

INTRAVENOUS THROMBOLYSIS BEYOND THE TIME AND AGE LIMITS.

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The clinical argument for a 3 hours time window from stroke onset to start of systemic thrombolysis with rt-PA are the results of the NIHSS study, which was able to show a significantly improved outcome in the rt-PA treatment arm compared with placebo [1]. Despite 4 other negative trials exploring the time window up to 6 hours, the NIHSS study forms the basis for licensing intravenous thrombolysis with rt-PA for acute ischemic stroke in the USA and Europe in the 3 hours time interval. Currently, only about 5 % of acute stroke patients can be treated by rt-PA. The main reason for that is late arrival in hospital. Although educational measures are able to increase the number of patients arriving in time, the largest impact on patient care would have an extension of the time window.

Despite 4 negative studies in the 0 – 6 hours time range, a metaanalysis of all randomized, placebo-controlled trials of intravenous thrombolysis with rt-PA results in a significant adjusted odds ratio for a favorable clinical outcome up to 4.5 hours from symptom onset (1.40, 95% confidence interval 1.05 – 1.85) [2]. In the 4.5 – 6.0 hours subgroup not only the odds ratio for improvement was insignificant, but the hazard ratio for death was significantly increased to 1.45 (95% CI 1.02 – 2.07). The effect of rt-PA in eligible but otherwise unselected patients is clearly time-dependent: in the time interval of 0 – 90 min the number needed to treat (NNT) lies at 3.5, in the time interval 91 – 180 min at 11, in the interval 181 – 270 min at 13, and in the interval 271 – 360 min already at > 30. Much research has been conducted to extend the time interval for systemic thrombolysis by selecting those patients who are most likely to profit beyond 3 hours after symptom onset.

A suitable way seems to be the application of diffusion and perfusion magnetic resonance imaging (DWI and PWI MRI). Several studies were able to show that systemic thrombolysis can be delivered not only safely between 3 to 6 hours in patients with a significant DWI/PWI mismatch, which resembles penumbral tissue [3, 4], but is more effective than otherwise unselected thrombolysis and significantly improves outcome even in the 3 to 6 hours interval [3]. This approach, however, is resource consuming and can only be provided in specialized centers.

The presence of mismatch is tightly related to the presence of vessel occlusion [5]. Because about 30% of acute stroke patients in a 6 hours window have no detectable vessel occlusion [6], this may explain why the large thrombolysis trials failed to show improvement in the 3 to 6 hours interval. The demonstration of vessel occlusion on MR-angiography has a sensitivity of 0.91 and a positive predictive value of 0.95 regarding the presence of DWI/PWI mismatch [5]. This might lead to the conclusion that patients with vessel occlusion are the main target for thrombolysis with the best benefit to risk ratio and it stands to debate whether the easiest approach to extend thrombolysis beyond 3 hours could be the simple demonstration of a vessel occlusion. Connected with the question of the time interval to treatment is the recanalization time window. While previous small studies suggested a 6 hours recanalization time window, recent studies were able to show that even patients who recanalize between 6 to 12 hours after thrombolysis have a better outcome and lesser lesion growth than patients with a persistent vessel occlusion [7, 8].

With the negative result of a phase III desmetoplas trial within 9 hours in MRI selected patients the study of new thrombolytic agents has received a serious blow.

In many centers the age restriction of up to 80 years is regarded not as arithmetic but rather as biological age. Several studies were able to show, that exclusion of elderly patients out of principal is not justified, since the hazard seems not to be increased when conscientious selection is applied [9, 10].

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