Dual antiplatelet therapy in aneurysmal subarachnoid hemorrhage: association with reduced risk of clinical vasospasm and delayed cerebral ischemia

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OBJECTIVE Clinical vasospasm and delayed cerebral ischemia (DCI) are devastating complications of aneurysmal subarachnoid hemorrhage (aSAH). Several theories involving platelet activation have been postulated as potential explanations of the development of clinical vasospasm and DCI. However, the effects of dual antiplatelet therapy (DAPT; aspirin and clopidogrel) on clinical vasospasm and DCI have not been previously investigated. The objective of this study was to evaluate the effects of DAPT on clinical vasospasm and DCI in aSAH patients.

METHODS Analysis of patients treated for aSAH during the period from July 2009 to April 2014 was performed in a single-institution retrospective study. Patients were divided into 2 groups: patients who underwent stent-assisted coiling or placement of flow diverters requiring DAPT (DAPT group) and patients who underwent coiling only without DAPT (control group). The frequency of symptomatic clinical vasospasm and DCI and of hemorrhagic complications was compared between the 2 groups, utilizing univariate and multivariate logistic regression.

RESULTS Of 312 aSAH patients considered for this study, 161 met the criteria for inclusion and were included in the analysis (85 patients in the DAPT group and 76 patients in the control group). The risks of clinical vasospasm (OR 0.244, CI 95% 0.097–0.615, $p = 0.003$) and DCI (OR 0.056, CI 95% 0.01–0.318, $p = 0.001$) were significantly lower in patients receiving DAPT. The rates of hemorrhagic complications associated with placement of external ventricular drains and ventriculoperitoneal shunts were similar in both groups (4% vs 2%, $p = 0.9$).

CONCLUSIONS The use of DAPT was associated with a lower risk of clinical vasospasm and DCI in patients treated for aSAH, without an increased risk of hemorrhagic complications.

<https://thejns.org/doi/abs/10.3171/2017.5.JNS17831>

KEY WORDS aneurysm rupture; aspirin; clopidogrel; coil; stent; vascular disorders

SUBARACHNOID hemorrhage (SAH) secondary to rupture of an intracranial aneurysm, aneurysmal SAH (aSAH), accounts for 2%–5% of all new strokes, is estimated to affect 21,000–33,000 patients each year in the US, and poses a high rate of mortality and morbid-

ity.^{17,29} About 50% of those who survive have long-term cognitive impairment or other significant functional disability.^{17,29}

Angiographic vasospasm, characterized by vasoconstriction of arterial blood vessels on imaging studies,

ABBREVIATIONS ACoA = anterior communicating artery; ADP = adenosine diphosphate; aSAH = aneurysmal SAH; ATP = adenosine triphosphate; CTA = CT angiography; DAPT = dual antiplatelet therapy; DCI = delayed cerebral ischemia; EVD = external ventricular drain; ICA = internal carotid artery; ICU = intensive care unit; MAP = mean arterial pressure; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; VP = ventriculoperitoneal.

SUBMITTED April 2, 2017. **ACCEPTED** May 15, 2017.

INCLUDE WHEN CITING Published online November 3, 2017; DOI: 10.3171/2017.5.JNS17831.

is seen in up to 70% of patients following aSAH.^{7,21,25,35} Clinical or symptomatic vasospasm refers to angiographic vasospasm associated with a neurological decline and occurs in approximately 20%–40% of aSAH cases.^{9,21,25} Delayed cerebral ischemia (DCI) is defined as a clinical deterioration along with associated ischemic changes observed on imaging studies and is noted in about 30% of aSAH cases.^{7,26} DCI is the most important predictor of mortality and morbidity in patients who survive the initial neurological insult from aSAH.^{9,15,26} The differential impact of angiographic vasospasm on DCI (i.e., lack of clear positive relationship between them), and thus on the clinical outcomes, highlights the complexity and multifactorial nature of the pathophysiological mechanisms involved in DCI.²⁶

The understanding of the pathophysiology of DCI has evolved over the recent years, and the focus of research has been directed to the multifactorial nature of DCI beyond mere angiographic vasospasm. Several theories have been postulated, including activation of the coagulation cascade, cortical spreading depression, activation of tissue factor leading to formation of microthrombi, inflammatory response, and oxidative stress,²⁶ as well as the effects of and complications from surgical/endovascular interventions. Disruption of the endothelium at the time of aneurysm rupture appears to initiate an inflammatory cascade.¹ This has been associated with release of several proinflammatory cytokines and the activation of platelets and coagulation cascades, leading to the development of DCI and worse outcome.^{18,22}

