Journal Club: Association between aspirin dose and subarachnoid hemorrhage from saccular aneurysms

A case-control study

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Risk factor modification is important in the prevention of aneurysmal subarachnoid hemorrhage (aSAH) in patients with unruptured aneurysms. Currently there are conflicting data on the role of antiplatelet and antithrombotic agents in the prevention of aSAH. Recent studies and meta-analyses show mixed findings, with some suggesting that the use of aspirin is associated with increased risk of aSAH^{1,2} and others demonstrating protective effects.³

The study by Can et al.⁴ contributes to this ongoing debate. This Journal Club discusses the study's strengths and weaknesses. The authors concluded that aspirin therapy at diagnosis was associated with a significantly decreased risk of aSAH, with an inverse dose-response relationship among aspirin users. However, once ruptured, aspirin is associated with an increased risk of re-rupture before treatment. Since prior studies have revealed a conflicting role of aspirin in the prevention of aSAH, it is imperative to discuss the findings of this study through a journal club.

Hypothesis and design

The authors sought to address the following questions: (1) Is there an association between aspirin use and aSAH? (2) Is there an association between aspirin dose and aSAH? (3) What is the association between aspirin use and re-rupture risk in patients with an untreated intracranial aneurysm?

This was a case-control study consisting of 4,701 patients and 6,411 aneurysms, and incorporated both cross-sectional data from retrospective chart review and prospectively collected data on a subgroup of patients.

Methods

The study first included a total of 6,063 patients with both retrospectively (4,862) and prospectively (1,201) collected data from the Partners Healthcare Research Patients Data Registry, as well as from datasets at the Brigham and Women's Hospital and Massachusetts General Hospital. The authors then reviewed the medical records and imaging studies to ultimately identify 4,701 patients with 6,411 definite saccular aneurysms. Presumably all identified aneurysms were both intracranial and intradural, though the authors do not specify if they excluded patients with cavernous carotid aneurysm, superior hypophyseal, or other intracranial extradural aneurysms. The authors also do not specify how many of these patients had prospective data compared to cross-sectional data at the time of presentation, nor do they specify the number of patients with unruptured aneurysms who were prospectively followed. The authors then divided these patients into 2 groups: disease group with ruptured aneurysms and

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control group with unruptured aneurysms. They then evaluated the association of exposure to aspirin therapy with aneurysm rupture status at presentation.

Analysis of the differences in the baseline characteristics between the 2 groups was done using *t* tests for continuous and Pearson χ^2 tests for categorical variables. It is unclear why the authors did not utilize nonparametric analyses for data that are not normally distributed. To evaluate the association between aspirin use/dosage and subarachnoid hemorrhage (SAH) from saccular aneurysm, the authors used univariable and backward stepwise, multivariable logistic regression models. Sensitivity analysis was conducted to examine if results in all patients with antiplatelet therapy were different from those with aspirin use.

Results

Of the 4,701 patients with saccular aneurysms, 4,102 patients were not taking any antiplatelet drugs, whereas 599 were on antiplatelet therapy. Of the patients on antiplatelet therapy, 517 were on aspirin and 82 were on nonaspirin antiplatelet medications. A total of 1,302/4,701 (28%) patients had aSAH. Overall, patients on aspirin therapy were significantly older and were less likely to present with SAH. In addition, patients on aspirin therapy were less likely to be current smokers but more likely to have coronary artery disease, myocardial infarction, atrial fibrillation, or hypertension, as well as to be taking antihypertensive medications. In weighted multivariable analysis, black race (odds ratio [OR] 2.03, 95% confidence interval [CI] 1.42–2.91), Hispanic race (OR 1.82, 95% CI 1.18–2.81), Asian race (OR 2.86, 95% CI 1.39–5.86), and current alcohol (OR 2.07, 95% CI 1.60–2.68) and tobacco use (OR 1.39, 95% CI 1.09–1.78) were significantly associated with aSAH, whereas aspirin use (OR 0.65, 95% CI 0.53–0.81) and female sex (OR 0.64, 95% CI 0.49–0.84) correlated with lower risk of aSAH. Higher aspirin dose (unweighted OR 0.72, 95% CI 0.60–0.85, weighted OR 0.65, 95% CI 0.53–0.81) was also significantly associated with decreased risk of aSAH. In a small subgroup of patients (*n* = 17) with aneurysm re-rupture (4 were on aspirin at the time of rupture), aspirin therapy was significantly associated with increased risk of re-rupture. Sensitivity analysis showed that the results for patients on all antiplatelet therapy were not any different from patients on only aspirin.

