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CLINICAL ARTICLE

Preventive effects of cilostazol against the development of shunt-dependent hydrocephalus after subarachnoid hemorrhage

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OBJECTIVE Chronic hydrocephalus develops in association with the induction of tenascin-C (TNC), a matricellular protein, after aneurysmal subarachnoid hemorrhage (SAH). The aim of this study was to examine if cilostazol, a selective inhibitor of phosphodiesterase Type III, suppresses the development of chronic hydrocephalus by inhibiting TNC induction in aneurysmal SAH patients.

METHODS The authors retrospectively reviewed the factors influencing the development of chronic shunt-dependent hydrocephalus in 87 patients with Fisher Grade 3 SAH using multivariate logistic regression analyses. Cilostazol (50 or 100 mg administered 2 or 3 times per day) was administered from the day following aneurysmal obliteration according to the preference of the attending neurosurgeon. As a separate study, the effects of different dosages of cilostazol on the serum TNC levels were chronologically examined from Days 1 to 12 in 38 SAH patients with Fisher Grade 3 SAH.

RESULTS Chronic hydrocephalus occurred in 12 of 36 (33.3%), 5 of 39 (12.8%), and 1 of 12 (8.3%) patients in the 0 mg/day, 100 to 200 mg/day, and 300 mg/day cilostazol groups, respectively. The multivariate analyses showed that older age (OR 1.10, 95% CI 1.13–1.24; p = 0.012), acute hydrocephalus (OR 23.28, 95% CI 1.75–729.83; p = 0.016), and cilostazol (OR 0.23, 95% CI 0.05–0.93; p = 0.038) independently affected the development of chronic hydrocephalus. Higher dosages of cilostazol more effectively suppressed the serum TNC levels through Days 1 to 12 post-SAH.

CONCLUSIONS Cilostazol may prevent the development of chronic hydrocephalus and reduce shunt surgery, possibly by the inhibition of TNC induction after SAH.

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KEY WORDS cilostazol; hydrocephalus; subarachnoid hemorrhage; tenascin-C; vascular disorders

Chronic shunt-dependent hydrocephalus occurs in 8.9% to 48% of patients with aneurysmal subarachnoid hemorrhage (SAH).[6] Post-SAH chronic hydrocephalus is frequently associated with poor neurological outcomes, which are not completely reversed after CSF shunting.[38] A number of retrospective studies have identified factors that are predictive of SAH-associated shunt-dependent chronic hydrocephalus.[6] Fenestration of the lamina terminalis during clipping surgery has been suggested to reduce the incidence of shunt-dependent chronic hydrocephalus, but the effects are conflicting.[6] As far as we know, there are no established treatments that prevent post-SAH chronic hydrocephalus.

The etiology of post-SAH chronic hydrocephalus is still uncertain, but it is most plausible that post-SAH inflammatory reactions or blood-clotting products trigger the proliferation of arachnoid cells and leptomeningeal fibrosis, which impair CSF circulation and/or reabsorption through the arachnoid villi and/or other routes, thereby causing chronic hydrocephalus.[3,20,27] A previous study reported the possible involvement of tenascin-C (TNC), a matricellular protein, in the development of post-SAH

ABBREVIATIONS cAMP = cyclic adenosine monophosphate; IL = interleukin; MAPK = mitogen-activated protein kinase; PDGF = platelet-derived growth factor; pSEED = Prospective Registry for Searching Mediators of Neurovascular Events After Aneurysmal Subarachnoid Hemorrhage; SAH = subarachnoid hemorrhage; TGF = transforming growth factor; TNC = tenascin-C; TNF = tumor necrosis factor; WFNS = World Federation of Neurosurgical Societies.

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chronic hydrocephalus.[32] TNC is induced by inflammation and promotes cell proliferation and fibrosis.[5,15] TNC was reported to be induced in the serum and CSF after aneurysmal SAH.[30,31] In a clinical setting, higher TNC levels in the CSF were observed in SAH patients with worse neurological grades on admission, more massive hemorrhage on CT, symptomatic vasospasm, and worse outcomes, in addition to chronic hydrocephalus, while patient age did not affect TNC levels.[30,32] TNC also caused brain injuries after experimental SAH.[12,29]

