Cerebral Hemorrhage Following Thrombolysis in Stroke

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SUMMARY

Hemorrhagic transformation (HT) of ischemic brain tissue occurs in treated and non-treated stroke patients with excess after thrombolytic therapy. It has different radiological appearances, and may be detected on CT when the patient deteriorates clinically. HT is thus the main safety concern after thrombolytic therapy. The exact assessment of this risk requires a clear definition of HT in general and especially the definition of hemorrhages that may cause clinical deterioration. This concept should include a description of the assessment of HT, a hypothesis of the cause of HT, and considerations regarding the effects of blood on cerebral function under the conditions of ischemic edema.

Observations on the radiological appearances of HT support the view that only dense hemorrhages (hematomas) causing mass effect are clinically relevant. In patients with extended ischemic infarcts causing compression of surrounding brain tissue and sometimes shift of midline structures, the effect of blood within the ischemic tissue is hard to assess. Because HT has a higher incidence in large ischemic lesions, the combination is often observed. It has been shown that HT is associated with tissue reperfusion. Tissue reperfusion is, however, the precondition to keep cerebral infarcts small. If HT is a marker for arterial recanalization and reperfusion of ischemic brain tissue, it may be associated with clinical improvement. The association of HT with reperfusion may explain the observation that treatment with thrombolytics is beneficial despite the excess of HT. The term “symptomatic hemorrhage” is, therefore, at least questionable and misleading, if not very carefully defined.
INTRODUCTION
Several large, randomized, placebo-controlled trials of thrombolytic therapy in acute ischemic stroke have been conducted during the past years. Secondary HT following ischemic stroke and thrombolytic therapy is frequently reported as the most important safety parameter in these studies, but HT also occurs as a natural event in the evolution of a cerebral infarct. The increase of HT in the actively treated arm is even used as evidence against the treatment tested. Three streptokinase trials were terminated prematurely because of a higher incidence of death and bleeding complications in the actively treated groups. Although the large European and American trials with recombinant tissue plasminogen activator (rt-PA) provided evidence for a benefit in ischemic stroke patients, intracranial bleeding is the most feared complication of thrombolytic therapy in acute stroke. The risk of brain hemorrhage has been the main argument of the European authorities not to approve rt-PA, and the fear of hurting patients with rt-PA 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." I intend to show and prove that this argument is false and based on misunderstanding and misconception.

THE PARADOX EFFECT OF HEMORRHAGIC TRANSFORMATION ON CLINICAL OUTCOME
The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group observed 2 patients (0.6%) with symptomatic and 1 patient (0.3%) with fatal hemorrhage in the placebo group (n = 312), and 20 patients (6.4%) with symptomatic and 9 patients (2.9%) with fatal hemorrhage in the rt-PA group (n = 312). Despite this supposed excess in risks caused by rt-PA treatment (odds ratios: 10.6 and 9.2), rt-PA 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%). In both European Cooperative Acute Stroke Studies (ECASS) 1 and 2, rt-PA increased the risk for parenchymal hematomas (odds ratios: 3.0 and 4.2), but reduced the overall risk for disability and death by 6% and 8% (n.s.). 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 a considerable beneficial effect of rt-PA in strokes without hemorrhagic transformation. 2) The concept of symptomatic and fatal hemorrhages is false, because the hemorrhagic transformation of ischemic brain tissue is not devastating in all patients, and the presence of HT does not per se mean that blood is the cause for the patient’s death or clinical deterioration.

TYPES OF HEMORRHAGIC TRANSFORMATION OF ISCHEMIC BRAIN TISSUE AND THE EFFECT ON CLINICAL COURSE

Unfortunately, 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.12,13 This definition suggests that hemorrhage in the brain tissue is per se responsible for clinical deterioration and neglects other pathological findings, e.g. ischemic edema that primarily affects brain tissue and may as well cause clinical deterioration by further extension and mass effect. Patients no. 12, 13, 18, 19, 21, and 22 reported by the NINDS rt-PA Study Group12 and patients no. 1, 2, 9, 11, and 12 reported by the PROACT II investigators14 represent examples of ischemic edemas with more or less hemorrhagic transformations that are unlikely to affect the clinical course. If we accept that hypoattenuated brain tissue on CT represent irreversible damage,15 some hemorrhagic transformation of dead brain tissue will not matter at all.

The ECASS investigators distrusted the concept of symptomatic hemorrhage and categorized the post-ischemic hemorrhagic transformations according to radiographic criteria.16 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.17,18 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. (Figure) 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. Because the extended ischemic tissue injury is the cause for a space occupying edema and HT, it should be considered as the first cause of clinical deterioration.

Figure: CT of 55 years old woman obtained 1 day after stroke and treatment with rt-PA. The patient deteriorated from a baseline NIHSS of 19 at baseline to 46 on day 1. The CT shows a complete MCA- and ACA-infarct with hematoma of the median portion of the infarct and blood within the ventricles. Tissue swelling caused a shift of midline structures to the left. The patient died 4 days after the stroke. Is the cause of death the extended ischemic injury with secondary hemorrhagic transformation of ischemic brain tissue or the hematoma?
CAUSES OF HEMORRHAGIC TRANSFORMATION

Larrue et al. showed that the treatment with rt-PA and a large volume of ischemic injury already on the baseline CT is associated with PH detected by follow-up CT.\(^\text{19}\) That means that extended ischemic injury is more likely to show HT, if treated with rt-PA. A study of reperfusion after treatment with rt-PA strongly supports this view.\(^\text{20}\)

Molina et al. nicely shed more light into the black box of stroke treatment.\(^\text{20}\) They assessed the time of recanalization in 32 patients with proximal MCA occlusions treated with rt-PA within 3 hours of stroke onset and found recanalization in 53% of patients within 6 hours, in 69% of patients within 12 hours, and in 78% of patients within 24 hours. These frequencies of MCA recanalization are considerable higher than in patients not consistently treated with rt-PA\(^\text{21}\) and support the impression that treatment with 0.9 mg/kg rt-PA I.V. can really recanalize cerebral arteries. They show 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.\(^\text{21}\) 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 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 HT 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 area of ischemic injury that is associated with poor clinical outcome. Slight hemorrhagic transformation of ischemic brain tissue is consequently 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 rt-PA 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 of major brain arteries will result in large infarcts without hemorrhagic transformation. We presume, that placebo treated patients have more extended infarcts without HT than rt-PA treated patients, whereas the extended infarcts may show HT after treatment with rt-PA. We suggest, therefore, to interpreting PH after ischemic stroke as a bad prognostic sign, but not as the cause of deterioration in the patient’s clinical condition.
Parenchymal hematoma is caused by reperfusion at a point of extended ischemic damage. The ischemic damage is the cause of clinical deterioration and poor outcome. The dense HT indicates a profound and extended ischemic injury and that rt-PA was inefficient in preventing this injury by timely recanalization.

The false definition of ”symptomatic or fatal hemorrhage” that does not respect the effect of the underlying extended ischemic injury incorrectly suggests in many patients that treatment with rt-PA had caused disability and death, although the cause was the inefficiency of this treatment to prevent the injury by early recanalization. Consequently, the treatment is still withheld from patients who may benefit from this treatment. In this view, the counting of ”symptomatic hemorrhages” in trials has not increased, but impaired the safety of stroke victims.

The author served as a consultant for Boehringer Ingelheim on the steering committees of ECASS 1 and 2.

REFERENCES


