

Clinical Presentation, Treatment, and Outcome of Nontraumatic Subarachnoid Hemorrhage in Patients with Preceding Antithrombotic Therapy

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Abstract

With the aging of the population, the number of people taking antithrombotic drugs is increasing. Few reports have described the clinical presentation, treatment, and outcomes of nontraumatic subarachnoid hemorrhage (SAH) in patients with preceding antithrombotic therapy. This study included 459 patients with nontraumatic SAH who had been treated between April 2009 and May 2021. Overall, 39 of the 459 patients with aneurysmal SAH were on antithrombotic therapy before ictus (8.5%). Therefore, we classified patients into two groups: Group A (n = 39), patients with preceding antithrombotic therapy and Group B (n = 420), patients without preceding antithrombotic therapy. Hunt and Kosnik (H&K) grade on admission was significantly higher in Group A than in Group B (p = 0.02). Patients in Group A more frequently received endovascular treatment. The rate of endovascular therapy for symptomatic vasospasm after SAH was significantly lower in Group A (2.6%) than in Group B (15.5%; p = 0.03). The outcomes at 3 months after onset were significantly poorer in Group A patients than in Group B patients (p = 0.03). Patients with preceding antithrombotic drugs tended to be at greater risk of unfavorable outcomes, but this difference was not significant in the univariate analysis. In the multivariate analysis, patient age, H&K grade ≥ 4 , and subdural hematoma remained as risk factors for poor outcomes; however, preceding use of antithrombotic drugs was not a significant risk factor.

Keywords: subarachnoid hemorrhage, treatment, outcome, antithrombotic therapy

Introduction

The influence of antithrombotic drugs on the risk of subarachnoid hemorrhage (SAH) has not been systematically studied, although these are widely used in the secondary prevention of thromboembolic diseases.¹⁾ Recent population-based studies have reported contradictory findings regarding the association between antithrombotic therapy and SAH risk.¹⁻⁶⁾ Garbe et al. reported that antiplatelet drugs and warfarin were associated with a small but significantly increased risk of SAH.⁷⁾ Conversely, a Northern Danish study did not report an increased risk of SAH for anticoagulant use.⁸⁾

Establishing the guidelines for proper management of SAH risk is of interest from both clinical and public health perspectives. Therefore, the present study was conducted to assess the influence of antithrombotic drugs on outcomes for patients with nontraumatic SAH.

Materials and Methods

This study included 458 patients with nontraumatic SAH who had been treated in the Department of Neurosurgery at Kawasaki Medical School Hospital between April 2009 and May 2021. One patient was admitted twice because of different aneurysmal ruptures; thus, 459 SAHs

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were evaluated in this study.

Overall, 39 of 459 patients suffering from nontraumatic SAH were on antithrombotic therapy before ictus (8.5%). Therefore, we classified patients into two groups: Group A (n = 39), comprising patients with preceding antithrombotic drugs and Group B (n = 420), comprising patients without preceding antithrombotic drugs.

Patients were initially assessed via computed tomography (CT) to diagnose SAH. All patients were consecutively assessed using conventional digital subtraction angiography or three-dimensional computed tomographic angiography to diagnose the location of the aneurysm.

The baseline conditions of patients were defined as follows. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive agents. Diabetes mellitus (DM) was defined as glycosylated hemoglobin A1c $> 6.5\%$ or the use of hypoglycemic agents. Hyperlipidemia was defined as low-density lipoprotein-cholesterol > 140 mg/dL or the use of antihyperlipidemic agents. Ischemic heart disease (IHD) was defined as a history of angina pectoris, myocardial infarction, or the use of antiplatelet agents for coronary artery disease. The diagnostic criteria for takotsubo cardiomyopathy comprise four components: 1) temporary hypokinesis, dyskinesis, or akinesis in LV segments with or without apical involvement; aberration in regional wall motion exceeding past a single vascular distribution; or the existence of stress elicitation; 2) a lack of significant coronary artery disease; 3) recent changes detected in the electrocardiogram (ST segment elevation and/or T-wave inversion) or significant elevation of serum cardiac troponins; and 4) nonexistence of pheochromocytoma or myocarditis.⁸⁾

Treatment with clipping or endovascular coil embolization was selected based on the consensus decision reached between the treating neurosurgeon and interventional neuroradiologist after analyzing the risks and chances of success of both therapeutic modalities for each case.

