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EDITORIAL

Treatment of ischemic stroke beyond 3 hours: is time really brain?

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From the outset, given that the beneficial effect has been shown only in patients treated during this short time-window, treatment of ischemic stroke with IV recombinant tissue plasminogen activator (rt-PA) has been restricted to patients who present within the first 3 hours of symptom onset and thus is not available to approximately 90% of stroke victims. [1] Importantly, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study investigators provided an explanatory analysis showing that stroke onset-to-treatment time (OTT) is associated with a progressive decline of beneficial treatment response, but not with an increasing risk of symptomatic brain hemorrhage. [2] The authors correctly state that they cannot draw conclusions regarding the OTT-treatment relationship beyond 3 hours. Moreover, even though there is no data to suggest that IV rt-PA therapy beyond 3 hours is either unsafe or ineffective, the United States Food and Drug Administration (FDA) still does not approve ischemic stroke treatment with IV rt-PA beyond the 3-hour window.

Infarct growth and disappearance of penumbra at a steady pace of neural circuitry loss in human ischemic stroke became a popular theory explaining the progressive decline of beneficial response to reperfusion therapy. [3–5] Old observations and, in particular, recent controlled randomized trials, challenge this theory and favor the view that brain infarct growth may happen, but is not the rule in individual stroke patients. Time does not mean progressive loss of brain tissue after each ischemic stroke, and there is a stroke population that can recover with arterial recanalization and restoration of blood supply far beyond 3 hours. [6, 7] The pathological conditions that enable or inhibit benefit from reperfusion therapy are still widely unknown, and the question which major artery occlusion strokes should *not* be treated remains unanswered. [8]

Neuronal recovery of cortical neurons is related to the degree and duration of ischemia. [9] Neurons can tolerate cerebral blood flow (CBF) below 10 ml/100g × min for a maximum of 30 minutes, and can survive ischemic CBF values above 18 ml/100g × min for an indeterminate period of time. Ischemic brain tissue with electrical failure but no neuronal damage was first observed lasting for hours after experimental MCA occlusion in non-human primates and was subsequently named "penumbra." [10] In fact, researchers found "penumbra" even years after MCA occlusion. [11] Modern brain imaging with diffusion-weighted and perfusion magnetic resonance imaging confirmed these findings in ischemic stroke patients showing no infarct growth and persistence of penumbra over 24 hours. [12–14] Additionally, autopsies performed weeks and months after middle cerebral artery (MCA) strokes have shown infarct volumes varying from small to large. [15] Corresponding to these autopsy findings, cerebral blood flow measurements after proximal MCA occlusion in 36 ischemic stroke patients showed a variation of ischemic core volumes between 7 and 70% of the MCA territory volume. Ischemic core volume, however, was not associated with time from onset to imaging. [16] Controlled randomized trials have now clearly demonstrated that thrombolytics and thrombectomy can facilitate neuronal recovery if applied 3 to 24 hours after stroke onset in well-selected patients and thus proved that general exclusion of stroke patients from reperfusion therapy-based on OTT estimates is not justified. [6, 7, 17, 18] If OTT is not associated with increasing loss of brain tissue, how can we explain the decline in treatment response to thrombolysis and thrombectomy with prolonged OTT? [19, 20].

The most recent meta-analysis of individual patient data from randomized trials on IV rt-PA showed excellent functional outcomes (modified Rankin score—mRS 0–1) after ischemic stroke in 259/787 patients (32.9%) treated with IV rt-PA within 3 hours and in 401/1229 patients (32.6%) treated beyond 4.5 hours. Excellent functional outcomes were observed after placebo in 176/762 patients (23.1%) with treatment within 3 hours and in 357/1166 patients (30.6%) treated

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beyond 4.5 hours. [19] This observation suggests that an excess of patients with spontaneous excellent outcomes in the late-treatment population has biased the decline in treatment response and does not indicate a failure of rt-PA. Small ischemic cores or spontaneous arterial recanalization may explain functional recovery in placebo-treated patients. The share of placebo-treated patients with excellent functional outcomes at 3 months after ischemic stroke was 45.2% in patients included between 3 to 4.5 hours and 41.8% in patients with unknown time of stroke onset, another observation suggesting that not all brain infarcts grow. [17, 18].

The DIAS-3 and -4 and DIAS-Japan trials studied the efficacy and safety of desmoteplase 3 to 9 hours after major artery occlusion stroke using functional independence (mRS 0–2) at 3 months as primary endpoint. [21] In a pooled analysis (N = 795), the median OTT was 7.1 hours and the baseline median National Institute of Health Stroke Score 11 (placebo) or 12 (desmoteplase). The primary endpoint was reached by 182/398 desmoteplase-treated patients (45.7%) and 167/397 placebo-treated patients (42.1%) ($p = 0.0786$). Arterial recanalization in this late time-window was achieved in 109/220 desmoteplase-treated patients (49.5%) and 86/224 placebo-treated patients (38.4%) ($p = 0.0168$), and was also closely associated with favorable functional outcome in both treatment groups suggesting that late arterial recanalization is beneficial in an unidentified group of patients.

The benefit from late recanalization is now confirmed by two late time-window thrombectomy trials. After thrombectomy, 6 to 24 hours after stroke with successful recanalization in 84% of treated patients, 52/107 patients (49%) reached functional independence (mRS 0–2) at 3 months compared to 13/99 patients (13%) in the control group. [7] After thrombectomy, 6 to 16 hours of stroke with successful recanalization in 76% of treated patients, 41/92 patients (45%) reached functional independence (mRS 0–2) at 3 months compared to 15/90 patients (17%) in the control group. [6] These results agree with a meta-analysis of the first five controlled randomized trials on thrombectomy that showed patients with successful recanalization at 7 hours after stroke onset reaching functional independence in 49.8%; likewise, 46.1% of patients reached functional independence when thrombectomy was successful at 8 hours, whereas the proportion of functional independent patients was 64.1% with recanalization at 3 hours. [20]

In summary, the decline in response to IV thrombolytics with increasing OTT is hard to explain because essential data such as arterial occlusion site, thrombus length and constitution, recanalization rate, time of recanalization, and development of infarct volume are missing, but late selection of patients with better spontaneous prognosis may explain some of this effect. Conversely, endovascular treatment has been studied in more severe strokes and shows a more pronounced beneficial effect compared to IV thrombolysis that declines less dramatically with increasing OTT. We should now differentiate between failure of thrombectomy and failure of brain tissue reperfusion. [22, 23] However, "successful thrombectomy" requires a clear definition. Thrombectomy may fail because of difficulty accessing the occlusion site with a catheter and thrombectomy device, the thrombus constitution, and/or the chosen thrombectomy technique. Brain tissue reperfusion after "successful thrombectomy" may fail to result in functional recovery because of incomplete reperfusion despite arterial recanalization, extended ischemic infarction, and/or brain hemorrhage. According to the recent late-window trials, patients with small ischemic core and extended penumbra may have the best chance of recovery after thrombectomy. Nevertheless, such patients bear the risk of collateral blood supply failure and second infarction as long as arterial occlusion persists. This is likely one variable explaining the increasing failure of late reperfusion and justifying the urgency of early treatment. Fortunately, early or late thrombectomy after ischemic stroke does not bear the risk of brain hemorrhage and reperfusion trauma. Thus, time is not a basis to exclude major artery occlusion stroke patients from thrombectomy.

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Compliance with ethical standards

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Conflict of interest The author declares he has no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This article does not contain any studies with human participants or animals performed by the author.

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