Aspirin and intracerebral hemorrhage

Where are we now?

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Summary

For the past 3 decades, aspirin has been widely used for prevention of ischemic stroke and myocardial infarction. Although the evidence supporting the effectiveness of aspirin in prevention of vascular events is clear, data regarding the risk of acute and recurrent intracerebral hemorrhage related to the use of this medication have been conflicting. We review past and contemporary data on aspirin use in relation to intracerebral hemorrhage.

Aspirin, or acetylsalicylic acid (ASA), was synthesized in 1897 by the German chemist Felix Hoffmann.¹ Its original and current indication is for control of pain and inflammation. Seventy years after its initial formulation, ASA was shown to block platelet aggregation by inhibition of thromboxane A₂.² Now it is well-known that ASA is effective in prevention of myocardial infarction (MI) and ischemic stroke (IS) and has been used in that capacity for the past 3 decades.³ Since its expanded utilization, the risk of bleeding has been a concern for physicians. For neurologists, this concern particularly involves balancing the risk of intracerebral hemorrhage (ICH) with the benefits afforded by IS prevention. The effectiveness of ASA in prevention of IS is indisputable. A meta-analysis of 18 trials reported a 23% reduction in IS risk with antiplatelet therapy.⁴ Because of its widespread availability and low cost, ASA is the most widely used drug in the world.⁵ However, studies regarding the effect of prior ASA use on ICH development, growth, and outcome have found conflicting results. The authors present past data and the most recent information on ASA use and ICH.

Pharmacology

The antithrombotic property of ASA is related to its inhibition of the cyclooxygenase (COX) enzyme. COX metabolizes arachidonic acid to a variety of prostanoids, including thromboxane

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp.**

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ASA, a potent vasoconstrictor and platelet agonist. ASA blocks the activity of this enzyme irreversibly and hence is effective in a once-a-day dosing regimen.⁶ ASA is also thought to have potential antioxidant properties that help decrease the progression of atherosclerosis and improve endothelial dysfunction in atherosclerotic vessels.⁶ The plasma half-life of ASA is only 20 minutes; however, because platelets cannot generate new COX, the effects of ASA last for the duration of the life of the platelets (10 days).⁶

Risk of acute ICH

Since the early use of ASA in secondary prevention of MI, the small but definitive risk of ICH has been recognized; this risk was noted with acute ASA therapy in MI as well as during preventative use of ASA in patients with chronic cardiovascular disease. The second International Study of Infarct Survival (ISIS-2) unequivocally proved the benefit of 160 mg/day of ASA in survival after MI. Only 5 cases of ICH were reported among over 8,000 patients who were randomized to ASA alone in ISIS-2.⁷ The first randomized double-blind prospective study of 75 mg/day of ASA in chronic stable angina was the Swedish Angina Pectoris Aspirin Trial, in which over 2,000 patients were enrolled.⁸ Only 13 subjects in this study had an ICH. Early trials investigating the benefit of ASA in IS showed similar rates. The International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) were 2 studies that demonstrated the benefit of ASA in reduction of recurrent IS and death when administered within 48 hours of symptom onset (300 mg/day in IST and 160 mg/day in CAST).^{9,10} Combined, these 2 trials enrolled over 40,000 patients. ICH was reported in 1.1% of patients in CAST and 0.9% in IST, not significantly different from placebo.^{9,10}

The reported risk of ASA-associated ICH varies from one study to another, but it is consistently low. Early studies looking at the risk factors for acute ICH revealed that the use of ASA (or other nonsteroidal anti-inflammatory drugs) in the week prior to the event onset was an insignificant contributor compared to controls (after adjusting for confounding variables).¹¹ A recent longitudinal, population-based study looking at 1,797 ICH cases showed that, after adjusting for age, sex, calendar year, alcohol use, body mass index, hypertension, and health services utilization, ASA was not associated with an increased risk of ICH compared with no therapy.¹² The results of 6 meta-analyses involving more than 300,000 patients over an 8-year time span allow a more precise estimate of the true risk of ICH associated with ASA.¹³ A reasonable estimate of that risk is 0.2 events per 1,000 patient-years, which translates into 1 ICH among 1,000 people treated with ASA over 5 years.¹³ Compared to the benefit of ASA in secondary prevention of IS, this risk is negligible.^{14,15}