Discussion/interpretation

The major strengths of this study include the use of machine learning algorithms and manual review of medical record and imaging data to identify patients from the organization registries and electronic medical records, which is likely much more reliable than diagnosis codes alone. Another strength of the study was the sensitivity analysis that demonstrated similar results among patients with aspirin or the use of any other antiplatelet agent.

Though the authors have done well to select a population of patients with unruptured intracranial aneurysms as the control group, there are some major limitations to the study design. First, it is unclear why patients with unruptured aneurysms presented in the first place, whether these aneurysms were incidental findings or generated symptoms leading to presentation. Second, a true control group would include a random sampling of an age-matched population of patients with unruptured intracranial aneurysms in the community, not merely patients who presented to the hospital or clinic and were found to have an unruptured aneurysm (selection bias). Though the authors attempt to identify and control for differences between those with ruptured vs unruptured aneurysms through propensity-weighted score matching and multivariable analysis, these do not account for lead time bias such that patients with unruptured aneurysms present earlier in the disease course and may have not been exposed to a rupture risk for as long as those who presented with aSAH. Not knowing the duration of time an aneurysm is present, and hence the time frame of risk exposure, makes it a significant limitation of this study and substantially mitigates against any conclusions that can be drawn about other exposures contributing to rupture (including aspirin use).

Overall, this study demonstrates that aspirin use is more common in patients who present with unruptured intracranial aneurysms than those who present with SAH. However, without knowing the time course of disease, it is impossible to conclude that aspirin reduces the risk of aneurysm rupture (since risk is inherently measured over time). Instead, it is possible that aspirin use among patients with cardiovascular disease (as in this cohort) increases the risk of undergoing a vascular study that reveals an incidental unruptured aneurysm. A preferable study design would have been one in which the authors presented their prospective data following patients with unruptured intracranial aneurysms who were or were not exposed to aspirin and then reported on the rate of aneurysm growth and rupture stratified by aspirin use.

Other limitations include the fact that the duration of aspirin or antiplatelet exposure was not identified in this study. While several studies suggest that inflammation is linked to aneurysm formation, growth, and rupture,⁵ short-term use of an antiplatelet agent does not plausibly reduce inflammation-mediated aneurysm rupture.¹ Further, since it is unclear why those with unruptured aneurysms came to medical attention, it is possible that headache related to an unruptured aneurysm led to short-term aspirin use.

Both hypertension and smoking are associated with an increased risk of aneurysm rupture.⁶ Aspirin users had lower rates of smoking and higher rates of antihypertensive medication use. Though this does not tell us about blood pressure control among aspirin users, it may represent a marker for better medical care in this group. Other important risk factors for aneurysm rupture are aneurysm size^{5,7} and the location of aneurysms,⁸ which were not accounted for in this study. The

authors did report size of the largest aneurysm but it does not inform about the average size of aneurysms in each group.

When evaluating the association of aneurysm re-rupture and aspirin use, the authors did not account for factors that affect re-rupture risk such as admission Hunt–Hess score, aneurysm size, or the use of antifibrinolytic agents.⁹ Furthermore, the authors report a low 1% rate of aneurysmal re-rupture (17/1,302), compared to the 7%–17% risk that has been reported in several cohorts.^{9,10} This leads one to believe that re-rupture rates were overall under-reported and that there may have been a reporting bias such that aspirin use may have been more frequently documented among those that re-ruptured.

The conclusion that can be drawn from these results is that the prevalence of aspirin use at the time of presentation is higher in patients with unruptured aneurysms than in those with aSAH. Data are lacking on how long these patients harbored the aneurysms or the duration of their aspirin therapy. Due to these limitations, it is not possible to draw conclusions about the use of aspirin and the risk of aneurysm rupture. We suggest that the element of time is critical to study design when evaluating risk and the true effect of antiplatelet therapies would best be evaluated prospectively or in a randomized study.

Author contributions

S. Agarwal: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval. T. Zhou: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. J. Frontera: drafting/revising the manuscript,

analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision.

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Disclosure

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