Aspirin and Aneurysmal Subarachnoid Hemorrhage

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Key words
- Aneurysm
- Antiplatelet
- Aspirin
- Hemorrhage
- Natural history
- Outcome
- Rupture

Abbreviations and Acronyms
CI: Confidence interval
HH: Hunt and Hess
ISUIA: International Study of Unruptured Intracranial Aneurysms
OR: Odds ratio
SAH: Subarachnoid hemorrhage

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OBJECTIVE: **Recent evidence has suggested a potential beneficial effect of aspirin on the risk of aneurysm rupture. This benefit must be weighed against its potential adverse effects as an antiplatelet agent in the setting of acute aneurysmal subarachnoid hemorrhage (SAH).**

METHODS: **A total of 747 consecutive patients with cerebral aneurysms were reviewed, comparing demographics, aneurysm features, presenting clinical and radiographic grades, vasospasm, and outcome at 1 year between patients with aneurysmal SAH taking aspirin on presentation and those who were not.**

RESULTS: **The rate of hemorrhagic presentation was significantly greater in patients not taking aspirin (40% vs. 28%; $P = 0.016$). Among 274 patients presenting with aneurysmal SAH, there was no significant difference in presenting clinical (Hunt and Hess) and radiographic (Fisher) grade between patients taking aspirin and those who were not. There was also no significant difference in the rate of subsequent angiographic and delayed cerebral ischemia. Multivariate analysis of outcome at 1 year found only increasing age (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.04–1.12), Hunt and Hess grade (OR 3.01, 95% CI 1.81–5.03), and associated hypertension (OR 3.30, 95% CI 1.39–7.81) to be statistically significant risk factors for poor outcome (death or dependence), whereas aspirin use was not associated with poor outcome (OR 1.19, 95% CI 0.35–4.09; $P = 0.78$).**

CONCLUSIONS: **In the present study, patients taking aspirin had a lower rate of hemorrhagic presentation. In addition, taking aspirin did not adversely impact presenting clinical grade or radiographic grade, vasospasm, and outcome in the setting of aneurysmal SAH.**

INTRODUCTION

As our understanding of the pathophysiology of cerebral aneurysms evolves, the discovery of potentially modifiable risk factors for rupture will bear considerable clinical value in patient management. Recent work by Hasan et al. (2) evaluating patients in the International Study of Unruptured Inracranial Aneurysms (ISUIA) demonstrated the intriguing finding that patients taking aspirin at least three times weekly had significantly lower odds of hemorrhage during the follow-up period (odds ratio [OR] 0.27, P = 0.03). This finding may have significant clinical implications in the management of patients with unruptured aneurysms deemed amenable for observation. However, the impact of active antiplatelet medication usage in the context of aneurysm rupture must be addressed. The present study reviews an institutional cohort of patients with cerebral aneurysms, comparing patients taking aspirin to those not taking aspirin overall and in the context of aneurysm rupture, addressing the impact of this antiplatelet agent on presenting clinical grade and hemorrhage as well as outcome.

METHODS

With approval from their local institutional review board, the authors performed a retrospective review of a consecutive series of patients with at least one cerebral aneurysm seen by the neurosurgical service during a 7-year period. Patients taking clopidogrel and/or warfarin were excluded. Baseline demographic information (age and sex), pertinent medical conditions (hypertension, smoking, family history of aneurysms), aneurysm location, and aneurysm rupture status were noted across this cohort, stratified by whether the patient took aspirin (81 or 325 mg daily) or not. For patients with ruptured aneurysms, treatment modality, presenting clinical (Hunt and Hess [HH]) and radiographic (Fisher) grade, the presence of vasospasm (angiographic and clinical), and outcome at 1 year was noted. It should be noted that all patients taking aspirin received one bag of pooled platelets upon arrival to our emergency department, and their aspirin was held through their hospital stay. No patients in this cohort with ruptured aneurysms were treated with stent-assisted coiling; none of them were started on aspirin after admission.

STATA 12.0 (StataCorp, College Station, Texas, USA) was used for statistical analysis. Univariate analysis between patients taking aspirin and those not taking aspirin was performed with Fisher's exact test for categorical variables and a two-tailed t-test

for continuous variables. A multivariate linear regression analysis of poor outcome at 1 year (dependence or death, modified Rankin scale score >2) was performed with age, sex, hypertension, smoking status, treatment modality, HH grade, Fisher grade, and aspirin usage at presentation as covariates. Probability values were considered statistically significant if $P < 0.05$.

