THROMBOLYSIS BEYOND 3 HOURS: IA OR CLOT RETRIEVAL APPROACH?

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Based on the results from the National Institute of Neurological Disorders and Stroke trial, intravenous (IV) recombinant tissue plasminogen activator (rt-PA) is the recommended treatment within 3 hours after stroke onset. Rt-PA increased by 30% the number of independent patients (mRS ≤1), and this benefit was observed despite an increase of symptomatic intracranial bleeding: 6.4% versus 0.6%, respectively for rt-PA and placebo groups (p<0,001). However, three other trials (ECASS I, ECASS II, ATLANTIS), failed to demonstrate IV rt-PA efficacy versus placebo, when the thrombolytic agent was administered within a larger therapeutic window. Improving patient selection with a specific focus on those with a mismatch in diffusion and perfusion MRI has been proposed. But, the DIAS trial, which evaluated another IV thrombolytic agent, the desmoteplase, between 3 to 9 hours in patients selected with the presence of a mismatch, showed no clinical benefit. On the other hand, the intra-arterial (IA) route has shown to be effective and part of therapeutic armamentum for the management of acute ischemic stroke patients beyond 3 hours. To date, there is one randomized, multicentric study, which demonstrated the benefit of IA thrombolysis in patients with an acute middle cerebral artery occlusion. These findings were observed in patients treated within 6 hours after symptoms onset (180 patients randomized, 2/3 in the pro-urokinase recombinant -r-Pro-UK- arm and 1/3 in the placebo arm). PROlyse in Acute Cerebral Thromboembolism trial (PROACT II) showed an absolute benefit of good clinical outcome (mRS ≤ 2) for IA thrombolysis of 15%, respectively 25% for placebo and 40% for r-Pro-UK (P< 0.05). Recanalization rates reached 66% in the r-Pro-UK group versus 18% in the placebo group (P< 0.001). These positive results were obtained despite an intracranial bleeding rate of 10 %.

Bridging IV and IA thrombolysis may be also an option to consider, in order to benefit from advantages of both routes: early administration for IV and better recanalization rates with IA. This approach has been evaluated in the Emergency Management of Stroke bridging trial. Patients with brain infarction < 3 hours received a dose of 0.6 mg/kg of rt-PA IV or placebo, then transferred to the cath lab for IA thrombolysis if an arterial occlusion remained. In 70% of the patients, a thrombus was documented in angiography after IV thrombolysis. Favorable outcome was noticed in 56% of the patients compared to 36% of patients in the NINDS study who had an initial NIHSS ≥ 10 (randomized in the IV rt-PA group) and 40% of the patients (r-pro-UK IA group) in the PROACT II study. Favorable results of the IV-IA combined approach were also reported in the Interventional Management of Stroke II study, which included 81 patients (median NIHSS = 19); the mortality at 3 months reached 16%, comparatively to 21% in the rt-PA group of the NINDS study.

It is currently accepted that prognosis is related to recanalization, but the hemorrhagic risk associated with thrombolysis is clearly a limiting factor of this therapy. In this context, the development of mechanical revascularization techniques are promising in terms of safety and efficacy. In fact, these approaches do not use thrombolytics and may be therefore associated with a lower hemorrhagic risk. Furthermore, this option can be considered when thrombolysis is contra-indicated, or after thrombolysis failure. Reported cases regarding mechanical revascularization successes after thrombolysis failure underlined this potential benefit. Angioplasty, stenting, tools designed for clot extraction in brain arteries (e.g.: Mechanical Embolus Removal in Cerebral Ischemia system) are examples of techniques used for vessel recanalization with or without thrombectomy. These devices achieve high recanalization rates until 8 hours after stroke onset, but are still considered investigational as prospective evaluations versus placebo are lacking. The IA approach, in combination or not with IV thrombolysis, holds great promises for the future, offering a large panel of therapeutic solutions for patients suffering acute ischemic stroke with arterial occlusion.