 cases.

Cerebral angiography was performed on day 9 ± 2 after SAH or at the time of sVS onset. In the cilostazol group, no or mild aVS, moderate aVS and severe aVS were seen in 28 cases (38%), 27 cases (36%), 19 cases (26%), respectively. In the control group, 19 cases (26%), 28 cases (38%), and 27 cases (36%) were seen, respectively. The

Table 1. Baseline characteristics of included subjects

	Cilostazol (n = 74)	Control (n = 74)	p value
Number of subjects	74	74	
Age, years	58±12	59±12	0.742
Women, n (%)	54 (73)	46 (62)	0.161
Hypertension, n (%)	34 (46)	33 (45)	0.868
Smoker, n (%)	27 (37)	31 (42)	0.501
Intraventricular hemorrhage, n (%)	6 (8)	8 (11)	0.574
Intracerebral hemorrhage, n (%)	6 (8)	9 (12)	0.414
Coiling, n (%)	13 (18)	9 (12	0.355
Hunt and Hess grade			0.984
Grade 1 or 2	42	43	
Grade 3	26	25	
Grade 4	6	6	
SAH on baseline CT scan			0.189
Thick local	4	8	
Thin diffuse	1	0	
Thick diffuse	69	66	
Aneurysm location			0.695
ACA	28	27	
ICA	19	25	
MCA	23	18	
VA/BA	4	4	
Rescue therapy			
Induced hypertension	8	18	0.031
Endovascular infusion of vasodilator	8	18	0.031
Balloon PTA	2	4	0.405

ACA = Anterior cerebral artery; ICA = internal cerebral artery; MCA = middle cerebral artery; VA = vertebral artery; BA = basilar artery; PTA = percutaneous transluminal angioplasty.

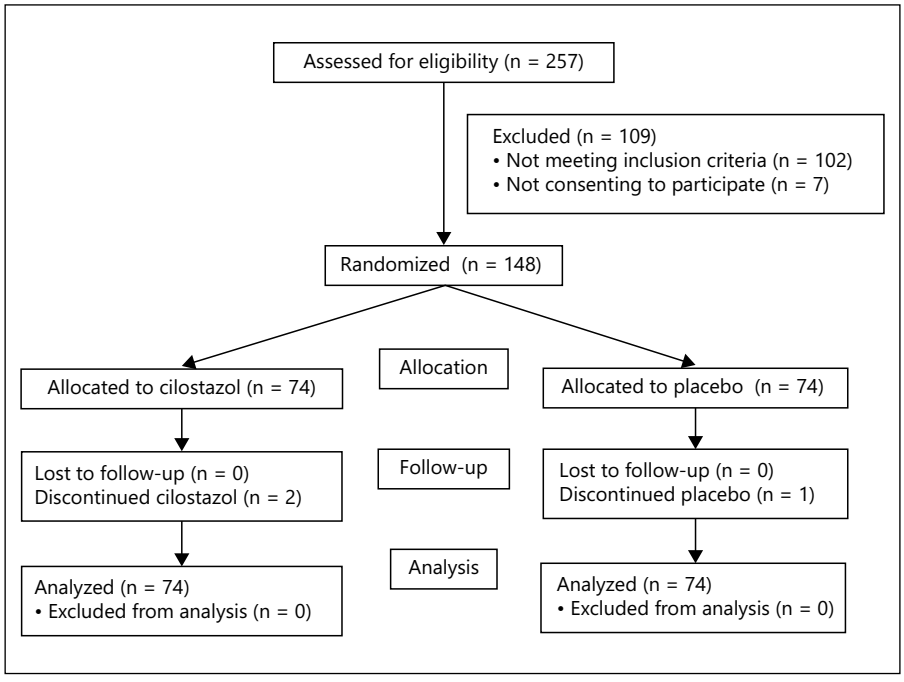

Fig. 1. Flow diagram of the trial patient recruitment according to the Consolidated Standards of Reporting Trials guideline.

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Table 2. Assessments of primary and secondary end points

	Cilostazol (n = 74), %	Control (n = 74), %	p value
sVS	8 (11)	18 (24)	0.031
aVS			
None or mild	28 (38)	19 (26)	0.112
Moderate	27 (36)	28 (38)	0.864
Severe	19 (26)	27 (36)	0.155
Cerebral infarction	4 (5)	8 (11)	0.228
Poor outcome	4 (5)	13 (18)	0.011

Table 3. Assessment of factors affecting sVS

sVS	Univariate analysis	p value	OR	95% CI
Cilostazol use	0.031	0.027	0.293	0.099–0.568
Hunt and Hess: grades 3–4	0.181	0.224	1.856	0.685–5.029
Age >65	0.108	0.585	1.332	0.475–3.732
SAH (diffuse, thick)	0.884	0.815	1.301	0.143–11.872
IVH	0.355	0.264	0.283	0.031–2.593
Clipping	0.135	0.085	0.317	0.086–1.172

cases with severe aVS were less in the cilostazol group than in the control group; however, there were no statistically significant intergroup differences for the 3 categories of aVS (p = 0.078), moderate and severe aVS (p = 0.112), and severe aVS (p = 0.155).