All patients received 0.9% normal saline at a rate of 1 mL/kg/h, with an appropriate dosage of supplemental 5% albumin solution administered to maintain positive fluid balance. All patients received intravenous fasudil hydrochloride hydrate (Asahi Kasei Pharma Corp., Tokyo, Japan) every 8 h from days 4 to 14. Oral statins and mineralocorticoids were not routinely administered. Persistent fever (temperature exceeding 38.5°C) was treated with acetaminophen and surface cooling devices. Angiography was routinely performed on patients in whom symptomatic vasospasm developed and endovascular treatment of vasospasm entailed either intra-arterial chemical vasodilation with fasudil hydrochloride hydrate or balloon angioplasty.

In patients with known preceding warfarin before hospitalization, urgent reversal was carried out following our institutional guidelines. Besides withdrawal of the warfarin, reversal of warfarin therapy with vitamin K antagonists

(VKAs) or fresh frozen plasma (FFP) was achieved through individual treatment approaches. Since April 2017, prothrombin complex concentrates (4F-PCC) have been used for the reversal of warfarin. In patients with preceding antiplatelet drugs, those agents were withdrawn, but reversal antiplatelet treatment was not performed.

Patients were divided into good grades (Hunt & Kosnik [H&K] grade I-III) or poor grades (H&K grade IV-V) on admission.

Outcomes were assessed according to the modified Rankin Scale score (mRS) at discharge and at 3 months, stratified into favorable (mRS 0-3) or unfavorable (mRS 4-6).

The ethics committee at our institution approved the protocol of this retrospective study and waived the requirement for patient consent (approval no. 5278).

Statistical analysis

Numerical data are expressed as mean \pm standard deviation or median (interquartile range). Categorical variables are expressed as numbers and percentages. Statistical analyses were performed using SPSS version 24 software (IBM Corp., Tokyo, Japan). For intergroup comparisons, we used the chi-square test, Fisher's exact test, Student's t-test, and the Mann-Whitney U-test. To assess independent predictors of poor outcomes, univariate logistic regression was first performed, and then, those possible predictors showing values of $p < 0.10$ were included in the multivariate analyses. In all analyses, values of $p < 0.05$ were considered statistically significant. Patients with missing information from one variable were only excluded from the corresponding statistical analyses, not from the entire study.

Results

Table 1 shows the characteristics of patients in Groups A and B. Patients were significantly older in Group A (73.1 \pm 13.5 years) than in Group B (64.8 \pm 15.0 years; $p = 0.001$). Moreover, comorbidity rates for hypertension, DM, hyperlipidemia, IHD, Atrial fibrillation, and dialysis were all significantly higher in Group A than in Group B (Table 1).

In Group A, 17 patients (43.6%) had preceding use of warfarin (n = 8) or direct oral anticoagulants (DOACs) (n = 9), 18 (46.2%) had preceding use of antiplatelet drugs, and 4 (10.2%) had preceding use of both.

1) Initial condition on admission and clinical conditions

In Group A, the grade on admission was good in 17 patients (43.6%) and poor in 22 (56.4%). In Group B, the grade on admission was good in 254 patients (60.5%) and poor in 166 (39.5%).

H&K grade on admission was significantly higher in Group A than in Group B (Fig. 1; $p = 0.02$).