Given the suspected critical role of inflammatory and coagulation cascades in development of DCI, several antiplatelet and anticoagulation agents, including aspirin, ticlodipine, and heparin, have been evaluated in clinical studies for their ability to mitigate the suspected effect of platelet aggregation and formation of microthrombi in DCI.^{5,6,27} A Cochrane Review of 7 clinical trials showed a trend toward better outcomes in aSAH patients treated with single antiplatelet agents, although not statistically significant, reflecting the need for further research.⁶ A retrospective analysis showed that low-dose intravenous infusion of heparin initiated after microsurgical clipping of ruptured aneurysms may be effective in reducing the risk of clinical vasospasm and delayed infarction without increasing hemorrhagic complications.²⁷

Multiple studies have suggested that formation of microthrombi contributes to development of DCI. Postmortem studies show those patients with large areas of ischemia had significantly increased number of microthrombi.³⁰ A study using intracranial Doppler ultrasonography showed a trend of increased occurrence of microthrombi in those patients who subsequently developed DCI.²⁴

To evaluate the likely critical role of platelets in development of clinical vasospasm and DCI, we investigated the effect of aggressive platelet inhibition by dual antiplatelet therapy (DAPT; aspirin and clopidogrel) on clinical vasospasm and DCI in a single-institution retrospective study. These medications were required for patients who underwent endovascular interventions involving use of a stent or flow diverter in order to prevent in-stent thrombosis.

Methods

This study was a single-institution retrospective study conducted at University of Iowa Hospitals and Clinics involving all qualifying consecutive patients who presented with aSAH during the period from July 2009 to April 2014 and who were managed based on the protocol detailed below. The relevant clinical information was collected during the study period and stored in a local clinical database for quality control. The presence of an aneurysm causing aSAH was confirmed with CT angiography (CTA) and diagnostic cerebral catheter angiography. The study was approved by the University of Iowa Institutional Review Board.

Inclusion/Exclusion Criteria

Patients selected for this study were those who suffered aSAH secondary to rupture of a saccular cerebral aneurysm, presented with Hunt and Hess Grade I–III or showed improvement of their neurological status to Hunt and Hess Grade I–III after ventriculostomy within 24 hours of the initial presentation (with Grade IV or V with clinical and imaging evidence of hydrocephalus), and had a CT perfusion study done on admission. All the patients with aSAH underwent a CT perfusion study on admission, according to our aSAH management protocol. The Hunt and Hess grade for individual patients was determined at the time of presentation for patients without initial evidence of hydrocephalus (and thus not requiring ventriculostomy) and within 24 hours of the presentation after improvement of neurological status, if any, for patients who initially exhibited evidence of hydrocephalus and required ventriculostomy. The exclusion criteria were as follows: SAH secondary to rupture of an aneurysm associated with an arteriovenous malformation or a mycotic aneurysm; microsurgical clipping of the aneurysm; coiling of the aneurysm with unintended protrusion of a portion of coil into the parent vessel requiring aspirin therapy; Hunt and Hess Grade IV or V; presence of intraparenchymal hemorrhage; aSAH-induced cardiomyopathy; death due to pulmonary embolism, myocardial infarction, sepsis, and/or any medical complications; and no follow-up clinic visits. Patients who underwent microsurgical clipping were excluded, given the risks of potential unique complications inherently associated with craniotomy and microsurgical manipulation of the brain and vasculature. Patients with Hunt and Hess Grade V were excluded because these patients, without improvement of their neurological status after ventriculostomy, did not undergo further endovascular interventions. Patients with Hunt and Hess Grade IV were excluded, since neurological examination of patients with poor Hunt and Hess grades can be difficult and limited, and we chose to include only patients with better clinical grades in whom neurological deterioration could be more clearly observed and documented.

aSAH Management Protocol

All the patients with a diagnosis of aSAH were managed by a single dual-trained vascular neurosurgeon, and a standardized protocol was strictly followed in all cases. In brief, noncontrast CT of the brain, CTA, and a CT per-

fusion study were performed on admission and/or prior to transfer to University of Iowa Hospitals and Clinics, a tertiary referral center for most aSAH cases in the state of Iowa. Noncontrast CT was used to assess the pattern of intracranial hemorrhage, the presence of hydrocephalus, and the degree of cerebral edema. CTA and CT perfusion studies were performed, respectively, to evaluate the presence, location, size, and geometry of the aneurysm and to gauge baseline potential cerebral blood flow changes related to vasospasm and/or DCI. All the patients were admitted and managed in the neurological intensive care unit (ICU) under the care of the neurosurgery service.