Cilostazol—a selective inhibitor of phosphodiesterase Type III and a cyclic adenosine monophosphate (cAMP)–elevating agent—is a clinically available antiplatelet agent and has pleiotropic actions, including vasodilatory and antiinflammatory effects.[25] It has been suggested that cilostazol reduces symptomatic vasospasm and is relatively widely administered to SAH patients in Japan.[28] Cilostazol has also been reported to inhibit TNC induction in cultured vascular smooth muscle cells.[13] Therefore, we speculated that cilostazol might prevent the occurrence of chronic hydrocephalus by inhibiting TNC induction after SAH. Thus, the goal of this study was to evaluate if the administration of cilostazol is a suppressing factor against the occurrence of chronic shunt-dependent hydrocephalus and if oral cilostazol inhibits serum TNC induction after aneurysmal SAH.

Methods

Retrospective Study to Determine Factors Related to Shunt-Dependent Hydrocephalus After SAH

This study was approved by the ethics committee at our institution. We reviewed the medical records of 153 SAH patients who were admitted to our hospital between January 2007 and January 2015. All neuroimages were reassessed using the Fisher scale,[11] and rebleeding, the development of cerebral infarction, and other clinical variables were assessed by an experienced neurosurgeon (F.K.) who was unaware of other clinical data. As a result, 87 patients met the following inclusion criteria: ≥ 20 years of age at onset, SAH classified as Fisher Grade 3 on admission CT scans,[11] saccular aneurysm as the cause of SAH confirmed on digital subtraction angiography, aneurysmal obliteration by clipping or coiling performed within 14 days of onset, and survival of more than 14 days after onset. Patients with dissecting, traumatic, mycotic, and arteriovenous malformation–related aneurysms or SAH of an unknown etiology were excluded from the study. After angiographic confirmation of the aneurysm, surgical clipping or endovascular coiling of the lesion was performed as deemed appropriate for the individual patient by the attending neurosurgeon. A ventricular catheter was placed in all patients with ventriculomegaly and a decreased level of consciousness that could not be attributed to causes other than acute hydrocephalus at admission. In other cases, according to the preference of the attending neurosurgeons, a ventricular drain was placed to control brain swelling, and a cisternal drain was placed in the basal cistern to promote SAH clearance after surgical clipping. If progressive ventriculomegaly was observed postoperatively and within 14 days of onset, a lumbar spinal drain was placed irrespective of clipping or coiling. Drainage was continued for 7 to 14 days, and the volume of drained CSF was maintained at 150 to 250 ml/day by changing the height of the drainage siphon. All patients without renal dysfunction received intravenous fasudil hydrochloride (30 mg administered twice per day; Asahi Kasei Pharma Co.) from Day 1 postclipping or postcoiling to Day 14 posthemorrhage. In addition, oral or enteral cilostazol (50 or 100 mg administered 2 or 3 times per day; i.e., 100, 150, 200, or 300 mg/day; Otsuka Pharmaceutical Co.) was administered from Day 1 postclipping or postcoiling to Day 14 posthemorrhage or later according to the preference of the attending neurosurgeons. For at least 14 days after SAH, patients were managed in the intensive care unit, vital signs and laboratory data were assessed, and antibiotics were administered while the CSF drain was in place in order to maintain normovolemia; prevent meningitis, pneumonia, and hypoxia; and correct anemia and hypoproteinemia. All patients with symptomatic vasospasm—as defined as otherwise unexplained clinical deterioration (i.e., a new focal deficit, a decrease in the level of consciousness, or both), a new cerebral infarction (delayed cerebral infarction) on CT that was not visible on the admission or immediate postoperative scan, or both—were treated with hypertensive hypervolemic therapy and/or endovascular therapy (intraarterial fasudil hydrochloride infusions or angioplasty). Other potential causes of clinical deterioration, such as hydrocephalus, rebleeding, or seizures, were rigorously excluded. Chronic hydrocephalus was diagnosed when clinical deterioration with no detectable causes other than hydrocephalus occurred after Day 14 posthemorrhage and when the ventricular size progressively increased and the Evans Index became greater than 0.30.[35] Chronic hydrocephalus was treated with ventriculoperitoneal shunting. Clinical outcome was evaluated using the modified Rankin Scale at discharge. Clinical variables—including age, sex, World Federation of Neurosurgical Societies (WFNS) grade at admission and before any treatment,[8] the modality used for aneurysmal obliteration, location of the ruptured aneurysm, acute hydrocephalus requiring ventricular drainage at admission, placement of lumbar drainage catheters the day after aneurysmal obliteration (or later), placement of other CSF drains, cilostazol administration, and the presence of symptomatic vasospasm, delayed cerebral infarction, and shunt-dependent hydrocephalus—were recorded, and factors influencing the development of shunt-dependent hydrocephalus were determined using univariate and multivariate analyses.

