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Effects of Antiplatelet Agents on Cerebral Vasospasm and Delayed Cerebral Ischemia in Aneurysmal Subarachnoid Hemorrhage Patients Treated with Coil Embolization

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Objective: This study aimed to investigate the role of antiplatelet agents (APAs) in preventing cerebral vasospasm (CVS) and delayed cerebral ischemia (DCI) in aneurysmal subarachnoid hemorrhage (SAH) patients treated with coil embolization.
Methods: We reviewced data from 131 consecutive patients who underwent coil embolization following aneurysmal SAH from January 2011 to May 2021. We finally recruited 108 patients and analyzed the occurrence of CVS and DCI, as well as the modified Rankin Scale (mRS) score at discharge according to the use of APA (APA group [n=32] vs. non-APA group [n=76]).
Results: The baseline characteristics, except patient age, were not significantly different between the APA and the non-APA groups. DCI (p=0.846), transcranial Doppler ultrasonographic vasospasm (p=0.449), angiographic vasospasm (p=0.176), and mRS scores at discharge (p=0.194) were also not significantly different between the groups. Newly developed cerebral infarction was significantly more frequent in the APA group (p=0.027).
Conclusion: APA use did not reduce the occurrence of CVS and DCI in aneurysmal SAH patients treated with coil embolization, indicating that the effect of APAs on clinical outcomes may be trivial compared with other risk factors.

Keywords: Aneurysm; Platelet aggregation inhibitors; Subarachnoid hemorrhage; Vasospasm

INTRODUCTION

Delayed cerebral ischemia (DCI) and cerebral vasospasm (CVS) following aneurysmal subarachnoid hemorrhage (SAH) are serious complications occurring within the first 2 weeks after ictus and lead to significant disabilities, worsening quality of life and even death. CVS is the phenomenon of arterial narrowing observed on angiography. The term "symptomatic vasospasm" is commonly used when clinical deterioration is related to CVS. Meanwhile, DCI is characterized by a new neurological deficit or decreased consciousness that should not have been apparent immediately after aneurysm occlusion and should not be attributable to other causes[19].

Recently, an increasing body of evidence has demonstrated that DCI does not always correlate with the vascular

distribution of CVS, and DCI could occur without CVS[6,9,17,18]. The pathophysiological mechanism of DCI is unclear, but inflammatory cascade, cortical spreading depolarization, microthrombi formation, and vasospasm have been proposed[4,6,9]. Along with the pathophysiology of DCI, it is presumed that increased platelet activity is contributed to the development of DCI. Several studies have investigated the role of antiplatelet agents (APAs) in preventing the development of CVS and DCI. Some studies have suggested that APA has a beneficial effect in preventing CVS and DCI after aneurysmal SAH, but others showed contrary results[1,3,5,7,8,12,14-16,20].

With the advent of endovascular aneurysm treatment, a growing number of SAH patients require APA medication following intervention due to stent or thromboembolic risk. The purpose of this study was to determine whether APA reduces the incidence of CVS or DCI in aneurysmal SAH patients treated using an endovascular tool.

MATERIALS AND METHODS

1. Study Population

The study protocol was approved by the Institutional Review Board (IRB). The requirement of obtain written informed consent to participate in this study was waived by IRB. We reviewed 131 consecutive patients who underwent coil embolization following aneurysmal SAH from January 2011 to May 2021. We divided the patients into two groups according to the use of APA following endovascular treatment. The use of APA was decided by the attending interventionist depending on the use of stent and the risk of thromboembolic event (coil protrusion into parent vessel). Patients receiving APA after coil embolization were assigned to the APA group and patients who were managed without APA were included in the non-APA group.

The exclusion criteria for this study were no transcranial Doppler ultrasonography (TCD) data, early death within 7 days after ictus, and insufficient clinical data. We eventually recruited 108 patients. We retrospectively collected the following data: age, sex, history of hypertension and diabetes mellitus, Hunt–Hess grade, modified Fisher grade, aneurysm location, newly developed cerebral infarction, newly developed hemorrhage, and the occurrence of DCI, TCD vasospasm, and angiographic vasospasm. First, we analyzed the clinical parameters associated with the clinical outcome (modified Rankin Scale [mRS] scores); then, we analyzed the occurrence of TCD vasospasm and DCI and the mRS score at discharge according to the use of APA.