The new cerebral infarctions related to cerebral vasospasm on CT scan or MRI were seen in 4 cases (5.4%) in the cilostazol group and in 8 cases (10.8%) in the control group, which showed no statistically significant difference (p = 0.228). All of the new cerebral infarctions related to cerebral vasospasm were detected only by CT scan.

Outcome assessed using GOS at 3 months after SAH, and poor outcome consisting of SD, VS, and D were seen in 4 cases (5.4%) in the cilostazol group, which was statistically and significantly less than 13 cases (17.6%) in the control group (p = 0.020).

Therefore, univariate analyses revealed that cilostazol use statistically and significantly reduced the occurrence of sVS and the incidence of poor outcome. As the confounding factors for multivariate analysis of sVS, the factors reported to have an influence on sVS, such as thick and diffuse SAH [21, 22] and the presence of intraventricular hemorrhage (IVH) [21, 22] were selected in addition to the factors with p value <0.2 in univariate analyses. For multivariate analysis of poor outcome, all of the factors reported to have an influence on poor outcome, such as clinical grade [15], age [15, 23], IVH [24], intracerebral hemorrhage [24, 25], had p values <0.2 in univariate analyses and were included in the confounding factors. Multiple logistic analysis showed that cilostazol use was the only independent factor reducing the occurrence of sVS (OR 0.293, 95% CI 0.099–0.568, p = 0.027; table 3). Multiple logistic analysis also showed that cilostazol use was an independent factor that reduced the incidence of poor outcome (OR 0.221, 95% CI 0.054–0.903, p = 0.035) and Hunt and Hess grade 3 or 4 was an independent factor increasing the incidence of poor outcome (OR 5.721, 95% CI 1.367–23.946, p = 0.017; table 4).

Safety

Adverse events were seen in ten cases, both in the cilostazol group and in the control group (table 5). Hemorrhagic events were not seen in the cilostazol group. Hepatic enzyme increase was seen in 5 cases of the cilostazol group and in 6 cases of the control group, and discontinuance of cilostazol was required in 1 case followed by improved hepatic enzyme increase. Sinus tachycardia between 100 and 120 bpm was seen in 2 cases with cilostazol, which did not require the discontinuation of cilostazol and improved after the study period. The other adverse event, an aneurysm recurrence, was noticed on the follow-up DSA on day 9 of SAH, in 1 case in the cilostazol

Table 4. Assessment of factors affecting poor outcome

Poor outcome	Univariate analysis	p value	OR	95% CI
Cilostazol use	0.011	0.035	0.221	0.054–0.903
Hunt and Hess: grades 3–4	0.004	0.017	5.721	1.367–23.946
Age >65	0.116	0.392	1.729	0.493–6.064
IVH	0.035	0.849	0.782	0.062–9.901
ICH	0.022	0.388	2.718	0.281–26.301

ICH = Intracerebral hemorrhage.

Table 5. Adverse events

	Cilostazol (n = 74), %	Control (n = 74), %	p value
Hemorrhagic events			
Intracerebral hemorrhage	0 (0)	1 (1.4)	0.500
Epidural hemorrhage	0 (0)	1 (1.4)	0.500
Gastrointestinal events			
Rectal bleeding	0 (0)	1 (1.4)	0.500
Diarrhea	3 (4.1)	1 (1.4)	0.310
Hepatic enzyme increased	5 (6.8)	6 (8.1)	0.500
Cardiac events			
Sinus tachycardia	2 (2.7)	0 (0)	0.248
Heart failure	0 (0)	0 (0)	–
Overall events	10 (13.5)	10 (13.5)	0.595

group. However, during the second surgery, this was confirmed to have originated in a small, residual neck after the first aneurysmal neck clipping; it was judged not to be attributable to cilostazol.

Discussion

Three clinical studies [15–17] published in English investigated the preventative efficacy of cilostazol for cerebral vasospasm; 2 studies [15, 16] were RCT, and one study [17] was a case–control study. However, none of the 3 studies used double-blinded assessment. As an end point, sVS, vasospasm-related cerebral infarction and clinical outcome were evaluated in all 3 studies [15–17], and aVS was evaluated in 2 studies [16, 17]. Although systematic review [26] evaluated using these 3 studies revealed that all endpoints could be ameliorated by cilostazol use with statistical and significant differences, no clinical study showed uniform results concerning the efficacies of cilostazol on each endpoint. Therefore, we evaluated all 4 endpoints above under double-blind design.