Prospective Study to Determine if Cilostazol Suppresses Serum TNC Levels After SAH

After searching for mediators of neurovascular events following aneurysmal SAH, we identified 90 patients registered in the Prospective Registry for Searching Mediators of Neurovascular Events After Aneurysmal Subarachnoid Hemorrhage (pSEED) who were treated at 9 tertiary referral centers in the Mie prefecture in Japan (*Appendix*) between September 2013 and October 2014. The inclusion criteria were as follows: ≥ 20 years of age at onset, SAH identified on CT scans or lumbar puncture, saccular aneurysm as the cause of SAH and confirmed on

digital subtraction angiography, and aneurysmal obliteration by clipping or coiling within 48 hours of onset. The timing of aneurysmal obliteration, selection of clipping or coiling, and other medical management or treatment strategies were decided by the onsite investigators and not limited. After written informed consent was obtained, clinical variables were recorded as in the retrospective study. After CT confirmation of no complications occurring the day after clipping or coiling, blood samples were serially collected with minimal stasis from a vein on Days 1 to 3, Days 4 to 6, Days 7 to 9, and Days 10 to 12 after onset. All samples were centrifuged for 5 minutes at 3000*g*, and the supernatant fluid was stored at –30°C until assayed. Among these patients, 38 were selected for the study because they had SAH of Fisher Grade 3 status at admission and survived for more than 14 days post-SAH with neither angiographic complications and surgical complications nor concomitant inflammatory, malignant, and other diseases that are known to upregulate TNC.[5,30–32] The serum TNC concentrations were determined using a commercially available enzyme-linked immunosorbent assay kit for high-molecular-weight human TNC variants (code no. 27767; IBL).

Statistical Analysis

There were no missing data in the patients who met the inclusion criteria in both the retrospective and prospective studies. Variables were recorded as categorical or continuous variables. Categorical variables were reported as the number and percentage and analyzed using the chi-square or Fisher exact test, as appropriate. Continuous variables were reported as the mean ± standard deviation and compared between 2 groups using the unpaired t-test. If significant variance was found, intergroup comparisons among 3 groups were determined by 1-way ANOVA and then the Tukey-Kramer multiple comparison procedure (95% CI). The impact of each variable on the development of shunt-dependent hydrocephalus was determined by multivariate unconditional logistic regression analysis using shunt-dependent hydrocephalus (presence or absence) as the dependent variable. All variables were considered independent variables irrespective of significance in the univariate analysis, although only the variable with the smallest probability value was used as a candidate variable among similar clinical variables that were intercorrelated. The adjusted ORs with 95% CIs were calculated, and the independence of the variables was tested using the likelihood ratio test on reduced models. A p value ≤ 0.05 was considered significant.

Results

Factors Related to Shunt-Dependent Hydrocephalus After SAH

Of the 87 patients (mean age 63.6 ± 12.9 years), 63 patients were female and 24 patients were male. Eighteen patients underwent ventriculoperitoneal shunting at 36.7 ± 18.2 days after SAH. There were no significant differences between the shunt-treated and non–shunt-treated groups in terms of patient sex, WFNS grade on admission, aneurysm location, and treatment modality. The univariate analyses showed that older age, acute hydrocephalus, CSF drainage, symptomatic vasospasm, and no cilostazol use were significant factors for the development of shunt-dependent hydrocephalus (Table 1). Head CT findings were assessed before clipping or coiling, at 12 to 24 hours after clipping or coiling, and on Days 3 to 4, Days 7 to 10, and Days 14 to 21 in all patients, which revealed that delayed cerebral infarction occurred in 6 of 18 shunt-treated patients (33.3%) and 12 of 69 non–shunt-treated patients (17.4%), but the difference did not reach statistical significance (Table 1). A cisternal drain was placed at the time of clipping in 3 patients, 2 of whom were treated with 0 or 200 mg/day cilostazol and did not undergo eventual shunting, while the other patient was treated with 100 mg/day cilostazol and underwent shunting. Shunt-dependent hydrocephalus was associated with worse outcomes.