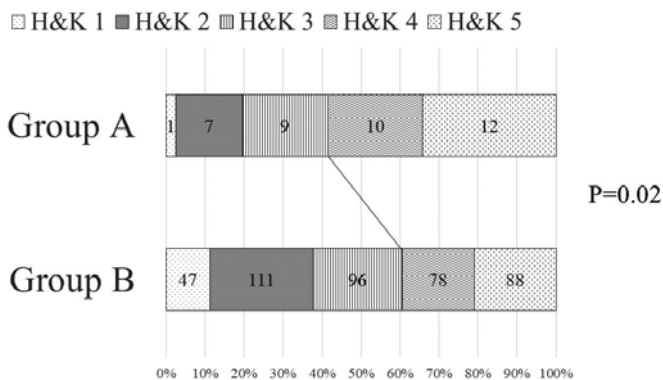
Acute subdural hematoma was present in two patients

Table 1 Characteristics and clinical state of patients in Groups A and B

	Group A	Group B	p Value
Number	39	420	
Age (Mean ± SD)	73.1 ± 13.5	64.8 ± 15.0	0.001*
Age range	37-96	15-95	
Male	16 (41.0%)	130 (31.0%)	0.38
Hypertension	29 (74.4%)	196 (46.7%)	0.001*
DM	8 (20.5%)	30 (7.1%)	0.01*
Hyperlipidemia	15 (38.5%)	54 (12.9%)	<0.001*
IHD	13 (33.3%)	6 (1.4%)	<0.001*
Af	13 (33.3%)	3 (0.7%)	<0.001*
Cancer	4 (10.3%)	38 (9.0%)	0.77
Dialysis	3 (7.7%)	3 (0.7%)	0.01*
Not investigated by angiography	5 (12.8%)	23 (5.5%)	0.08
Location & characteristics of aneurysm #			0.50
Saccular, anterior circulation	27 (79.4%)	310 (78.1)	
Saccular, posterior circulation	3 (8.8%)	36 (9.1%)	
Dissecting, vertebrobasilar	0	7 (1.8%)	
Dissecting, other	1 (2.9%)	29 (7.3%)	
Unknown	3 (8.8%)	15 (3.8%)	
Hunt and Kosnik grade (median (quartile))	4 (3-5)	3 (2-4)	0.02*
Fisher grade 1	0	19 (4.5%)	0.12
2	11 (28.2%)	118 (28.1%)	
3	13 (33.3%)	184 (43.8%)	
4	15 (38.5%)	99 (23.6%)	
Subdural hematoma	2 (5.1%)	21 (5.0%)	>0.99
Deterioration of neurological state before treatment	5 (12.8%)	46 (11.0%)	0.79
Takotubo cardiomyopathy	3 (7.7%)	20 (4.8%)	0.31
Endovascular treatment for vasospasm	1 (2.6%)	65 (15.5%)	0.03*
Ventricular drainage	9 (23.1%)	108 (25.7%)	0.85
Shunt-dependent hydrocephalus	6 (15.4%)	72 (17.1%)	>0.99

*: statistically significant.

DM: Diabetes mellitus, IHD: Ischemic heart disease, Af: Atrial fibrillation

**Fig. 1** Neurological grade on admission for each group.

in Group A (5.1%) and 21 patients in Group B (5.0%; $p > 0.99$). Deterioration of the level of consciousness before treatment was seen in five patients in Group A (12.8%) and 46 patients in Group B (11.0%; $p = 0.79$). Takotsubo cardiomyopathy was seen in three patients in Group A (7.7%) and 20 patients in Group B (4.8%; $p = 0.31$). None of these clinical conditions differed significantly between groups (Table 1).

2) Treatments for aneurysms and vasospasm

In Group A, clipping was performed in five patients (12.8%), endovascular surgery in 20 patients (51.3%), and conservative treatment in 14 patients (35.9%). Eleven of the 14 patients (78.6%) with conservative treatment in Group A received this treatment due to poor neurological grade. In Group A, clipping was performed for four pa-