All patients underwent TCD every other day for 14 days and TCD vasospasm was defined as a mean velocity of the middle cerebral artery >120 cm. Angiographic vasospasm was defined as the narrowing of the vessel lumen by greater than 25% of the original vessel diameter on digital subtraction angiography (DSA). We only performed DSA when TCD vasospasm with clinical deterioration was identified. DCI was defined as the occurrence of clinical deterioration, such as aphasia or hemiparesis, and a decrease in the level of consciousness that were not apparent immediately after aneurysm embolization and were not attributed to other causes in radiological and laboratory studies[19]. Newly developed cerebral infarction and hemorrhage (not hemorrhagic infarction) were defined as the presence of new cerebral infarction and hemorrhage in follow-up radiological studies not present in radiological studies within 48 hr after aneurysm embolization. The infarction associated with initial brain damage and hypodense lesions surrounding the cerebral hematoma was not regarded as a newly developed infarction. A favorable outcome was defined as an mRS score of 0 to 2. We dichotomized other variables as follows: age at 60 years, Hunt–Hess grade 1–3 vs. 4–5, modified Fisher grade 1–2 vs. 3–4, and aneurysm location as anterior (anterior cerebral artery, internal carotid artery, and middle cerebral artery) vs. posterior (vertebrobasilar and posterior cerebral artery).

2. Antiplatelet Medication Protocol

Before coil embolization, we evaluated 3-dimensional computed tomographic angiography and predicted the possible use of a stent. Those patients were administered 400 mg of aspirin as a loading dose. Heparin (2,000 IU) was administered as a bolus after angiography and intermittently 1,000 IU bolus per hr until the end of the procedure. In the case of stent-assisted coil embolization and coil protrusion into the parent vessel, aspirin 100 mg and clopidogrel 75 mg were administered daily for at least 12 weeks and aspirin was maintained lifelong after the procedure. The platelet function test was not routinely used.

3. Statistical Analysis

Continuous variables are presented as the mean (with

standard deviation) and categorical variables are presented as the number of cases. For the comparison of baseline variables, the χ^2 test and Fisher's exact test were used for categorical variables, and Student's *t*-test was used for continuous variables. We considered differences significant at p=0.05 in the univariate analysis and entered into a binary logistic regression analysis. A probability value of less than 0.05 was considered statistically significant.

RESULTS

Among 108 patients (70 women, 64.8%) with a mean age of 57.6 ± 13.4 years (range, 23–91 years), 32 patients were allocated to the APA group and 76 patients to the non-APA group.

Unfavorable clinical outcome (mRS scores at discharge 0–2) was significantly associated with old age (p=0.000), diabetes mellitus (p=0.049), Hunt–Hess grade (p=0.000), modified Fisher grade (p=0.034), location of the aneurysm (p=0.048), newly developed cerebral infarction (p=0.000), newly developed hemorrhage (p=0.000), and DCI (p=0.000) (Table 1). Old age (odds ratio [OR], 14.173; confidence interval [CI], 1.644–122.176; p=0.016), newly developed cerebral infarction (OR, 6.376; CI, 1.209–33.637; p=0.029), and DCI (OR, 57.593; CI, 6.071–546.356; p=0.000) were significantly associated with unfavorable clinical outcome in binary logistic regression analysis (Table 2).

Baseline characteristics, except patient age were not significantly different between the APA and the non-APA groups (Table 3). DCI (p=0.846), TCD vasospasm (p=0.449), angiographic vasospasm (p=0.176), and mRS scores at discharge (p=0.194) were not significantly associated with the

Table 1. Baseline characteristics of the study population related to clinical outcomes at discharge

Characteristic	mRS score 0–2 (n = 80)	mRS score 3–6 (n = 28)	p-value
Sex			0.323
Male	26 (32.5)	12 (42.9)	
Female	54 (67.5)	16 (57.1)	
Age (year)	54.5 ± 11.5	66.6 ± 14.6	**0.000**
Age (year)			**0.001**
<60	57 (71.2)	10 (35.7)	
≥60	23 (28.8)	18 (64.3)	
Hypertension			0.213
Yes	32 (40.0)	15 (53.6)	
No	48 (60.0)	13 (46.4)	
Diabetes mellitus			**0.049**
Yes	4 (5.0)	5 (17.9)	
No	76 (95.0)	23 (82.1)	
Hunt-Hess grade			**0.000**
1	1 (1.3)	0 (0.0)	
2	51 (63.8)	7 (25.0)	
3	26 (32.5)	13 (46.4)	
4	2 (2.5)	8 (28.6)	
5	0 (0.0)	0 (0.0)	
Hunt-Hess grade			**0.000**
Grade 1-3	78 (97.5)	20 (71.4)	
Grade 4-5	2 (2.5)	8 (28.6)	
Modified Fisher grade			0.100
1	8 (10.0)	0 (0.0)	
2	4 (5.0)	0 (0.0)	
3	32 (40.0)	9 (32.1)	
4	36 (45.0)	19 (67.9)	
Modified Fisher grade			**0.034**
Grade 1-2	12 (15.0)	0 (0.0)	
Grade 3-4	68 (85.0)	28 (100.0)	
Location of the aneurysm			**0.048**
ACA	16 (20.0)	13 (46.4)	
ICA	53 (66.3)	12 (42.9)	
MCA	1 (1.3)	0 (0.0)	
VBS	10 (12.5)	3 (10.7)	
Location of the aneurysm			1.000
Anterior circulation	70 (87.5)	25 (89.3)	
Posterior circulation	10 (12.5)	3 (10.7)	
TCD vasospasm			0.811
Yes	21 (26.3)	8 (28.6)	
No	59 (73.8)	20 (71.4)	
Angiographic vasospasm			0.648
Yes	4 (5.0)	2 (7.1)	
No	76 (95.0)	26 (92.9)	
DCI			**0.000**
Yes	8 (10.0)	21 (75.0)	
No	72 (90.0)	7 (25.0)	
New cerebral infarction			**0.000**
Yes	5 (6.3)	15 (53.6)	
No	75 (93.8)	13 (46.4)	
New hemorrhage			**0.000**
Yes	1 (1.3)	7 (25.0)	
No	79 (98.8)	21 (75.0)	