Multivariate analyses were performed using all of the variables listed in Table 1 (except the use of CSF drains, most of which were placed to treat delayed progressive ventriculomegaly and therefore highly correlated with the development of shunt-dependent hydrocephalus and the modified Rankin Scale at discharge), although only the variable with the smallest probability value was used as a candidate variable among similar and intercorrelated clinical variables. The multivariate analyses revealed that older age (OR 1.10, 95% CI 1.13–1.24; p = 0.012) and acute hydrocephalus (OR 23.28, 95% CI 1.75–729.83; p = 0.016) were independent predictive factors for the development of shunt-dependent hydrocephalus, while cilostazol (OR 0.23, 95% CI 0.05–0.93; p = 0.038) independently suppressed it.

Regarding the cilostazol dosage, 12 of 36 patients (33.3%) treated with no cilostazol eventually needed shunting, while the 100 to 200 mg/day and 300 mg/day cilostazol groups required less shunting (5 of 39 patients [12.8%] in the 100–200 mg/day cilostazol group, and 1 of 12 patients [8.3%] in the 300 mg/day cilostazol group). The incidence of shunt-dependent hydrocephalus was significantly lower in patients treated with cilostazol than patients treated without cilostazol (Fig. 1). There were no significant differences in the clinical features among the patients treated with different cilostazol doses, except for the incidence of shunt-dependent hydrocephalus (Table 2). Adverse events due to cilostazol occurred in 2 patients in the 200 mg/day cilostazol group: in 1 patient, the dose of cilostazol was reduced to 100 mg/day due to headache, and in the other patient cilostazol was discontinued on Day 2 post-SAH due to severe headache. Tachycardia or hemorrhagic complications affecting cilostazol usage did not occur.

Effects of Cilostazol on Serum TNC Levels After SAH

Of 38 patients studied prospectively, 5 patients were treated without cilostazol, 23 patients were treated with 100 to 200 mg/day cilostazol, and 10 patients were treated with 300 mg/day cilostazol. There were no adverse events such as headache, tachycardia, or hemorrhagic complications that affected cilostazol usage. The 300 mg/day cilostazol group underwent endovascular coiling of aneurysms most frequently, but the other clinical features were not significantly different among the 3 groups (Table 3). The inci-

TABLE 1. Clinical features in patients with and without shunt-dependent hydrocephalus after SAH*

Variable	Total	w/o Hydrocephalus	w/ Hydrocephalus	p Value†
No. of patients	87	69	18	
Mean age ± SD, yrs	63.6 ± 12.9	61.7 ± 12.9	70.6 ± 10.7	0.010
Sex				0.568
Female	63 (72.4)	49 (71.0)	14 (77.8)	
Male	24 (27.6)	20 (29.0)	4 (22.2)	
Admission WFNS grade				0.137
I–III	52 (59.8)	44 (63.8)	8 (44.4)	
IV–V	35 (40.2)	25 (36.2)	10 (55.6)	
Aneurysm location				0.980
ACoA	27 (31.0)	21 (30.4)	6 (33.3)	
ICA	32 (36.8)	26 (37.7)	6 (33.3)	
MCA	15 (17.2)	11 (15.9)	4 (22.2)	
Posterior circulation	5 (5.7)	5 (7.2)	0 (0)	
Other	8 (9.2)	6 (8.7)	2 (11.1)	
Treatment modality				0.120
Endovascular coiling	57 (65.5)	48 (69.6)	9 (50.0)	
Surgical clipping	30 (34.5)	21 (30.4)	9 (50.0)	
Acute hydrocephalus	6 (6.9)	2 (2.9)	4 (22.2)	0.004
CSF drainage	20 (23.0)	9 (13.0)	11 (61.1)	<0.0001
Lumbar drainage	12 (13.8)	4 (5.8)	8 (44.4)	<0.0001
Other drainage	9 (10.3)	5 (7.2)	4 (22.2)	0.063
Symptomatic vasospasm	23 (26.4)	14 (20.3)	9 (50.0)	0.011
Delayed cerebral infarct	18 (20.7)	12 (17.4)	6 (33.3)	0.137
Cilostazol	51 (58.6)	45 (65.2)	6 (33.3)	0.014
mRS Score 0–2 at discharge	49 (56.3)	47 (68.1)	2 (11.1)	<0.0001