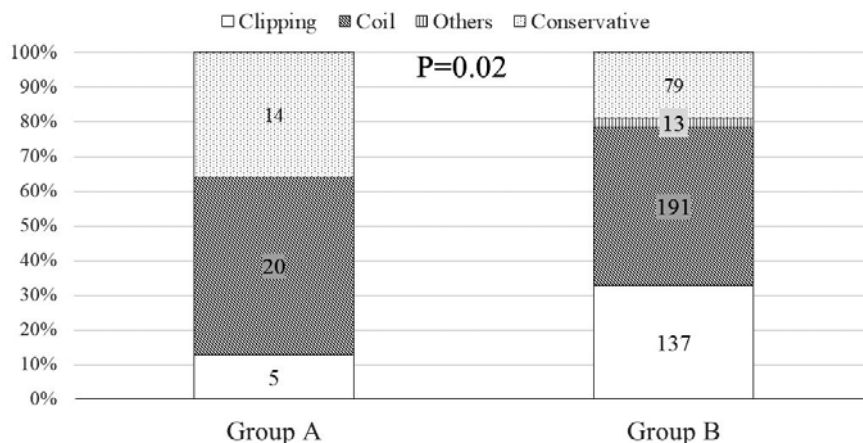


Fig. 2 Treatment of each group.

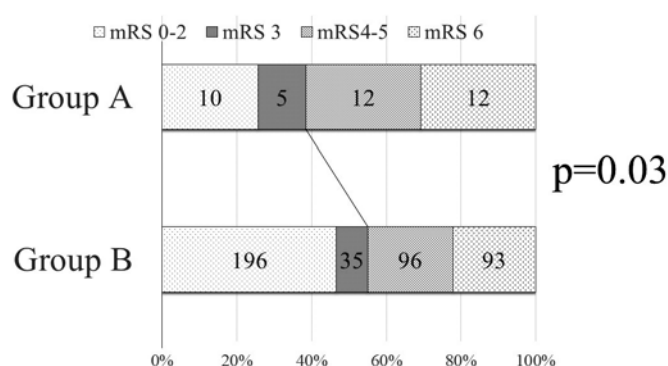


Fig. 3 Outcome at 3 months after onset for each group.

tients with middle cerebral artery (MCA) aneurysm and one patient with anterior communicating artery aneurysm. We chose clipping based on the aneurysm location and the unsuitability of coil treatment. For all other patients, treatment with coil placement was chosen.

Conversely, in Group B, clipping was performed in 137 patients (32.6%), endovascular surgery in 191 patients (45.5%), conservative treatment in 79 patients (18.8%), and other interventions in 13 patients (3.1%). Sixty-four of the 79 patients (81%) with conservative treatment in Group B received this treatment due to poor neurological grade on admission.

The rate of clipping treatment was lower and the rate of conservative treatment due to poor grade was higher in Group A than in Group B. Therapeutic methods were significantly different between Groups A and B (Fig. 2; $p = 0.02$).

In Group A, only one symptomatic spasm was identified, in a patient with MCA aneurysm who underwent clipping. The rate of symptomatic spasm and endovascular therapy for symptomatic vasospasm after SAH was significantly lower in Group A (2.6%) than in Group B (15.5%; $p = 0.03$) (Table 1).

3) Shunt-dependent hydrocephalus

Ventricular drainage for acute hydrocephalus was performed for nine patients (23.1%) in Group A and 108 patients (25.7%) in Group B. Shunt-dependent hydrocephalus was seen in six patients (15.4%) in Group A and 72 patients (17.1%) in Group B. These frequencies did not differ significantly between groups (Table 1).

4) Reversal of antithrombotic drugs in Group A patients

Prothrombin time international normalized ratio was significantly higher in patients with preceding warfarin. Reversal of warfarin was applied to eight of the 12 patients (66.7%) with preceding warfarin. As reversal agents, VKAs were used in six patients, FFP in one patient, and 4F-PCC in one patient.

5) Outcomes

Favorable outcome rates at discharge were 33.3% in Group A and 49.3% in Group B. Unfavorable outcome rates at discharge were 66.7% in Group A and 50.7% in Group B. The mRS at discharge was significantly worse for patients in Group A than for those in Group B ($p = 0.03$). Furthermore, favorable outcome rates at 3 months after onset were 38.5% in Group A and 55.0% in Group B ($p = 0.03$). The mRS at 3 months after onset was thus significantly worse for patients in Group A than for those in Group B (Fig. 3).