Mean arterial pressure (MAP) was maintained below 80 mm Hg until the aneurysm was secured. An external ventricular drain (EVD) was immediately placed if/when obstructive hydrocephalus was noted, either prior to or subsequent to treatment of the unsecured aneurysm. The aneurysm was secured with microsurgical clipping, coil embolization alone, stent-assisted coil embolization, or flow diverter placement alone. The choice of treatment was based on several factors: patient age, medical comorbidities, presence of intraparenchymal hemorrhage and associated mass effect, and Hunt and Hess grade on admission, as well as aneurysm location, size, and morphology. Platelet function tests were not routinely performed for the patients included in this study.

If a stent or a flow diverter was used, tirofiban infusion was started at the maintenance dosage without bolus doses immediately after deployment of the stent or flow diverter and was continued for 2 hours after the procedure. These patients also received 600 mg of crushed clopidogrel and 325 mg of aspirin via an orogastric tube at the end of the procedure and continued to receive both clopidogrel and aspirin (i.e., DAPT) daily. Those patients who underwent coil embolization alone without use of a stent or flow diverter and therefore received neither clopidogrel nor aspirin made up the control group. Patients who underwent endovascular intervention involving coiling only without use of a stent or flow diverter but who required daily aspirin postoperatively due to partial protrusion of a coil were excluded from this study and not included in the control group.

In all cases, regardless of the type of treatment to secure the aneurysm, the patients were subsequently cared for in the neurological ICU, and their MAP was maintained above 80 mm Hg after the aneurysm was secured. Additional CT perfusion studies were performed if neurological decline was noted on serial neurological examinations, and the results were compared with the baseline perfusion results obtained on admission. If perfusion changes related to vasospasm were noted, interventions tailored to individual cases were performed. These interventions included any of the following: elevation of the MAP goal to over 90 mm Hg; continuous intravenous nicardipine infusion for 5 days; diagnostic catheter angiography followed, if possible, by interventions such as balloon angioplasty and/or intraarterial administration of nicardipine; and noncontrast CT and/or MRI during the admission to assess DCI.

If an EVD was placed for obstructive hydrocephalus, the patient was gradually weaned from it, using a strict

protocol, after the acute phase, typically 7–21 days after admission. The EVD was replaced by a ventriculoperitoneal (VP) shunt, if the patients were not able to tolerate weaning from the EVD. Given the possible increased risk of hemorrhagic complications for patients on DAPT (which could be required and started for any aSAH patients depending on the type of endovascular intervention that may precede or follow EVD placement), a strict surgical protocol was followed for placement of the EVD and VP shunt in all cases in which these interventions were needed. In brief, all surgical procedures were performed in the operating room by a senior-level neurosurgery resident under the supervision of the faculty neurosurgeon. After a small area of the pia was coagulated with bipolar cautery, the ventricular catheter was placed with the use of a Ghajar guide to approximate the appropriate trajectory of the catheter and minimize need for repeated catheter insertion. If the ventricular space was not entered appropriately at the first pass, the faculty surgeon took over to place the ventricular catheter.

Definition of Angiographic/Clinical Vasospasm and DCI

All the imaging studies were reviewed locally by clinicians with expertise in vascular neuroradiology who were not necessarily blinded to the types of endovascular interventions. Angiographic vasospasm was stratified as mild, moderate, or severe, according to the degree of narrowing of the diameter of cerebral arteries noted on the diagnostic cerebral catheter angiogram independently by 2 interventional neuroradiologists at the time of the procedure. If there was disagreement, a third radiologist adjudicated. Narrowing by greater than 75% of the original vessel diameter was classified as severe vasospasm, 25%–75% narrowing as moderate vasospasm, and less than 25% as mild vasospasm. When different degrees of angiographic vasospasm were noted in different vascular territories in an individual patient, the most severe category was used to classify the overall angiographic vasospasm in that particular case. Focal narrowing or narrowing localized to 1 arterial branch was considered to be focal vasospasm, whereas diffuse narrowing involving multiple arteries from different distributions was regarded as diffuse vasospasm. Rescue therapy (i.e., induced hypertension, continuous intravenous infusion of nicardipine, and/or endovascular intervention involving balloon angioplasty with or without intraarterial administration of nicardipine) was indicated and performed only if the patients were noted to have an associated neurological decline (i.e., clinical vasospasm).