ACoA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale.
* Data are presented as the number of patients (%) unless stated otherwise.
† The unpaired t-test, chi-square test, or Fisher exact test was used to compare patients with and without shunt-dependent hydrocephalus.

dence of shunt-dependent hydrocephalus was lower in the 300 mg/day cilostazol group (1 of 10 patients; 10.0%) compared with the 0 mg/day (2 of 5 patients; 40.0%) and 100 to 200 mg/day cilostazol groups (8 of 23 patients; 34.8%), but the difference did not reach statistical significance due to the limited number of patients. The administration of 300 mg/day cilostazol significantly decreased the serum TNC levels compared with the 0 mg/day and 100 to 200 mg/day cilostazol groups through Days 1 to 12 (Fig. 2), irrespective of WFNS grade on admission (Table 4).

Discussion

This is the first study to demonstrate that the administration of cilostazol is an independent factor that reduces the development of chronic shunt-dependent hydrocephalus after SAH. In addition, a higher dosage of cilostazol suppressed the serum TNC levels more. These results suggest that cilostazol would be the first treatment to prevent chronic shunt-dependent hydrocephalus, possibly by suppressing TNC induction.

The key mechanisms that disrupt CSF homeostasis and the leptomeninges (the arachnoid mater and pia mater) forming the subarachnoid space may be mediated by an inflammatory reaction and blood-clotting products. A rap-

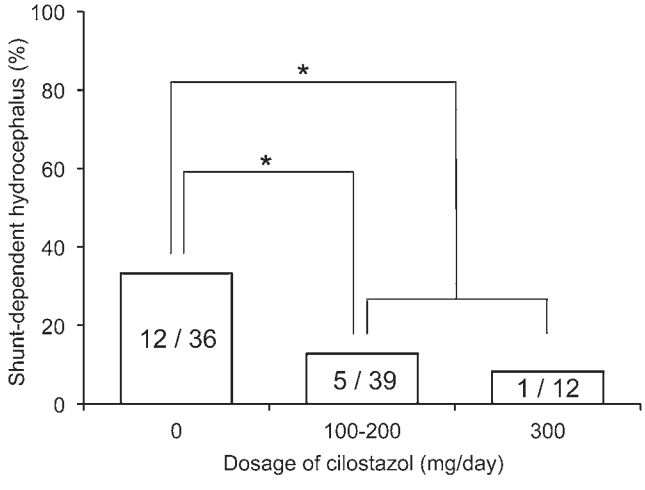

FIG. 1. The incidence of shunt-dependent hydrocephalus among patients treated with 0 mg/day, 100 to 200 mg/day, and 300 mg/day cilostazol. The numbers depicted in the bar express the number of shunt-treated patients divided by the total number of patients in the group. Cilostazol usage significantly decreases the incidence of shunt-dependent hydrocephalus. *p < 0.05, Fisher exact test.

TABLE 2. Clinical features in SAH patients treated with different cilostazol doses in the retrospective study*

Variable	Cilostazol Dose (mg/day)		
	0	100–200	300
No. of patients	36	39	12
Mean age ± SD, yrs	65.6 ± 13.3	61.1 ± 12.9	65.4 ± 10.4
Sex			
Female	24 (66.7)	30 (76.9)	9 (75.0)
Male	12 (33.3)	9 (23.1)	3 (25.0)
Admission WFNS grade			
I–III	20 (55.6)	24 (61.5)	8 (66.7)
IV–V	16 (44.4)	15 (38.5)	4 (33.3)
Aneurysm location			
ACoA	10 (27.8)	11 (28.2)	6 (50.0)
ICA	16 (44.4)	13 (33.3)	3 (25.0)
MCA	5 (13.9)	9 (23.1)	1 (8.3)
Posterior circulation	1 (2.8)	3 (7.7)	1 (8.3)
Other	4 (11.1)	3 (7.7)	1 (8.3)
Treatment modality			
Endovascular coiling	22 (61.1)	26 (66.7)	9 (75.0)
Surgical clipping	14 (38.9)	13 (33.3)	3 (25.0)
Acute hydrocephalus	3 (8.3)	2 (5.1)	1 (8.3)
CSF drainage	12 (33.3)	6 (15.4)	2 (16.7)
Lumbar drainage	7 (19.4)	3 (7.7)	2 (16.7)
Other drainage	6 (16.7)	3 (7.7)	0 (0)
Symptomatic vasospasm	12 (33.3)	9 (23.1)	2 (16.7)
Delayed cerebral infarction	10 (27.8)	7 (17.9)	1 (8.3)
Shunt-dependent hydrocephalus	12 (33.3)	5 (12.8)†	1 (8.3)
mRS score 0–2 at discharge	17 (47.2)	24 (61.5)	8 (66.7)

* Data are presented as the number of patients (%) unless stated otherwise.
† $p < 0.05$ versus the 0 mg/day cilostazol group according to the Fisher exact test.