In patients from Group A, the favorable outcome rate at 3 months after onset in patients with preceding anticoagulant, preceding antiplatelet, and preceding use of both were 35.3%, 44.4%, and 25%, respectively. No significant differences were evident among these three groups.

In Group A, the outcomes at 3 months after onset were poor in 10 of 20 patients who underwent coiling and in two of five patients who underwent clipping; thus, the unfavorable outcome rate was 50% in patients treated with coils and 40% in patients treated with clipping.

Table 2 Univariable and multivariable analyses among the risk factors for the unfavorable outcomes at 3 months after SAH

	Crude model				Multivariable model			
	OR	95% CI		p value	OR	95% CI		p Value
		Lower	Upper			Lower	Upper	
Age	1.06	1.04	1.07	<0.001*	1.07	1.05	1.09	<0.001*
Male	0.83	0.56	1.23	0.34				
Hypertension	1.40	0.97	2.02	0.07	1.13	0.67	1.89	0.65
DM	1.86	0.95	3.67	0.07	1.90	0.73	4.95	0.19
Hyperlipidemia	1.00	0.60	1.67	>0.99				
IHD	3.39	1.20	9.58	0.02*	1.18	0.32	4.34	0.80
Af	1.97	0.70	5.52	0.20				
Cancer	1.79	0.94	3.42	0.08	0.85	0.36	2.02	0.72
Dialysis	2.34	0.42	12.88	0.33				
Hunt and Kosnik grade ≥ 4	10.36	6.67	16.08	<0.001*	8.19	4.70	14.28	<0.001*
Fisher grade 1	0.25	0.08	0.79	0.02*	0.52	0.12	2.17	0.37
2	0.25	0.15	0.42	<0.001*	0.38	0.20	0.71	0.003*
3	Ref				Ref			
4	2.33	1.43	3.82	0.001*	1.39	0.74	2.61	0.30
Subdural hematoma	8.39	2.46	28.66	0.001*	5.01	1.13	22.30	0.03*
Takotubo cardiomyopathy	1.85	0.79	4.37	0.16				
Location and characteristics of aneurysm #								
Saccular, anterior circulation	Ref				Ref			
Saccular, posterior circulation	0.82	0.42	1.60	0.56	0.55	0.23	1.32	0.18
Dissecting, vertebrobasilar	0.47	0.09	2.46	0.37	1.48	0.18	12.58	0.72
Dissecting, other	0.68	0.31	1.47	0.33	1.16	0.42	3.21	0.78
Unknown	0.069	0.01	0.53	0.01*	0.07	0.01	0.93	0.04*
Anti-platelet	1.71	0.72	4.09	0.23				
Anti-coagulant	2.40	0.95	6.07	0.06	0.86	0.24	3.15	0.82

* show statistically significant. #: 431 patients are analyzed after excluding 28 patients without radiographical investigation to identify hemorrhagic origins.

Risk factors for the unfavorable outcomes (mRS ≥ 4) at 3 months after SAH on univariate analyses were patient age, presence of IHD, H&K grade ≥ 4 on admission, Fisher grade, and presence of a subdural hematoma. Preceding antithrombotic drugs tended to be a risk factor for poor outcomes but were not significant (Table 2). In the multivariate analysis, risk factors for the unfavorable outcomes (mRS ≥ 4) at 3 months after SAH were patient age, H&K grade ≥ 4 on admission, and subdural hematoma on initial CT (Table 2). The association between patient prognosis and treatment of aneurysm via clipping or coil embolization was assessed. After adjusting for age, H&K grade, Fisher grade, and presence of subdural hematoma, the odds ratio for the unfavorable outcomes at 3 months after SAH was 1.66 (95% confidence interval, 0.85-3.27; $p = 0.14$) for coil embolization in comparison with clipping. Differences in aneurysmal treatment did not appear to affect patient prognosis. Preceding antithrombotic drugs was not a

risk factor in the multivariate analysis. Conversely, Fisher grade 2 on initial CT and unknown origin of SAH were factors associated with favorable outcomes (Table 2).