Clinical vasospasm was defined as a significant decline in neurological examination findings (e.g., level of consciousness and ability to follow commands), accompanied by impaired flow changes noted on CT perfusion study or radiographic evidence on diagnostic cerebral catheter angiography. A significant decline in neurological examination findings was defined as a significant change that was clinically judged to necessitate evaluation with a CT perfusion study, including worsening level of consciousness (e.g., new somnolence, decreased ability to be aroused, change in ability to follow commands) and development of new motor and/or language deficits. The duration of

those changes was variable and not necessarily specifically documented. The standard laboratory tests were routinely performed to monitor and rule out metabolic derangements, and bedside continuous scalp electroencephalography was performed as indicated to rule out seizures. Clinical vasospasm required medical (e.g., induced hypertension, continuous intravenous infusion of nicardipine) and/or endovascular interventions (e.g., balloon angioplasty with or without intraarterial administration of nicardipine), although medical/endovascular interventions were not required as part of the criteria for clinical vasospasm in this study.

DCI was defined as any ischemic changes noted on noncontrast CT as hypodense areas and/or on MRI as diffusion-restricted areas corresponding to the territories of angiographic vasospasm, as determined by board-certified neuroradiologists who were not necessarily blinded to the types of endovascular interventions. Small punctate ischemic changes noted on a diffusion-weighted MRI sequence were excluded, as these areas likely represented small air emboli or thrombi unintentionally introduced during endovascular procedures. All the patients who developed clinical vasospasm and who required medical and/or endovascular interventions were imaged subsequently with noncontrast CT and MRI with the stroke protocol. All the patients in the study underwent multiple noncontrast CT scans during their hospital course, typically after EVD placement, after aneurysm repair, before/after EVD weaning trials, and at times of significant neurological changes. DCI was defined as any new ischemic change that was not present after aneurysm repair and larger than embolic lesions that could be explained by aneurysm repair.

Statistical Analysis

The data were presented as means and ranges for continuous variables and as frequencies for categorical variables. Analysis was performed using an unpaired t-test, Wilcoxon rank sum, chi-square, and Fisher's exact tests as appropriate. Univariate analysis was used to test covariates predictive of the following dependent variables: clinical vasospasm, DCI, and unfavorable discharge outcomes (modified Rankin Scale [mRS] scores of 3–6). Interaction and confounding variables were assessed through stratification and relevant expansion covariates. Factors predictive in univariate analysis ($p < 0.20$) were entered into a multivariate logistic regression analysis. A p value ≤ 0.05 was considered statistically significant. Statistical analysis was performed with SAS, version 9.4 (SAS Institute, Inc.).

Results

A total of 312 patients with aSAH were admitted and managed during the interval from July 2009 to April 2014; 161 met the inclusion criteria and were selected for this study (Fig. 1). Of those 161 patients, 85 patients were treated with either stent-assisted coiling or placement of a flow diverter, requiring subsequent daily clopidogrel and aspirin (DAPT group). The remaining 76 patients who were treated with coil embolization without use of a stent or flow diverter required neither clopidogrel nor aspirin and made up the control group. Table 1 shows the baseline characteristics of both groups. There were no statistically significant differences between the groups with respect to age, Hunt and Hess grade, Fisher grade, hydrocephalus

FIG. 1. Abbreviated flowchart for patients included in this study based on the inclusion and exclusion criteria. AVM = arteriovenous malformation.