TABLE 3. Clinical features in SAH patients treated with different cilostazol doses in the prospective registry study*

Variable	Cilostazol Dose (mg/day)		
	0	100–200	300
No. of patients	5	23	10
Mean age ± SD, yrs	51.6 ± 8.1	65.5 ± 14.4	64.1 ± 12.3
Sex			
Female	3 (60.0)	10 (43.5)	7 (70.0)
Male	2 (40.0)	13 (56.5)	3 (30.0)
Admission WFNS grade			
I–III	4 (80.0)	11 (47.8)	7 (70.0)
IV–V	1 (20.0)	12 (52.2)	3 (30.0)
Aneurysm location			
ACoA	2 (40.0)	5 (21.7)	4 (40.0)
ICA	1 (20.0)	11 (47.8)	3 (30.0)
MCA	1 (20.0)	3 (13.0)	1 (10.0)
Posterior circulation	1 (20.0)	3 (13.0)	2 (20.0)
Other	0 (0)	1 (4.3)	0 (0)
Treatment modality			
Endovascular coiling	1 (20.0)	1 (4.3)	8 (80.0)†‡
Surgical clipping	4 (80.0)	22 (95.7)	2 (20.0)
Acute hydrocephalus	1 (20.0)	13 (56.5)	3 (30.0)
CSF drainage	1 (20.0)	8 (34.8)	2 (20.0)
Lumbar drainage	0 (0)	5 (21.7)	2 (20.0)
Other drainage	1 (20.0)	4 (17.4)	0 (0)
Symptomatic vasospasm	2 (40.0)	4 (17.4)	0 (0)
Delayed cerebral infarction	1 (20.0)	3 (13.0)	0 (0)
Shunt-dependent hydrocephalus	2 (40.0)	8 (34.8)	1 (10.0)
mRS score 0–2 at discharge	3 (60.0)	6 (26.1)	6 (60.0)

* Data are presented as the number of patients (%) unless stated otherwise.
† $p < 0.0001$ versus the 100 to 200 mg/day cilostazol group.
‡ $p < 0.05$ versus the 0 mg/day cilostazol group according to the Fisher exact test.

id inflammatory cell response occurs in the leptomeninges after SAH, with polymorphonuclear cells dominating during the first 24 hours and mononuclear cells thereafter.[26,33] These inflammatory cells secrete cytokines that trigger a fibroproliferative reaction by acting as mitogens and chemoattractants for fibroblasts.[17,18] Reportedly, inflammatory cytokines and growth factors such as tumor necrosis factor (TNF)–α, interleukin (IL)-1, IL-6, platelet-derived growth factor (PDGF), and transforming growth factor (TGF)–β are upregulated in the acute stage of SAH.[2,9,19,21,40] Thrombin is also released by the blood-clotting cascade in the CSF of patients with SAH.[34] Thrombin, TGFβ, and PDGF promoted human leptomeningeal cell proliferation in vitro,[23] and hydrocephalus developed in mice after an intracerebral injection of TGFβ,[36] a potent fibrogenic cytokine. CSF studies in humans have suggested that leptomeningeal collagen synthesis was induced within the first 48 to 72 hours after SAH.[27] Autopsy studies have shown blood and inflammatory cell accumulation within the arachnoid villi during the 1st week, greater mitotic activity and the proliferation of leptomeningeal cells during the 2nd and 3rd weeks, and dense collagen fibers in the subarachnoid space in the 4th week after SAH.[20,22] Impaired CSF circulation and the occlusion of CSF drainage channels by cell proliferation and collagen deposits may cause chronic shunt-dependent hydrocephalus, but the initial reactions are induced acutely after SAH. In this study, cilostazol was administered from the day following aneurysmal obliteration, usually within 48 to 72 hours after onset, to Day 14 post-SAH or later. The administration timing and period of cilostazol use may be reasonable to prevent chronic hydrocephalus, but further studies are needed to determine the optimal protocol, including the dosage of cilostazol and the timing and period of administration.