First, regarding aVS, our study, in which modality and timing of examination were strictly uniform, did not show a significant reduction of aVS. Two previous studies [16, 17] showed that aVS was significantly reduced by cilostazol use, although multivariate analysis was not performed in one study [17] and modality of evaluation was not rendered uniform by using DSA or CT angiography in one study [16]. A systematic review including these 2 studies also demonstrated that overall relative risk of aVS was reduced to 0.48 (95% CI 0.28–0.82) by cilostazol use [26]. Further studies are necessary to determine the effect of cilostazol on aVS, while the mechanism of action of cilostazol on aVS has been considered to be attributable for the inhibition of PDE3, which increases intracellular cAMP and protein kinase A and is an isoform strongly expressed not only in platelets but also in vascular smooth muscle cells [27]. Normal, large cerebral arteries are suggested to be dilated by cilostazol administration, because the oral administration of cilostazol induces a significant decrease in flow velocity in the middle cerebral arteries in healthy participants, as measured by transcranial Doppler [28]. In addition to vasodilating capacity for normal arteries, experimental studies have re-

vealed that cilostazol has the potential to work against the pathogenesis of cerebral vasospasm: suppressing lipid peroxidation [9], reducing ROS [12], inducing NO production [14], preventing endothelial damage [7, 27, 28], and inhibiting vascular smooth muscle proliferation [7, 8]. These various actions may cause the amelioration of aVS.

Recent reports, however, have suggested that aVS does not always correlate with the occurrence of sVS and/or poor clinical outcome [29–31]. A systematic review investigating the effect of pharmaceutical treatment on vasospasm has also revealed that DCI and poor outcome are not improved by preventing aVS, which might be due to the existence of processes other than vasospasm, such as microthrombosis, microcirculatory dysfunction, and cortical spreading ischemia that contribute to DCI and outcome [6].

Therefore, the true value of pharmaceutical effects on cerebral vasospasm should be evaluated by an improvement in sVS and outcome. In our study, an interesting point was that amelioration of sVS and outcome were accomplished by cilostazol use in spite of failing to obtain statistically significant improvement of aVS. It suggested that the efficacy of cilostazol was based not only on an improvement in aVS but also on other mechanisms inducing DCI. Microthrombosis has been evaluated as a factor inducing DCI after SAH, both in the experimental studies [32–34] and in the human autopsy studies [35, 36]. Antiplatelet therapy, such as aspirin [37], dipyridamole [38], and OKY-046 [39]; a thromboxane synthesis inhibitor, have been tried, and systematic review revealed that antiplatelet drugs reduce the risk of DCI after SAH [40]. Therefore, the effect of cilostazol on sVS and outcome might be attributable to its antiplatelet effect and preventing micorothrombosis after SAH. In addition, constriction or increased contractility in the microcirculation after SAH have both been proved at the pial arterioles [32, 33, 41, 42] and at the intraparenchymal arterioles [43]. Cilostazol has been proved to have vasodilatory capacity not only for large cerebral arteries but also for cerebral microcirculatory vessels [44, 45]. Thus, cilostazol might prevent the constriction of microvessels after SAH, resulting in the amelioration of DCI. Therefore, cilostazol use could decrease sVS through its pleiotropic effects.

As an adverse effect of cilostazol, based on its mechanism of action, a hemorrhagic event is of the greatest concern. Hemorrhagic events were not seen in this study, but were seen in a few cases in the previous studies [15–17]. Recent clinical studies on the secondary prevention of ischemic stroke showed that cilostazol results in significantly fewer hemorrhagic events than aspirin [10]. And another systematic review investigating the effect of antiplatelet therapy for aneurysmal SAH showed no obvious side effects because of using antiplatelet agents including aspirin, ozagrel sodium, and ticlopidine [46]. Therefore, cilostazol is estimated to be safe for use in aneurysmal SAH patients for limited periods, such as 2 weeks.

There were several weaknesses and limitations to this study. We did not include patients aged over 80, those with local thin SAH, or those with severe clinical condition on admission. Thus, our results might not be applicable to all patients with SAH. Although recent clinical trials for improving outcome in severe SAH patients were reported [1, 2], cases with a severe clinical grade or those aged over 80 generally have less chance of undergoing aneurysm repair [23, 47], which makes administering cilostazol impossible because of its anti-platelet action and was the reason why these patients were excluded from this study. Also, those patients with local thin SAH were excluded, as was true in most previous studies investigating the efficacy of drugs for prevention of cerebral vasospasm in aneurysmal SAH, because cerebral vasospasm hardly occurs in those cases [21]. Cilostazol has fewer adverse effects than previously described, and the administration of cilostazol to elderly cases, cases with severe clinical grade, and cases with less SAH might be worthwhile. Also, cilostazol administration should have been initiated within 48 h after SAH in our study, and can also be the factor that limits generalizing this result to other cases. However, a recent report investigating the optimal timing of surgery for ruptured cerebral aneurysms indicated surgery within 48 h after SAH was related to a favorable outcome [48]. There is then the possibility that aneurysm repair within 48 h will be encouraged in the future, which will enable the initiation of drug administration within 48 h of SAH. All of the new cerebral infarctions related to cerebral vasospasm were diagnosed only by CT scan, since MRI was not performed in all cases. MRI is superior to CT scan in sensitivity to detect cerebral infarction. Therefore, the rate of cerebral infarctions related to cerebral vasospasm might be underestimated, which was also a limitation of this study. The other limitations of this study were that it consisted of fewer cases and included only Japanese people. A large-volume clinical study on the efficacy of cilostazol on SAH should also be performed in the future and, if possible, it should involve countries other than Japan.

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