TABLE 1. Characteristics of 161 patients with aSAH

Characteristic	Controls, n = 76 (%)	DAPT Group, n = 85 (%)	p Value
Age in yrs, mean (SD)	51.5 (11.5)	56.1 (12.3)	NS
Age ≥60 yrs	33 (43)	32 (38)	NS
Female sex	18 (24)	33 (39)	0.039
Aneurysm location			
ACoA	44 (58)	23 (27)	0.0001
ICA	4 (5)	18 (21)	
Coil	76 (100)	80 (94)	0.032
Hunt & Hess grade			
II	26 (34)	37 (44)	NS
III	29 (38)	28 (33)	
Fisher grade			
1	3 (4)	7 (8)	NS
2	36 (47)	37 (44)	
3	22 (29)	26 (31)	
4	15 (20)	15 (18)	
Hydrocephalus	47 (62)	52 (61)	NS
EVD	47 (62)	52 (61)	NS
VP shunt	18 (24)	10 (12)	NS
Complications	3 (4)	2 (2)	NS

NS = nonsignificant.

on presentation, placement of an EVD, or placement of a VP shunt (Table 1). The proportion of female patients was greater in the DAPT group (39% vs 24%, $p = 0.039$). As expected due to technique preference, there was a statistically significant difference in the aneurysm location; supraclinoid internal carotid artery (ICA) aneurysms were more common in the DAPT group (21% vs 5%, $p = 0.0001$), whereas anterior communicating artery (ACoA) aneurysms were more common in the control group (58% vs 27%, $p = 0.0001$). There was no statistically significant difference between the 2 groups in the occurrence of hemorrhagic complications or infection associated with placement of EVD and/or VP shunt (2% in the DAPT group vs 4% in the control group).

The DAPT group had a significantly decreased inci-

FIG. 2. The proportion of patients with clinical vasospasm and DCI in the DAPT and control groups. The rates of clinical vasospasm and DCI were significantly lower in the DAPT group than in the control group. Error bars indicate 95% confidence intervals.

FIG. 3. The distribution of severity of clinical vasospasm in the DAPT and control groups. The rate of clinical vasospasm remained significantly lower in the patients on DAPT after adjustment for degree of angiographic vasospasm.

dence of clinical vasospasm compared with the control group (OR 0.303, CI 95% 0.014–0.671, $p = 0.003$). After adjustment for potential confounders, such as age, sex, aneurysm location, Hunt and Hess grade, and Fisher grade, the DAPT group still had a significantly decreased incidence of clinical vasospasm compared with the control group (OR 0.244, CI 95% 0.097–0.615, $p = 0.003$) (Fig. 2). The rate of clinical vasospasm remained significantly lower among the patients on DAPT after adjustment for the degree of angiographic vasospasm (Fig. 3).

The DAPT group had a significantly lower incidence of DCI compared with the control group (OR 0.084, CI 95% 0.019–0.376, $p = 0.001$). After adjusting for age, sex, aneurysm location, Hunt and Hess grade, and Fisher grade, the DAPT group still had significantly less DCI compared with the control group (OR 0.056, CI 95% 0.01–0.318, $p = 0.001$) (Fig. 2).

Clinical outcome assessed using mRS scores at 6 weeks after discharge showed that increased age (especially > 65 years) (OR 3.34, 95% CI 1.07–10.38, $p = 0.037$) and clinical vasospasm (OR 7.61, 95% CI 2.46–23.51, $p = 0.0001$) were predictors of poor outcome (mRS scores of 3–6) when multivariate analysis was performed (Fig. 4). When dichotomizing clinical outcome to good (mRS scores of 0–2) and poor (mRS scores of 3–6), the DAPT group had a statistically nonsignificant trend toward bet-

FIG. 4. Clinical outcome as measured by mRS score depending upon use of DAPT. Increased age and clinical vasospasm were significantly associated with poor outcome. The mRS score ranged from 0 (no symptoms) to 6 (death), with higher scores indicated by increasingly dark shades of gray. The percentage values indicate proportions of the DAPT or control group.

FIG. 5. Dichotomized clinical outcome as measured by mRS score depending upon use of DAPT. The DAPT group showed a trend toward better outcomes when compared with the control group, although the difference was not statistically significant due to the limited sample size of this single-institution study. The data points represent the percentage of patients in each group who had a good outcome (mRS score of 1 or 2) at discharge; the error bars indicate 95% confidence intervals.

ter outcomes when compared with the control group ($p = 0.15$) (Fig. 5).