The expression of TNC is extremely limited in normal adult tissues, but is spatiotemporally upregulated by various pro- and antiinflammatory cytokines,[5,13] including TNFα, IL-1, PDGF, and TGFβ, which are upregulated after SAH.[2,9,19,40] Since TNC is reported to regulate the cell phenotype and promote the migration and proliferation of

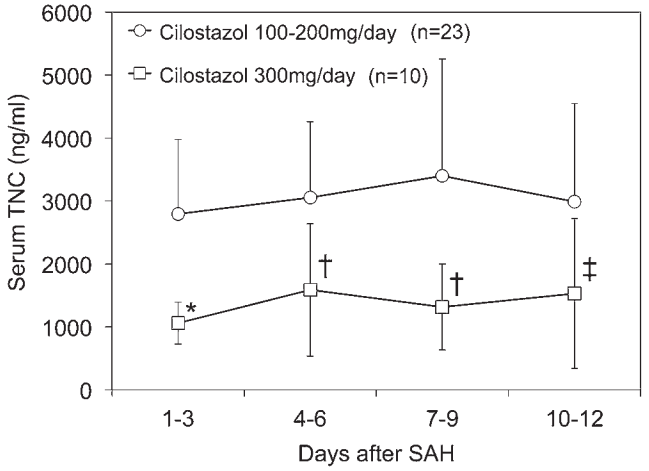

FIG. 2. Serum TNC concentrations after cilostazol treatment. Data represent the mean ± standard deviation. Serum TNC concentrations are significantly lower in the 300 mg/day cilostazol group than in the 100 to 200 mg/day cilostazol group. *$p < 0.0005$, †$p < 0.005$, and ‡$p < 0.05$ according to the unpaired t-test.

myofibroblasts, TNC induction may cause the proliferation of the leptomeningeal cells observed after SAH.[5,37] TNC also promotes tissue fibrosis by increasing Type I and III collagen synthesis,[10] and the synergistic effects of TNC and TGFβ—one of the most potent profibrogenic substances—have been reported.[16] Leptomeningeal cells may therefore become more activated and induce more massive fibrosis in an environment that is rich in TNC. Our previous study demonstrated that SAH patients who eventually needed ventriculoperitoneal shunting had significantly higher TNC levels in their CSF than patients who did not require shunting.[32] Higher TNC levels in the CSF were also associated with a worse WFNS grade on admission, symptomatic vasospasm, and worse outcomes, but the treatment modality (clipping or coiling) did not affect the TNC levels.[30] The highest increase in the CSF concentration of TNC was in the first 3 days, which is consistent with a CSF study in humans that suggested that leptomeningeal collagen synthesis was induced within the first 48 to 72 hours after SAH.[27] TNC might be an important substance that mediates post-SAH inflammation and leptomeningeal fibrosis, leading to the development of post-SAH chronic hydrocephalus. This study suggested that cilostazol prevented chronic shunt-dependent hydrocephalus, and the effect was greater with a higher dosage of cilostazol and associated with suppressed serum TNC levels through Days 1 to 12 post-SAH. In a prospective registry study, although cerebral aneurysms in the 300 mg/day cilostazol group were most frequently treated with endovascular coiling, endovascular treatment might not affect TNC levels as our previous study suggested.[30] Cilostazol is reported to inhibit the proliferation of cultured vascular smooth muscle cells in a concentration-dependent manner: an increase in cilostazol concentration from 100 to 200 μM suppressed the proliferation to one-tenth.[39] A multicenter, randomized, double-blind, placebo-controlled trial also showed that 100 to 200 mg/day cilostazol produces a dose-dependent improvement in the treadmill walking distance in patients with intermittent claudication.[1] In addition, a Phase I study showed that a single administration of 25 to 300 mg cilostazol dependently increased the blood concentration dose, which peaked after 3 to 4 hours and declined with half-lives of 2.6 to 3.2 hours.[24] These findings support our result that 300 mg/day cilostazol (100 mg cilostazol administered 3 times per day) suppressed the TNC levels more effectively compared with 100 to 200 mg/day cilostazol.