Does the benefit also outweigh the risk in primary prevention of IS? Primary prevention of general cardiovascular disease is recommended for persons whose risk for coronary artery disease is $\geq 10\%$ over 5 years.¹⁶ This is a recommendation by the American Heart Association (AHA) to improve the likelihood of a positive balance of coronary risk reduction over bleeding and ICH caused by ASA.¹⁷ This approach is not recommended specifically for primary prevention of IS.¹⁷ Based on the most recent AHA guidelines specifically addressing stroke, ASA is not beneficial in primary stroke prevention for persons at low risk, but can be useful in women with sufficiently high risk factors.¹⁷ These risk factors included hypertension, hyperlipidemia, diabetes, or having a 10-year cardiovascular risk $\geq 10\%$.¹⁷ This recommendation is based on the results of a study that showed the benefit of alternating-day ASA in primary IS

prevention was substantial (24%) compared to the insignificant risk of ICH.¹⁸ The benefit was most consistent in women above age 65 years over a 10-year period. Pooled data from all 5 randomized primary prevention trials showed that therapy with ASA had no effect on the incidence of IS, unless there was a preexisting history of vascular disease.¹⁹ Considering these results, ASA should not be used for prophylaxis against first IS, except for women above age 65 years and in situations where specific risk factors are present.

Although there is no consensus on when to restart ASA in ICH survivors, studies have shown that ASA use does not significantly increase the risk of recurrent ICH.²⁰ However, this largely depends upon the etiology of the ICH. Preexisting susceptibility factors need to be considered. In multivariate analyses adjusting for baseline clinical predictors, ASA independently increased the risk of lobar ICH recurrence.²¹ A population-based, cross-sectional analysis using MRI demonstrated that antiplatelet agent use, especially ASA, was significantly related to the presence of cerebral microhemorrhages (CMH).²² ASA, but not other antiplatelet medications, was associated with CMH in patients presenting with ICH.²³ A major determinant of safety of ASA use in patients with preexisting CMH (who have not had an ICH) appears to be the quantity of CMH. In 252 patients with a history of IS and known CMH, the benefit of ASA use outweighs the risk of ICH unless ≥ 5 CMH were present.²⁴

Aside from CMH, other factors could contribute to the occurrence of ASA-associated ICH. Because hypertension is the most common cause of ICH and many patients with hypertension are on ASA for cardiovascular disease prevention, it is natural to assume a synergistic effect of the 2 in development of ICH. In the Hypertension Optimal Treatment trial, in which nearly 19,000 patients with a history of hypertension were randomized to ASA 75 mg/day vs placebo and followed for a mean period of 3.8 years, the rates of fatal and nonfatal ICH were similar in both arms.²⁵

Major hemorrhage related to ASA appears to occur in a dose-related fashion, but gastrointestinal (GI) bleeding is probably a greater concern than ICH.²⁶ The treatment arms of the United Kingdom Transient Ischemic Attack trial received either 300 mg or 1,200 mg of ASA.²⁷ There was no difference in the rate of ICH between the 2 dosage arms, although the investigators contended that this was an underestimate of the true number. Presently, prescribing doses as high as 1,200 mg is rare, even in clinical trials. Physicians realize the increased risk of GI symptoms with high-dose ASA, equivalent benefit at lower doses, and the availability of alternative antiplatelet agents. Therefore the practice of ASA dose escalation and its associated risks are now rare occurrences.

Effect on outcome

Assessing the potential effect of ASA use on ICH requires consideration of the established factors known to affect outcome. The chief determinant of outcome after ICH is size of the hematoma.²⁸ Despite the qualitative impairment of platelet function resulting from ASA use, retrospective assessment of its effect on initial hematoma volume is conflicting.^{29,30} The association of ASA use with hemorrhagic expansion is less controversial. Hematoma enlargement after spontaneous ICH is well-documented and common.^{e1} Perhaps the only circumstances limiting our capacity to observe expansion in all patients is the sensitivity of detection and acuity of neuroimaging.^{e2} Furthermore, this expansion is not clinically benign, and is associated with the natural history of deterioration seen in this patient population. Patients with antecedent ASA use have been shown to have a greater propensity for hemorrhagic expansion.^{e3,e4} Whereas hematoma enlargement, in general, is thought to result in poorer outcomes, the link of ASA-associated expansion to worsened morbidity and mortality has been difficult to prove unequivocally. Saloheimo et al.^{e5} reported that ASA was an independent risk for death among 208 ICH patients in a retrospective Finnish study. One report relating worsened outcome to prior ASA use cites hypertension as a contributing factor to this decline.^{e6} Yet other studies fail to document any adverse effect of ASA use on ICH outcome.^{e7} It is uncertain whether measurables, such as platelet aggregometry or detection of a “spot sign,” may improve correlation. In previous studies assessing acute hemostatic treatment of ICH, reduction in hemorrhage expansion has

Supplemental Data

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not readily correlated with improved outcome.^{e8} As a result, it is important that the effect of ASA use not be extrapolated from observations on expansion, nor the necessity of treatment be presumed based upon perceived platelet function.