Discussion

SAH secondary to rupture of an intracranial aneurysm represents a life-threatening condition of high mortality and morbidity.^{17,29} In particular, DCI has become recognized as the most serious complication that contributes to neurological deterioration and poor long-term functional outcome. The pathophysiology of DCI likely involves not only the traditionally emphasized vasospasm, but also multifactorial processes, including platelet activation, coagulation, and inflammation,²⁶ as well as the effects of and complications from surgical/endovascular interventions. Taking advantage of the recent evolution of endovascular treatment of aneurysms with use of a stent or flow diverter, which inevitably requires DAPT (with both aspirin and clopidogrel), we conducted a retrospective study to evaluate the effect of DAPT on the risks of clinical vasospasm and DCI. Our study suggests that DAPT reduces the risk of clinical vasospasm and DCI without a significant increase of hemorrhagic complications related to EVD or VP shunt placement. Given the small sample size of our study, we were not able to detect statistically significant long-term differences with the relatively insensitive clinical outcome measures used, but there was a trend toward better long-term neurological outcomes for patients treated with DAPT. There was no statistically significant difference between the 2 groups in the occurrence of hemorrhagic complications and infection associated with EVD or VP shunt placement.

Our current study has several aspects that are unique: 1) the use for the first time in this population of a more aggressive dual antiplatelet regimen (previous studies used a single antiplatelet agent, such as aspirin or ticlopidine); 2) the use of CT perfusion studies on admission and at times of neurological decline to assess clinical vasospasm based on cerebral blood flow, cerebral blood volume, and mean transit time; and 3) careful evaluation of the risk of hemorrhagic complications of EVD and/or VP shunt placement that could be associated with use of the antiplatelet agents.

The results of this study suggest that the use of DAPT for management of aSAH is feasible, safe, and potentially efficacious in reducing the risk of clinical vasospasm and DCI, which may lead to better survival and long-term outcome. These results are consistent with the critical role that platelets are thought to play in the coagulation/inflammation cascade, as previously described in the literature (Fig. 6).

Platelets are rich in prostanoid and nonprostanoid substances. These cytokines play critical roles in platelet aggregation, formation and propagation of microthrombi, activation of inflammation, and arterial vasoconstriction leading to clinical vasospasm and DCI.²⁶ These cytokines include thromboxane A2 and B2, serotonin, adenosine diphosphate (ADP), and adenosine triphosphate (ATP), which are contained within dense granules in platelets and released upon platelet activation and aggregation.³² Endothelial damage and mechanical injury to the artery upon aneurysm rupture lead to platelet activation and aggregation, which in turn lead to release of these cytokines, causing vasoconstriction and formation of microthrombi. Furthermore, the incidence of DCI appears to be more frequent in patients with higher serum levels of these vasoactive substances.^{13,20,34}

Lam et al. noted a statistically significant positive exponential correlation between the severity of vasoconstriction and the degree of platelet deposition in a porcine *in vivo* model.¹⁶ Importantly, they also demonstrated that treatment with an antiplatelet agent, namely aspirin, significantly reduced both the degree of platelet deposition and the severity of vasoconstriction.

Thromboxane B2 (TXB2), released by platelets along with other vasoactive substances, plays a critical role in inducing severe angiographic vasospasm. Juvela et al. analyzed the level of serum TXB2 in 49 patients with aSAH and noted that the TXB2 levels were significantly higher in patients who had diffuse and severe angiographic vasospasm.¹⁴ Serotonin is another cytokine released by activated platelets.³² Exogenous serotonin has been shown to cause contraction of isolated canine coronary arteries, and this contraction was further enhanced with removal of endothelium.²⁻⁴

Several autopsy studies have suggested that microthrombi may play a critical role in the development of DCI.^{19,28,30,31,33} It was observed that patients who died of DCI had significantly more microthrombi in areas showing cerebral infarction on CT scans when compared with patients who died of rebleeding or acute hydrocephalus.³⁰

Endothelial damage from aneurysm rupture can cause increased concentrations of platelet-activating factor, von Willebrand factor, and various other inflammatory cytokines and coagulation factors in the systemic circulation and cerebrospinal fluid.^{8,10-12,23} Elevation of some of these factors, including platelet-activating factor, has been noted during the acute period after aSAH and has been associated with DCI, cerebral infarction, and poor outcome.^{8,10-12,23}

