Aspirin-Use Before ICH
A Potentially Treatable Iatrogenic Coagulopathy?

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See related article, pages 129–133.

Oral anticoagulant use and, to a lesser extent, antiplatelet therapy increase the risk of intracerebral hemorrhage (ICH). Individuals who experience ICH while taking anticoagulants tend to have larger hemorrhages and poorer outcomes, and may be more likely to experience enlargement of their hematomas after hospital admission. In this issue of Stroke, Saloheimo and colleagues report data from a single center that suggest the same may be true of patients taking aspirin at the time of their hemorrhage. In this population-based study, regular aspirin-use at onset was an independent risk factor for death by 3 months after hemorrhage (RR 2.5; 95% CI, 1.3 to 4.6). However, only three quarters of the 208 patients in the study were scanned initially on the day of ictus, and only half had repeat scans. Warfarin users had a 73% mortality rate, by far the highest. However, the 43% mortality rate among aspirin users was significantly higher than the 22% mortality rate among nonusers of aspirin or warfarin. Because their initial ICH scores and hematoma sizes were comparable, the authors speculate that hematoma growth may have been the cause. Indeed, by one measure, aspirin use was significantly associated with relative hematoma growth among those individuals who were rescanned, although the association between hematoma growth and mortality did not reach statistical significance. The authors acknowledge that regular aspirin-use may have acted as a proxy for several factors, such as age, diabetes and preexisting vascular disease that, although not independent predictors of mortality, may have collectively increased the risk of mortality. Of course, these 2 explanations may be synergistic rather than mutually exclusive; older patients with more advanced vascular disease may be more susceptible to the mass effect induced by hemorrhage expansion.

Despite its limitations, this study provides added evidence that aspirin-use before ICH is a risk factor for continued bleeding and poorer outcome. The results are comparable to those of 2 other recent studies: Roque et al1 identified antiplatelet (primarily aspirin) use as an independent predictor of 30-day mortality in ICH, and Toyoda et al found 2-fold increased risk of hematoma enlargement, need for surgical evacuation, and mortality among patients who developed ICH while on antiplatelet therapy (aspirin, ticlopidine or cilostazol). Again, those on antiplatelet therapy were older and more likely to have diabetes and pre-existing cerebrovascular or cardiovascular disease.6

Despite earlier, less convincing, studies to the contrary and the possible alternative explanation that aspirin-use is merely a marker for older patients with more advanced vascular disease, it is certainly biologically plausible that the antiplatelet effect of aspirin and similar agents is contributing, via hematoma growth, to increased morbidity and mortality. In fact, in these studies the effect of aspirin-use on early hemorrhage growth may be underestimated if those not rescanned because of worsening necessitating surgical intervention or death were experiencing increased mass effect and were more likely to have been taking antiplatelet agents.

The recent report of a (somewhat unanticipated) marked effect of recombinant activated factor VII (rFVIIa) on reduction in mortality in ICH patients when given within 4 hours of hemorrhage symptom onset suggests improving coagulation processes may be an important avenue of ICH treatment. It would be interesting to know if the benefit of rFVIIa was greater in patients taking aspirin in this Phase II trial.7 This would be consistent with the observations above and with the concept that the mechanism of action of high-dose rFVIIa in enhancing hemostasis in patients with thrombocytopenia and platelet dysfunction, as well as hemophilia, relates to its ability to restore platelet surface thrombin generation.8

Early hematoma growth occurs in 20% to 40% of ICH patients.9,10 Other than a coagulopathy, predictors have not been identified, although inflammatory markers and elevated blood pressure have been implicated.11,12 Antiplatelet use and its attendant platelet dysfunction appear to be another cause. Approximately one third of ICH patients in a recent study were taking antiplatelet agents at the time of their hemorrhage,3 so this may represent a substantial potential target for intervention.

ICH remains the most lethal form of stroke. Clinical trials of surgical interventions have to date failed to demonstrate a significant benefit.13 Ongoing trials of innovative, less invasive evacuation techniques, more aggressive blood pressure control, thrombolysis of intraventricular blood and the pivotal phase III trial of the early use of rFVIIa may demonstrate efficacy of these approaches. Because they can provide larger sample sizes, more systematic data collection, and more standardized and complete imaging information, they also represent an opportunity to validate and expand on the observations of Salokeimo et al. Conceivably, this may lead to an intuitively attractive, albeit less creative, therapeutic approach of directly and rapidly enhancing platelet function.
in ICH patients with presumed platelet dysfunction secondary to antiplatelet agents.

References


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