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Antiplatelet Therapy and the Risk of Intracranial Hemorrhage After Intravenous Tissue Plasminogen Activator Therapy for Acute Ischemic Stroke

Hen Hallelevi, MD and James C. Grotta, MD

Intravenous administration of tissue plasminogen activator (tPA) is currently the only approved therapy for acute ischemic stroke. The drug works by splitting plasminogen into plasmin, ultimately leading to fibrin degradation at the site of cerebral artery occlusion. Even today, more than 10 years after the drug was approved in the United States (and subsequently around the world), its use has been hampered by the fear of inducing symptomatic intracerebral hemorrhage (SICH). This adverse event was seen in 6% of patients treated in the original National Institute of Neurological Disorders and Stroke trial¹ that led to tPA's approval and was subsequently confirmed in multiple postmarketing studies.^{2,3} The predictors of SICH after tPA administration are well known: severe stroke (high National Institute of Health Stroke Scale score) and large hypodensity on the admission computed tomography. Other possible predictors include advanced age, elevated blood glucose, a platelet count of less than 50 000/mL, and systolic blood pressure above 180 mm Hg.^{2,4} Previous works have examined the relationship between prior antiplatelet (AP) therapy and SICH after tPA administration. Notably, in the National Institute of Neurological Disorders and Stroke tPA trial, there was no association between prior aspirin therapy and SICH.⁴ Another multicenter stroke survey showed an association of SICH with aspirin therapy that was lost after controlling for clinical and laboratory variables.² Contrary to that, in this issue of *Archives*, Uyttenboogaart et al⁵ report a surprisingly high rate of SICH after tPA administration in patients undergoing long-term AP therapy. In their cohort of 309 patients derived from a single center in the Netherlands, AP therapy (mostly aspirin or an aspirin and di-pyridamole combination) before the stroke was associated with a 13.5% rate of SICH compared with 2.8% in patients without AP therapy. Drug compliance was not assessed in this study. As expected, patients undergoing AP therapy were older and had more vascular risk factors than patients not taking AP drugs. There were no differences in stroke severity, stroke subtype, blood pressure, blood glucose, or early changes on the admission computed tomographic scan. Despite the high rate of SICH, AP therapy was associated with an odds ratio of 2 for a favorable outcome. How does one settle these seemingly contradictory results and what lessons can we draw from this observation? Let us first look at the role of platelets in acute ischemic stroke.

Platelets react mostly to endothelial injury. Commonly, a fissured atherosclerotic plaque will attract platelets by exposing collagen and releasing mediators, such as thromboxane A₂, into the bloodstream to act on neighboring platelets in a paracrine manner. The result is platelet activation and degranulation and exposure of the platelet IIb/IIIa receptor. In addition, the activated platelets incite a chain reaction through release of adenosine di-phosphate, thrombin,

Correspondence: Dr Grotta, The Vascular Neurology Program, University of Texas at Houston, 6431 Fannin St, MSB 7.044, Houston, TX 77030 (james.c.grotta@uth.tmc.edu).

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and other mediators, resulting in massive local and systemic platelet activation. Activated platelets form platelet-platelet and platelet-leukocyte aggregates and adhere to the injured endothelium. The platelet surface also acts as a workbench for thrombin generation, which results in fibrin deposition in the clot. Fibrin creates a scaffold to which platelets firmly adhere via the IIb/IIIa receptor to form a clot. Therefore, it is clear that platelets assume an active role in the pathogenesis and maintenance of the intra-arterial clot.

Now let us look at recanalization after tPA therapy. Intravenous tPA administration leads to fibrin degradation and clot breakdown. Although tPA is successful in recanalizing the occluded artery in up to 78% of cases, this enviable rate of success is dampened by a high rate of acute reocclusion leading to an ultimate rate of 33% partial and 30% full recanalization.⁶ Timely recanalization is one of the most important factors determining patients' recovery from a stroke.⁷ It is very likely that activated platelets, as well as clotting factors, participate in the violent struggle between fibrinolysis and clot formation, pushing the pendulum toward reocclusion. Indeed, this line of thought has led to the formation of 2 National Institutes of Health-funded clinical trials looking at adjunct therapy to tPA in an effort to prevent reocclusion and improve recanalization rates: one using argatroban (a thrombin inhibitor)⁸ and the other using eptifibatide (a IIb/IIIa-receptor antagonist) (clinicaltrials.gov identifier: NCT00250991). Both trials are ongoing, but so far, there are no reports of excess SICH rates.

The mechanisms behind the production of SICH are complex. Recanalization is probably necessary.⁹ Once arterial flow is restored to the ischemic tissue, a lot depends on the injured vasculature beyond the occluded segment. Small, asymptomatic hemorrhagic transformation is commonly seen in patients given tPA (or without therapy) and may result from microvascular leakage in the infarcted tissue. The larger parenchymal hematoma leading to neurological worsening (ie, SICH) is probably the result of a larger arterial breakdown. This may occur if the vessel has been ischemic for long enough to cause severe endothelial and adventitial necrosis, allowing for vessel rupture. Support for this comes from the identification of a malignant pattern on pretreatment magnetic resonance imaging in patients who have had a stroke. This pattern, consisting of a large volume of tissue with positive diffusion-weighted imaging (indicating infarction), has been correlated with a high likelihood of developing SICH after tPA treatment.⁹ It is quite possible that any factor contributing to coagulopathy in these settings will increase the likelihood or severity of SICH. The most important one is probably tPA itself, but platelet inhibition may also play a role.

Based on previously published studies and our personal experience, it is doubtful that prior AP therapy alone is responsible for a rate of SICH greater than 13%. Because recanalization needs to occur to produce SICH, it is possible to conclude that the high rate of SICH in the Dutch cohort simply indicates that platelet inhibition before tPA therapy improves the rate of recanalization. The 2-fold increase in the rate of a favorable outcome, despite older age and comorbidities in the AP group, is a clear signal that this may in fact be the case.

How should we proceed as clinicians given these new data? Acute stroke care is still wrought with uncertainties and we have an obligation to ensure patient safety while struggling to reduce stroke morbidity. Certainly, we need to monitor the rates of SICH and keep identifying modifiable predictors. One way to improve the quality of our data is to look at large multicenter cohorts. The recently reported European tPA registry of 6483 patients given tPA within 3 hours of symptom onset is an excellent example.³ Analysis of this cohort should generate reliable data regarding any possible association among AP therapy, SICH, and favorable outcomes. Patient reporting of prior medication use is often inaccurate and compliance is hard to determine, especially in acute settings. If prior AP therapy is indeed shown to be associated with an unacceptably high rate of SICH in a large cohort, it may be possible to better assess the risk using rapid platelet function testing. At the present time, we firmly believe that prior

AP use should not discourage physicians from administering tPA to patients undergoing an acute stroke. The association of favorable outcomes with prior AP therapy makes good clinical sense and should encourage us in the effort to devise better recanalization strategies using additional manipulations of selected hemostatic components in addition to tPA. Fear of SICH is understandable but should not deprive stroke patients of effective therapy or a chance to recover from the devastating effects of an ischemic stroke.

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