These studies collectively implicated platelets and related cytokines in the development of clinical vasospasm and DCI (Fig. 6). These findings motivated clinicians and scientists to conduct clinical studies to assess the role of antiplatelet agents in reducing the incidence of clinical va-

FIG. 6. Schematic of proposed pathophysiological mechanisms that may underlie clinical vasospasm and DCI in aSAH. Platelets are thought to play a critical role in the development of clinical vasospasm and DCI, and DAPT may mitigate the devastating impacts of clinical vasospasm and DCI through its antiplatelet and antiinflammatory actions. ASA = acetylsalicylic acid (aspirin); Plavix = clopidogrel; TXA₂ = thromboxane A₂; TXB₂ = thromboxane B₂. Figure is available in color online only.

sospasm and DCI. Dorhout Mees et al. summarized these studies in a systematic review.⁶ They identified 7 randomized clinical trials that evaluated the role of a single antiplatelet agent in decreasing DCI and improving functional outcome. They concluded that treatment with a single antiplatelet agent led to a reduction of DCI (RR 0.79, 95% CI 0.56–1.22) and of poor outcome (RR 0.79, 95% CI 0.62–1.01), although the decreases were not statistically significant. However, there were increased intracranial hemorrhagic complications (RR 1.36, 95% CI 0.59–3.12) with use of these antiplatelet agents, although again the difference was not statistically significant.

We recognize that our study has limitations. First, the choice of treatment types to secure the aneurysm was clinically determined, and thus treatment types and subsequent use of DAPT were not randomized. The lack of randomization could raise a concern for a selection bias. For instance, there was a statistically significant difference in aneurysm location (i.e., ICA vs ACoA) between

the DAPT and control groups. However, there were no statistically significant differences in patients' clinical status (i.e., Hunt and Hess score, Fisher grade, and the presence of hydrocephalus) between the 2 groups at initial presentation. Second, the 2 groups of patients underwent different types of endovascular interventions (i.e., stent or flow diverter placement vs coil embolization only), which raises concerns about the potential confounding effect of these individual endovascular interventions. For instance, one might suspect that the use of a stent or flow diverter could potentially lead to a lower risk of angiographic spasm. However, there was no significant difference in the rate of the angiographic vasospasm or ischemic changes in the territories supplied by the parent artery where a stent or a flow diverter was deployed. (The rate of angiographic vasospasm in the territory supplied by the parent artery of the treated aneurysm was 82% [9 of 11 cases] with use of a stent or flow diverter and 88.5% [22 of 25 cases] without, $p = 0.99$.) Third, all of the imaging studies were performed

as part of the patients' regular care and were interpreted by clinicians who have expertise in neuroradiology but who were not necessarily blinded to the type of the treatment the patient received, rather than being interpreted at a central location by clinicians blinded to the treatment group. Fourth, review of the inclusion/exclusion illustrates that there were some differences across the groups. Fifth, this study was innately limited by its cohort size and its retrospective nature. In addition, due to selection biases and the relatively small size of the study groups, we were unable to definitively assess the potential beneficial effect of DAPT on the long-term neurological functional outcome. Larger, prospective, controlled, randomized studies will be needed to assess the safety and long-term outcome of the DAPT approach in patients treated for aSAH. Future trials should also include cognitive testing, which was done in only a fraction of subjects included in this study.

Conclusions

The results of this study strongly suggest that DAPT decreases the risk of clinical vasospasm and DCI in patients with aSAH. To confirm these findings, we propose a larger, multicenter, prospective, controlled, randomized trial of DAPT versus single antiplatelet therapy (i.e., aspirin only) versus placebo in patients treated with coiling, named SPASM (Suppressing Platelets in Aneurysm SAH Management).

Acknowledgments

This work was supported by grants R03NS079227 and K08NS082363 (D.H.) from the National Institutes of Health.

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Disclosures

Dr. Broderick reports a financial relationship with AstraZeneca in which the Departments of Neurology and Rehabilitation received money for input on the results of the SOCRATES trial.

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Conception and design: Hasan, Nagahama, Allan, Starke, Jabour, Torner. Acquisition of data: Hasan, Allan, Zanaty. Analysis and interpretation of data: all authors. Drafting the article: Hasan, Nagahama. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hasan. Statistical analysis: Torner. Study supervision: Hasan.

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