The data is presented as number (%) or mean ± standard deviation.
mRS: modified Rankin Scale; ACA: anterior cerebral artery; ICA: internal carotid artery; MCA: middle cerebral artery; VBS: vertebrobasilar system; TCD: transcranial doppler; DCI: delayed cerebral ischemia.

Table 2. Risk factors for unfavorable clinical outcomes

Parameter	OR (95% CI)	p-value
Age ≥ 60 years	14.173 (1.644–112.176)	0.016
Newly developed CI	6.376 (1.209–33.637)	0.029
DCI	57.593 (6.071–546.356)	0.000

OR: odds ratio; CI: confidence interval; CI: cerebral infarction; DCI: delayed cerebral ischemia.

Table 3. Baseline characteristics of patients in the APA and nAPA groups

Characteristic	APA group (n = 32)	non-APA group (n = 76)	p-value
Sex			0.442
Male	13 (40.6)	25 (32.9)	
Female	19 (59.4)	51 (67.1)	
Age (year)	62.4 ± 14.4	55.6 ± 12.6	**0.017**
Age (year)			**0.035**
<60	15 (46.9)	52 (68.4)	
≥60	17 (53.1)	24 (31.6)	
Hypertension			0.191
Yes	17 (53.1)	30 (39.5)	
No	15 (46.9)	46 (60.5)	
Diabetes mellitus			1.000
Yes	2 (6.3)	7 (9.2)	
No	30 (93.8)	69 (90.8)	
Hunt-Hess grade			0.766
1	0 (0.0)	1 (1.3)	
2	16 (50.0)	42 (55.3)	
3	12 (37.5)	27 (35.5)	
4	4 (12.5)	6 (7.9)	
5	0 (0.0)	0 (0.0)	
Hunt-Hess grade			0.478
Grade 1-3	28 (87.5)	70 (92.1)	
Grade 4-5	4 (12.5)	6 (7.9)	
Modified Fisher grade			0.113
1	3 (9.4)	5 (6.6)	
2	1 (3.1)	3 (3.9)	
3	7 (21.9)	34 (44.7)	
4	21 (65.6)	34 (44.7)	
Modified Fisher grade			0.747
Grade 1-2	4 (12.5)	8 (10.5)	
Grade 3-4	28 (87.5)	68 (89.5)	
Location of the aneurysm			0.096
ACA	4 (12.5)	25 (32.9)	
ICA	23 (71.9)	42 (55.3)	
MCA	0 (0.0)	1 (1.3)	
VBS	5 (15.6)	13 (17.1)	
Location of the aneurysm			0.521
Anterior circulation	27 (84.4)	68 (89.5)	
Posterior circulation	5 (15.6)	8 (10.5)	

The data is presented as number (%) or mean ± standard deviation.
APA: antiplatelet agent; ACA: anterior cerebral artery; ICA: internal carotid artery; MCA: middle cerebral artery; VBS: vertebrobasilar system.

use of APA. Newly developed cerebral infarction was significantly higher in the APA group (p=0.027) (Table 4).