The role of platelet transfusion

The utility of platelet transfusion (PLT) in ICH patients who have used ASA prior to the event (and have normal platelet count) is unknown. In its Evidence-Based Platelet Transfusion Guidelines, the American Society of Hematology does not specifically address this question for any type of hemorrhage, including ICH.^{e9} Ducruet et al.^{e10} retrospectively analyzed 66 ICH patients who had been on antiplatelet agents prior to the hemorrhage. Thirty-five patients were transfused with platelets; 31 were not. The 2 groups were not randomized, but were well-matched. There were no significant differences in rates of hematoma expansion between cohorts.^{e10} Creutzfeldt et al.^{e11} reviewed records of 121 patients who were taking antiplatelet agents (105 taking ASA) prior to ICH, 53 of whom received PLT. The investigators noted that PLT did not prevent hospital death or have any benefit on outcome.^{e11} On the other hand, in patients who have measured platelet dysfunction on admission, PLT may be beneficial.^{e4} Naidech et al. identified patients with aggregometer-proven platelet dysfunction as “high risk” and reported that in this particular group of ICH patients, early (within 12 hours) PLT improved platelet activity assay results and was associated with smaller final hemorrhage size and more independence at 3 months.^{e4} In all 3 studies, PLT was given at the “discretion of the attending physician” and the latency from ictus to treatment varied among patients. An important lesson from these analyses is that timing of PLT may be a factor that affects outcome. Rapid aggregometry techniques could play an essential role in selecting patients who are candidates for PLT.

DISCUSSION

As the population ages, ASA is increasingly used in patients with cardiovascular and ischemic cerebrovascular disease. The effect of ASA on ICH occurrence is difficult to predict given comorbidities that exist among those taking this medication. Another impediment to accurate assessment of this effect is the low incidence of ASA-associated ICH. ASA seems to be more of an exacerbating factor for hematoma expansion, rather than a direct cause.

Since a reasonable understanding of the risks and benefits of ASA exists, neurologists should take several points into consideration when prescribing this medication. First, there should remain no doubt that the benefit of ASA in secondary prevention of IS is greater than its risk for ICH. A Cochrane review of 8 trials involving 41,325 patients conclusively substantiates this fact. Even in the 771 ICH patients who were included (which occurred before brain CT scan), the trend towards a better outcome in the ASA group persisted, although this was no longer significant.^{e12} Whether or not ASA use following ICH reduces coronary events or overall death is unknown.

Second, the use of ASA for primary prevention of IS should not be indiscriminate and only be reserved for a subset of patients who have defined risk factors. The prospect of a fixed-dose combination cardiovascular pill, or the “polypill” (comprised of ASA, an antihypertensive agent, and a statin), may determine if the benefit of ASA in primary and secondary prevention of cardiovascular events are equivalent. Once available, the polypill could theoretically show if management of cardiovascular risk factors in combination with ASA is more effective than ASA alone in primary prevention of IS and coronary events. The effect of the polypill on ICH—harmful or beneficial—awaits a randomized trial to determine its benefit in clinical outcomes of patients with established coronary artery disease.

Third, although some evidence suggests that the risk of ASA-associated ICH may not be dose-dependent, the risk of GI hemorrhage is. Considering this risk and the ineffectiveness of high-dose ASA in providing extra protection against IS, the practice of using doses larger than 325 mg should be abandoned.

Fourth, in patients with lobar hemorrhages, the perceived benefit of starting or restarting ASA must be weighed against the potential risk of ICH recurrence. Whereas lobar hemorrhage location has been tied to greater risk of ICH recurrence, it is unclear if these risks surpass the benefits of secondary prevention from ischemic vascular disease. Quantification of CMH foci on MRI may assist in making that determination.

Finally, for acute therapy of ASA-associated ICH with PLT, more studies are needed to prove that a positive effect on outcome incontestably exists. Prior to undertaking studies designed to demonstrate improved outcome related to PLT, poor outcome causality should be clearly established first.

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STUDY FUNDING

No targeted funding reported.

DISCLOSURES

R. Behrouz serves as a Contributing Editor to *Practical Neurology* and as an Associate Editor for *BioMed Central Neurology* and has participated in medico-legal cases. C.M. Miller reports no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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