RESULTS

The review afforded 747 patients, of which 30 were excluded as they were taking clopidogrel and/or warfarin. This left 717 patients with 897 intradural aneurysms for analysis (Table 1). Comparing patients taking aspirin (n = 114) with those who did not (n = 603), those taking aspirin were significantly older (mean age, 61.5 vs. 51.9 years; $P < 0.0001$) and had a significantly greater rate of hypertension (65% vs. 34%; $P < 0.0001$). There was a trend toward a greater prevalence of women among patients not taking aspirin (76% vs. 68%; $P = 0.08$). There was no significant difference in the prevalence of patients actively smoking or in those with a family history of cerebral aneurysms. Comparing 150 intradural aneurysms in patients taking aspirin to 747 in patients not taking aspirin, there was no significant difference in aneurysm location. Notably, the rate of hemorrhagic presentation was greater in patients not taking aspirin (40% in patients not taking aspirin vs. 28% in patients taking aspirin; $P = 0.016$).

Ruptured Cases

Of the 717 patients, 274 presented with aneurysmal subarachnoid hemorrhage (SAH) (38%). Thirty-two of these patients were taking aspirin (81 or 325 mg) at the time of presentation (12%). Table 2 compares background data of patients taking aspirin compared with those not taking aspirin with ruptured aneurysms. Similar to the overall cohort, patients taking aspirin were significantly older (mean age, 63.5 vs. 53.1 years; $P < 0.0001$) and had a significantly greater prevalence of hypertension (81% vs. 41%; $P < 0.0001$). There was no significant difference in patient sex, smoking status, or family history of aneurysms between these two groups. There was also no significant difference in aneurysm location and treatment modality between the two groups.

A comparison between these two groups also revealed no significant difference in presenting clinical (HH) and radiographic (Fisher) grade (Table 3). The frequency of angiographic vasospasm (determined by digital subtraction angiography and rarely computerized tomography angiography), moderate or severe angiographic vasospasm, and delayed cerebral ischemia (clinical vasospasm) did not differ between the two groups either.

Outcome

Given the potential for confounders, such as patient age and a history of hypertension, an initial multivariate analysis was performed to evaluate the impact of aspirin use along with other potential risk factors on poor patient outcome, defined as death or dependence at 1 year (modified Rankin scale of at least 3; Table 4). Significant risk factors for death or dependence at 1 year included increasing patient age (OR 1.07, 95% confidence interval [CI] 1.04–1.12; $P < 0.0001$), hypertension (OR 3.30, 95% CI 1.39–7.81; $P = 0.007$), and increasing presenting HH grade (OR 3.01, 95% CI 1.81–5.03; $P < 0.0001$). Trends were also seen for surgical clipping (OR 2.37, 95% CI 0.83–6.76; $P = 0.11$) and increasing Fisher grade (OR 2.09, 95% CI 0.59–7.44; $P = 0.26$). Notably, aspirin usage at presentation did not emerge as a significant risk factor for poor outcome (OR 1.19, 95% CI 0.35–4.09; $P = 0.78$).

Table 1. Overall Comparison of Patients with Aneurysms Taking Aspirin Compared with Those not Taking Aspirin at the Time of Aneurysm Discovery

	Taking Aspirin	Not Taking Aspirin	*P* Value
Patients	114	603	
Aneurysms*	150	747	
Mean age (years)	61.5 (12.6)	51.9 (12.8)	< 0.0001
% Female	78/114 (68%)	461/603 (76%)	0.08
Associated hypertension	74/114 (65%)	203/603 (34%)	< 0.0001
Smokers	32/114 (28%)	205/603 (34%)	0.23
Family history	18/114 (16%)	94/603 (16%)	1.0
Aneurysm location			
Anterior communicating	28/150 (19%)	139/747 (19%)	1.0
Posterior communicating	24/150 (16%)	119/747 (16%)	1.0
Other anterior circulation	77/150 (51%)	387/747 (52%)	0.93
Posterior circulation	21/150 (14%)	102/747 (14%)	0.90
Presentation with rupture			
By patients	32/114 (28%)	242/603 (40%)	0.016
By aneurysms	32/150 (21%)	242/747 (32%)	0.0066

*Includes only intradural aneurysms.

DISCUSSION

Consistent with results from this study, increasing patient age and presenting clinical and radiographic grades are known risk factors for poor outcome after aneurysmal SAH (3, 5, 6, 9, 11). One study (10) has also demonstrated that anticoagulation therapy is associated with worse outcome. On the other hand, the impact of antiplatelet usage on outcome after SAH is less clear. One study (12) revealed no significant impact of prehemorrhage aspirin usage on long-term outcome after aneurysmal SAH. Other studies (4, 7), amalgamated in a comprehensive review (1), have suggested a potential beneficial effect of antiplatelet