6) Resumption of antithrombotic drugs in Group A patients

In 15 of the 27 patients in Group A who survived after initial treatment, we resumed antithrombotic drugs. Because no indications for the administration of antiplatelet drugs were considered present, only four of the 13 patients with preceding antiplatelets resumed antithrombotics.

Conversely, 10 of the 12 patients who survived had preceding anticoagulant use, and one of the two patients with preceding antiplatelet and anticoagulant use resumed anticoagulant drugs. The timing of resumption was inconsistent, with anticoagulants resumed between 0 and 384 days and antiplatelet drugs resumed between 1 and 365 days after onset.

Discussion

1. Rate of preceding antithrombotic drugs in patients with nontraumatic SAH

In this study, 8.5% of patients suffering from nontraumatic SAH were on antithrombotic therapy before ictus (anticoagulant, 3.7%; antiplatelet, 3.9%; both, 0.9%). In previous reports, frequencies of preceding antithrombotic drugs in patients with nontraumatic SAH were quite variable, at 0%-10.6%.^{1,5,7,9-13} Toussaint et al. reported the rate of preceding aspirin as 9.5%,⁹ and Schmidt et al. demonstrated that 9.2% of SAH patients had preceding antiplatelets.⁵ These reported rates are higher than our own findings. Nilsson et al. reported no patients with preceding anticoagulants.¹⁰ Rinkel et al. demonstrated that 10.6% of SAH patients had preceding anticoagulants.¹²

Hassen et al. demonstrated that on multivariable risk factor analyses, patients with preceding aspirin ranging from three times weekly to daily had a significantly lower odds ratio for hemorrhage of an unruptured aneurysm (adjusted odds ratio, 0.27; $p = 0.03$) compared with those who had never taken aspirin.¹⁴ Conversely, Schmidt et al. demonstrated that long-term dipyridamole use and new aspirin use were associated with an increased risk of SAH.⁵ Another database study demonstrated that preceding aspirin did not affect the odds ratio for SAH.¹⁵

The relationship between anticoagulation and the risk of SAH is poorly understood. Population-based and institutional studies have found a significant association between preceding anticoagulants and SAH,^{2,3,7,15} but the information remains limited. However, we must consider separately the bleeding risk and severity of the neurological state after SAH in patients with preceding antithrombotic drugs.

We can easily imagine that great differences might exist in background characteristics between patients with and without preceding antithrombotic drugs. In our study, patients with preceding antithrombotic drugs were significantly older than patients without such a history. Most reports have supported this observation.^{11,12,16} Moreover, users of antithrombotic drugs typically show more comorbidities than nonusers. Can et al. showed that patients with preceding anticoagulants had more comorbidities without such a history.¹³ Anticoagulant use was a risk factor for aneurysm rupture, but these authors demonstrated that preceding anticoagulants were not associated with mortality or complication rate after SAH.¹³

2. Treatment for SAH

In our study, clipping was performed for only five patients in Group A (12.8%), in comparison with endovascular surgery in 20 patients (51.3%) and conservative treatment in 14 patients (35.9%). Moreover, 11 of the 14 patients with conservative treatment received this due to poor neurological grade. Patients in Group A received en-

dovascular treatment due to poor neurological grade and high age. This tendency agrees with the results of other studies.^{11,12,16} Schuss et al. demonstrated that only 14% of patients with preceding anticoagulants underwent surgical clipping, whereas 86% underwent endovascular coiling.¹¹ Although endovascular surgery is now becoming more frequent as a treatment for patients without antithrombotic drugs, endovascular treatment seems likely to become the main treatment for patients with preceding antithrombotic drugs.

In this study, symptomatic vasospasm was less frequent among patients with preceding antithrombotic drugs. Although the neurological grade of the patients was poor and symptoms of vasospasm might have been underestimated, preceding antithrombotic drugs may protect against the development of vasospasm. To clarify why patients with preceding antithrombotic drugs less frequently experienced vasospasm, further studies are necessary.

The appearance of shunt-dependent hydrocephalus was not increased among patients with preceding antithrombotic drugs. We showed that patients with preceding antithrombotic drugs did not experience elevated complication rates during treatment.

