Brain Hemorrhage After Thrombolysis: Good or Bad?

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Intracranial bleeding is the most feared complication of thrombolytic therapy in acute stroke. The risk of brain hemorrhage is the main argument of the European authorities not to approve recombinant tissue plasminogen activator (rtPA), and the fear of hurting patients with rtPA explains its limited use in North America. The common argument is, “Treatment with rt-PA may have some beneficial effect, but that is traded off by a considerable risk of symptomatic hemorrhage.”

This argument is false and based on misunderstanding and misconception. The misunderstanding: There is no such trade-off. The National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study Group observed 2 patients (0.6%) with symptomatic and 1 patient (0.3%) with fatal hemorrhages in the placebo group (n = 312) and 20 patients (6.4%) with symptomatic and 9 patients (2.9%) with fatal hemorrhages in the rtPA group (n = 312).1 Despite this supposed excess in risks caused by rtPA treatment (odds ratios [OR], 10.6 and 9.2), rtPA treatment significantly reduced the risk for disability and death (modified Rankin Scale > 1 at 12 months after stroke) from 73% to 59% (reduction for death alone: 28% to 24%).2 In both European Cooperative Acute Stroke Studies (ECASS) 1 and 2, rtPA increased the risk for parenchymal hematomas (OR, 3.0 and 4.2), but reduced the overall risk for disability and death by 6% and 8% (NS).3,4 A similar observation—an overall risk reduction for disability and death despite an increased risk for intracranial hemorrhages—was made in the Multicenter Acute Stroke Trials (MAST) -Europe and -Italy.

Why does an excess of symptomatic and fatal hemorrhages not result in an excess of disability and death at the end of the studies? How can an agent that bears such risks be paradoxically beneficial? There are 2 possible answers: (1) the devastating effect of intracerebral hemorrhages (ICH) is traded off by the beneficial effect of rtPA in strokes without hemorrhagic transformation; and (2) the concept of symptomatic and fatal hemorrhages is misleading, because the hemorrhagic transformation of ischemic brain tissue is not devastating in all patients, and the presence of ICH is not itself a proof of blood being the cause for the patient’s death or clinical deterioration.

The article by Molina and colleagues in this issue5 and previous work6,7 show that the widely accepted association between ICH after ischemic stroke and poor clinical outcome is questionable at least.

Symptomatic intracerebral hemorrhage was defined as any CT-documented hemorrhage within 36 hours of stroke onset that was temporally related to deterioration in the patient’s clinical condition.8,9 This definition suggests that hemorrhage in the brain tissue is per se responsible for clinical deterioration and neglects other pathological findings, eg, ischemic edema, that may as well cause clinical deterioration. Patients 12, 13, 18, 19, 21, and 22 reported by the NINDS rtPA Study Group8 and patients 1, 2, 9, 11, and 12 reported by the PROACT II investigators10 represent examples of ischemic edemas with more or less hemorrhagic transformations that may or may not contribute to the clinical course. If we accept that hypodense brain tissue on CT represent irreversible damage,11 some hemorrhagic transformation of dead brain tissue will not matter at all.

The ECASS investigators distrusted the concept of symptomatic hemorrhage and categorized the posts ischemic hemorrhagic transformations according to radiographic criteria.12 Neither the presence of hemorrhagic infarctions (HI) nor the presence of small parenchymal hematomas without a prominent space occupying effect (PH1) influenced the risks of early deterioration, disability, or death at 3 months.6,7 Only parenchymal hematomas with substantial space-occupying effect covering more than one third of the infarcted tissue volume were associated with an increased risk of early deterioration, disability, and death. This association does not, however, prove that the hematoma per se causes the risks. A hemorrhagic transformation of ischemic brain tissue consists of a mixture of ischemic edema and secondary evasion of blood into the tissue. On CT, the hemorrhage may completely obscure the edema. The ischemic damage is primarily responsible for the functional disturbance. Edema, hemorrhage, or both may cause the space-occupying effect that could cause further functional impairment. It is human that we like to accuse the visible hematoma of being responsible for the patient’s symptoms and neglect the effect of the underlying invisible edema.

Molina and colleagues now nicely shed more light onto the black box of stroke treatment.5 They assessed the time of recanalization in 32 patients with proximal middle cerebral artery (MCA) occlusions treated with rtPA within 3 hours of stroke onset and found recanalization in 53% of patients within 6 hours, in 69% within 12 hours, and in 78% within 24 hours. These frequencies of MCA recanalization are considerably higher than in patients not consistently treated with rtPA13 and support the impression that treatment with 0.9

See article on page 1551

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mg/kg rtPA IV can actually recanalize cerebral arteries. We learn that treatment within 3 hours of stroke onset does not mean reperfusion within 3 hours in all patients. Moreover, these data show, in agreement with Ringelstein et al,11 that the time period between stroke onset and arterial recanalization affects the volume of infarcted brain tissue and the type of hemorrhagic transformation. Early recanalization is associated with HI, reduced infarct size, and good clinical outcome, whereas delayed recanalization is associated with increased infarct size and parenchymal hematoma (PH). The observations of Molina et al can resolve the contradiction between an increased risk of symptomatic hemorrhage and a beneficial clinical outcome caused by thrombolytic treatment: A slight hemorrhagic transformation of ischemic infarcts is a marker of reperfusion and may be associated with good clinical outcome. A PH after ischemic stroke is a marker of delayed reperfusion and consequently increased infarct size and may be associated with poor clinical outcome. Early treatment with rtPA is beneficial. In about one quarter of patients with proximal MCA occlusions, recanalization is, however, delayed and results in extended infarcts with PH. In another quarter of patients treated with rtPA, as in patients without thrombolytic treatment, recanalization cannot be achieved, and extended infarcts without hemorrhagic transformation may result.

In summary, slight hemorrhagic transformation of ischemic brain tissue is associated with relatively small infarcts and a good prognosis. More dense and extended hemorrhagic transformation (PH) is associated with delayed reperfusion and often large infarcts, indicating a poor prognosis. Early treatment with rtPA provides a chance to keep infarcts small and to avoid disability and death. If recanalization is delayed, brain infarcts may be more extended and carry PH. No recanalization will result in large infarcts without hemorrhagic transformation. We should interpret PH after ischemic stroke as a bad prognostic sign, but not as the cause of deterioration in the patient’s clinical condition. To make it very simple, the treatment with rtPA enables reperfusion that restricts the extent of ischemic damage and may redden the infarcted brain tissue. It is, however, not the color the patients suffer from; it is the ischemic tissue damage. The pure effect of extravasal blood is hard to assess. The term symptomatic or fatal hemorrhage falsely suggests that treatment with rtPA increases the risk of disability and death. Consequently, the treatment is withheld from patients who may benefit from this treatment, and the European Agency for the Evaluation of Medical Products (EMEA) likes to see another randomized trial, which means to withhold the effective dose of rtPA from acute stroke patients. The term symptomatic hemorrhage is an example of how language can spoil thinking; it should be deleted.

References


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