Invited Commentaries

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Thrombolytic treatment in acute cerebral infarction

“Hyperacute thrombolysis with IV rtPA of acute ischemic stroke: Efficacy and safety profile of 54 patients at a tertiary referral center in a developing country” in this issue of Neurology India have provided further evidence of the high benefits of timely thrombolytic therapy in acute cerebral infarction. In the majority of cases, ischemic stroke is caused by an embolus occluding a cerebral artery and early thrombolytic treatment allows re-establishment of bloodflow before a definite and irreversible brain infarction develops. Meta-analysis of studies of thrombolytic therapy confirms that in patients treated within the first 3h after stroke onset, thrombolysis is more effective than placebo in the reduction of mortality rate or functional dependence. The high benefit of thrombolytic therapy with intravenous t-PA is related to the prevention of death or functional dependence in one of each seven patients treated. Recently, it has been shown that benefits of intravenous t-PA includes not only the use of this agent during the first 3h window after the onset of ischemic stroke, but also up to 4.5h after the onset of symptoms. In daily practice, however, thrombolysis is used in less than 4% of patients with cerebral infarction mostly due to the fact that patients continue to arrive too late to hospitals, so that the majority
of patients are attended out of the range of the 3h window for intravenous thrombolytic therapy and out of the first 6h recommended for the use of intra-arterial thrombolysis.[5] Despite the high benefits of t-PA administration, arterial re-vascularization is not achieved in 30-40% of patients and potentially life-threatening hemorrhagic complications occur in 5-10% of patients.[6]

The SIST-MOST study is an observational pharmaco-surveillance study carried out in different countries of the European Union, the objective of which is to assess the results of thrombolytic treatment with t-PA within the first 3h after stroke onset in patients with well-defined inclusion criteria and attended in qualified centers, although without previous experience in the use of this treatment modality, with an expected follow-up of three years. This study will answer whether satisfactory results obtained in clinical trials are reproducible to clinical conditions of daily practice in medical centers without experience in the use of thrombolytic therapy.[6]

Future challenges of thrombolytic therapy include a significant increase in the frequency of administration and use of this therapy, to increase arterial re-vascularization rates, to decrease the occurrence of post-treatment bleeding and to extend the therapeutic window for the inclusion of candidates to this treatment modality. In this respect, healthcare education continues to be an essential step to achieve the first goal. The administration of t-PA together with the use of ultrasound (known as sonothrombolysis) has shown to increase the frequency of arterial re-permeabilization in preliminary studies. In addition, the therapeutic usefulness of third-generation thrombolytic drugs (tenecteplase, reteplase, lanoteplase, pamiteplase and staphylokinase) is potentially greater because of a higher resistance than t-PA to neutralization by t-PA endogenous inhibitors or a longer mean half-life. Another therapeutic approach would be the concomitant use of conventional thrombolytic therapy and neuroprotector drugs with the aim of maximal preservation of the ischemic shadow territory limiting the extension of the cerebral infarcted area. The use of diffusion-perfusion MRI is a further potential alternative, which may allow the administration of thrombolytic treatment independently of the temporal window in cases in which potentially recoverable cerebral tissue could be demonstrated. This would occur when cerebral ischemia in perfusion sequences is significantly greater than cerebral infarction visualized in the diffusion sequences (the so-called “mismatch” phenomenon). Mechanical disruption of thrombi by embolectomy is another potentially interesting possibility in non-responders to intravenous or intra-arterial t-PA administration. Finally, the usefulness of plasma biomarkers related to the efficacy and safety of thrombolytic treatment and that would alert to the risk of hemorrhagic transformation[4] will be another future challenge that will allow optimization and individualization of thrombolytic therapy in the patient suffering from an acute cerebral infarction.

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References