In this study, reversal of anticoagulant was performed on eight of the 12 patients (66.7%) with preceding warfarin. In Japan, idarucizumab is the only approved neutralizer of DOACs, but we did not use this drug, because none of the patients were dabigatran users. For one patient with preceding warfarin, 4F-PCC was used on admission. Vitamin K was the most common neutralizer for warfarin users. No complications were associated with neutralizer use; hence, appropriate reversal of anticoagulants may be mandatory to prevent aneurysm re-rupture. In the future, 4F-PCC and neutralizers of DOACs will be used for patients with preceding warfarin or DOACs.¹⁷

3. Outcomes

In our study, the outcomes at 3 months after onset in patients with preceding antithrombotic drugs were significantly poorer than those in patients without preceding antithrombotic drugs. The relationship between preceding antithrombotic drugs and the outcome of SAH remains controversial. Hui et al. demonstrated that patients with an antithrombotic state experienced worse outcomes even after adjusting for the amount of hemorrhage as assessed using modified Fisher grade.¹⁸ Dasenbrock et al. demonstrated that patients with long-term anticoagulant treatment demonstrated poor outcomes, but multivariable regression models found no significant differences in these outcomes because these patients showed poorer baseline health.¹ Rinkel et al. demonstrated that outcomes among patients on anticoagulant treatment were extremely poor.¹² Moreover, Schuss et al. demonstrated that patients without anticoagulation therapy achieved favorable functional outcomes significantly more often than patients with preced-

ing anticoagulation therapy.¹¹⁾ Nevertheless, preceding anticoagulation therapy was not identified as a significant independent predictor of unfavorable outcomes in their multivariate logistic regression analysis.¹¹⁾ They showed that high age was a more significant risk factor for unfavorable outcomes than preceding anticoagulants. Our study agrees with these results. Patients with preceding anticoagulants tend to be elderly and have numerous comorbidities; therefore, poor condition is more significant than the absence of anticoagulants.

Touissant et al. demonstrated that preceding aspirin was not associated with differential outcomes, although a trend was seen toward a higher rate of rebleeding and a lower rate of permanent disability from vasospasm for aspirin users.⁹⁾ In our study, the rate of neurological deterioration before treatment of SAH did not differ between patients with and without preceding antithrombotic drugs, so the rebleeding rate may not differ between the two groups.

Conversely, Gross et al. reported no impact from preceding aspirin on the presentation, short-term, or 1 year outcomes after SAH among patients with preceding ASPIRIN.¹⁹⁾ Dasenbrock et al. and Garbe et al. also demonstrated that patients with preceding aspirin did not show different outcomes.¹⁷⁾ In our study, risk factors for the unfavorable outcomes (mRS ≥ 4) at 3 months after SAH in the univariate analysis were patient age, IHD, H&K grade ≥ 4 on admission, Fisher grade, and subdural hematoma. Preceding antiplatelets or anticoagulants tended to be risk factors for poor outcomes but were not significant factors (Table 2). In the multivariate analysis, risk factors for the unfavorable outcomes (mRS ≥ 4) at 3 months after SAH were patient age, H&K grade on admission, and subdural hematoma on initial CT (Table 2). Preceding antithrombotic drugs was not a significant risk factor in the multivariate analysis. We believe that greater age or presence of IHD or subdural hematoma were more serious factors for patients with preceding antithrombotic therapy suffering from SAH.

4. Limitations

Some limitations must be considered for this study. First, this study was a retrospective, single-center study, and the backgrounds of the two groups differed. Second, this study included a small number of cases of patients with a history of using antithrombotic drugs; thus, the period of use of preceding antithrombotic drugs was not evaluated. However, the recruited patients were consecutive, and the outcomes of all patients were collected.

Conclusion

Patients with preceding antithrombotic drugs were significantly older and had more comorbidities than those without. Furthermore, the neurological grade on admission and outcomes in those patients were significantly worse.

However, in the multivariate analysis, the preceding use of antithrombotic drugs was not a significant risk factor.

Conflicts of Interest Disclosure

All authors have no conflicts of interest to declare.

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