TNC has been reported to cause brain injuries such as neuronal apoptosis and blood–brain barrier disruption after experimental SAH.[12,29] Such brain injuries may decrease brain parenchymal volume and contribute to ventriculomegaly with time, thereby explaining why the poor neurological status and cognitive deficits associated with chronic hydrocephalus may not be completely reversed after CSF shunting. This study also showed that most patients with chronic hydrocephalus had a poor neurological status even after CSF shunting. It will be meaningful to examine if cilostazol can inhibit brain TNC induction and therefore directly suppress brain injury after SAH.

Some Japanese neurosurgeons administer cilostazol—a selective inhibitor of phosphodiesterase Type III and a cAMP-elevating agent—to prevent cerebral vasospasm in SAH patients.[28] However, in this study, cilostazol reduced the incidence of chronic shunt-dependent hydrocephalus independent of vasospasm occurrence, possibly by the inhibitory effects on TNC induction. Reportedly, cilostazol completely inhibited TNC induction by PDGF-BB at the transcriptional level in cultured vascular smooth muscle cells.[13] It has been shown that the cAMP–protein kinase

TABLE 4. Serum TNC levels in SAH patients treated with different cilostazol doses in the prospective registry study*

Variable	Cilostazol Dose (mg/day)		
	0	100–200	300
All cases	2618 ± 1230	3154 ± 1494	1373 ± 904†‡
No. of patients	5	23	10
Admission WFNS Grade I–III	2318 ± 997	2850 ± 1156	1572 ± 1000†‡
No. of patients	4	11	7
Admission WFNS Grade IV–V	3820 ± 1336	3433 ± 1701	908 ± 292†‡
No. of patients	1	12	3

* Data are presented as the mean ± SD unless stated otherwise. TNC was measured 4 times chronologically on Days 1 to 12 per patient.
† $p < 0.005$ versus the 100 to 200 mg/day cilostazol group.
‡ $p < 0.05$ versus the 0 mg/day cilostazol group according to 1-way analysis of variance.

A signaling pathway inhibits the transmission of Ras signals from the plasma membrane by preventing the Ras-dependent activation of Raf-1, resulting in the inhibition of mitogen-activated protein kinase (MAPK) activation.[7,14] MAPK is involved in the induction of TNC,[4] and thus cilostazol may have inhibitory effects on TNC expression through the cAMP–protein kinase A signaling pathway and its inhibitory effect on the downstream MAPK pathway. However, since cilostazol has pleiotropic actions such as antiinflammatory effects,[25] we cannot exclude the possibility that cilostazol prevents chronic shunt-dependent hydrocephalus via TNC-unrelated mechanisms.

This study has some limitations. First, the use of cilostazol and its dosages were administered according to physician preference, and therefore there is a concern as to selection bias, although the multivariate analyses showed that cilostazol use was an independent suppressing factor for shunt-dependent hydrocephalus in this study. Second, the numbers of patients who received each different cilostazol dose were small. Third, the diagnosis of chronic hydrocephalus and the decision to shunt were somewhat subjective, and blind evaluation is needed to avoid these issues. To confirm the findings of this study, a large-scale, double-blind, randomized control trial is needed. Lastly, this is a descriptive study. Basic research is also needed to determine the pathophysiological relationships between TNC and chronic hydrocephalus.

Conclusions

The present study is the first to show the finding that cilostazol can reduce chronic shunt-dependent hydrocephalus after aneurysmal SAH, possibly by suppressing TNC induction. Cilostazol could be a novel therapeutic approach to prevent chronic hydrocephalus after SAH.

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Appendix

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Disclosures

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

Author Contributions

Conception and design: Suzuki. Acquisition of data: all authors. Analysis and interpretation of data: Suzuki, Nakatsuka, Kawakita, Toma, Sakaida. Drafting the article: Suzuki, Nakatsuka. Critically revising the article: Suzuki, Nakatsuka, Toma, Sakaida. Reviewed submitted version of manuscript: Suzuki, Nakatsuka, Yasuda, Umeda, Toma, Sakaida. Approved the final version of the manuscript on behalf of all authors: Suzuki. Statistical analysis: Suzuki, Nakatsuka. Administrative/technical/material support: Suzuki, Sakaida. Study supervision: Suzuki, Kawakita, Yasuda, Umeda, Sakaida.

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