DISCUSSION

This study did not show a beneficial effect of APA on the occurrence of TCD vasospasm, angiographic vasospasm, and DCI; rather it showed a significantly negative effect. Also, clinical outcomes in patients who received APA were significantly worse. However, risk factors for unfavorable clinical outcomes (old age, newly developed infarction, and DCI)

Table 4. Clinical characteristics of patients in the APA and nAPA groups

Characteristic	APA group (n = 32)	non-APA group (n = 76)	p-value
TCD vasospasm			0.449
Yes	7 (21.9)	22 (28.9)	
No	25 (78.1)	54 (71.1)	
Angiographic vasospasm			0.176
Yes	0 (0.0)	6 (7.9)	
No	32 (100.0)	70 (92.1)	
DCI			0.846
Yes	9 (28.1)	20 (26.3)	
No	23 (71.9)	56 (73.7)	
New cerebral infarction			**0.027**
Yes	10 (31.3)	10 (13.2)	
No	22 (68.8)	66 (86.8)	
New hemorrhage			0.432
Yes	1 (3.1)	7 (9.2)	
No	31 (96.9)	69 (90.8)	
mRS score at discharge			0.512
0	8 (25.0)	27 (35.5)	
1	12 (37.5)	23 (30.3)	
2	1 (3.1)	9 (11.8)	
3	3 (9.4)	5 (6.6)	
4	3 (9.4)	4 (5.3)	
5	2 (6.3)	5 (6.6)	
6	3 (9.4)	3 (3.9)	
mRS score at discharge			0.194
Favorable (mRS 0–2)	3 (9.4)	4 (5.3)	
Unfavorable (mRS 3–6)	29 (90.6)	72 (94.7)	
Mortality			0.358
Yes	3 (9.4)	3 (3.9)	
No	29 (90.6)	73 (96.1)	

APA: antiplatelet agent; TCD: transcranial doppler; DCI: delayed cerebral ischemia; mRS: modified Rankin Scale.

were consistent with those of previous studies. Therefore, it is presumed that the baseline characteristics of study population were not different from those of previous studies.

To date, the beneficial effect of APA on the occurrence of CVS and DCI in aneurysmal SAH patients is controversial. This discrepancy is attributed to heterogenous study designs and inconsistency of the definition of DCI. An international ad hoc panel of experts proposed a definition of DCI be used as an outcome measure and recommended restricting the use of "vasospasm" in descriptions of radiological tests[17,18]. We have no clear explanations for our findings, but some possible factors should be discussed. First, the dosage and kinds of APA used may not be enough to prevent CVS or DCI. We prescribed a daily dose of 100 mg aspirin and 75 mg clopidogrel, but this dosage might not be sufficient. Nagahama et al.[12] reported the beneficial effect of dual antiplatelet therapy on clinical vasospasm and DCI without an increased risk of hemorrhagic complications. However, the patients received 600 mg of clopidogrel and 325 mg of aspirin daily. On the contrary, a retrospective study of 166 patients showed the beneficial effect of dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg daily) on symptomatic vasospasm and DCI[14]. In this study, posterior circulation aneurysms were 44.6% in the control group and 35.4% in the antiplatelet group, limiting the generalizability of the results of this study. The kinds of APA may also be important. In 2013, a prospective study demonstrated that oral cilostazol 100 mg twice daily effectively prevented CVS[13]. A second explanation may be the use of a stent. Although we preoperatively administered 400 mg aspirin to prevent thromboembolic complications in the case of stent-assisted coiling, stent insertion in the acute stage of SAH had a significant influence on the inflammatory response of the vessel wall and the formation of microthrombi, resulting in the development of DCI. A third explanation may be the difference in patient's age. The APA group was older than the non-APA group. Severe atherosclerotic change in old age combined with the use of a stent may attribute to the development of vasospasm and DCI in the APA group. Finally, a significant proportion of patients do not respond to antiplatelet therapy: up to 25% of patients are resistant to clopidogrel and 10% to aspirin[10,11]. Because we did not routinely perform platelet function tests preoperatively, this resistance to APAs may affect the results.

The main limitation of this study is its retrospective design and small sample size. In addition, we excluded the patients treated by surgical clipping. Therefore, the results could not be generalized to all aneurysmal SAH patients. Moreover, it is difficult to detect CVS or DCI in poor-grade SAH patients. Although TCD is a simple, non-invasive, bedside test, and increased blood flow velocity on TCD is useful as a surrogated tool, it has a lower power to diagnose CVS than angiography[2]. Finally, the decision on treatment type might influence clinical outcomes, possibly resulting in selection bias. A prospective study on the comparison of the group with and without APA in patients who underwent coil embolization without using a stent will be helpful in elucidating the role of APA on CVS and DCI in aneurysmal SAH.

CONCLUSION

In this study, there was no evidence that the use of APA decreased the occurrence of CVS and DCI in aneurysmal SAH patients treated by endovascular tools, indicating that the effect of APA on clinical outcomes may be trivial compared with other risk factors. Future studies should focus on the dosage and kinds of APA to elucidate the role of APA in the management of aneurysmal SAH.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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