Intravenous or Intra-Arterial Thrombolysis? It’s Time to Find the Right Approach for the Right Patient

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See related article, pages 2191–2195.

Intravenous recombinant tissue plasminogen activator (rt-PA) given within 3 hours of stroke onset is considered the standard treatment of stroke and is approved by the health authorities of most countries. It increases the rate of favorable outcomes from the range of 20% to 38% to 31% to 50%. Patients with mild or moderate strokes, persons younger than 75 years, and patients treated very early have the best chance for a favorable outcome to treatment. Nevertheless, more than half of stroke victims face a bleak outlook. Therefore, better means to treat stroke are needed. Intra-arterial thrombolysis (IAT) with pro-urokinase and a small dose of heparin has been tested in a phase III trial to treat stroke patients of <6 hours duration because of middle cerebral artery (MCA) main stem (M1 segment) and main branch (M2 segment) occlusion. Recanalization rates were 66% when treated with pro-urokinase and 18% with placebo ($P<0.001$). At 90 days, 40% of patients treated with pro-urokinase but only 25% assigned to placebo had regained independency (modified Rankin scale of 0, 1, or 2; $P=0.04$).

The FDA has not approved pro-urokinase for stroke treatment. Nevertheless, IAT mostly with rt-PA or urokinase is used increasingly at stroke centers by interventionists. Since the FDA granted approval of the MERCI retriever for arterial embolectomy, mechanical recanalization has gained popularity as well. Forty-five percent of occluded MCAs and 53% of occluded intracranial carotid arteries were recanalized successfully with the MERCI retriever. Vessel recanalization rose to 69% when mechanical procedures were combined with rt-PA. On multivariate analysis, successful recanalization after mechanical thrombectomy was associated with better clinical outcomes.

These developments have brought us to an impasse. On one side there is the approved stroke treatment with intravenous rt-PA within 3 hours of the onset of symptoms. According to American and European guidelines, there is class I evidence that this treatment is effective. Intravenous rt-PA increases recanalization of occluded vessels. One study using magnetic resonance arteriography found a TIMI 2 or 3 grade recanalization of occluded MCA main stems in 39%. On the other side there are endovascular recanalization techniques that improve recanalization rates substantially up to 70% to 80%.

However, they have not been tested in randomized trials as rigorously as intravenous rt-PA. They are only at a stage where one phase III study (PROACT II) and multivariate analyses of many open series have shown a strong association of recanalization and favorable outcomes. What shall we do in this deadlocked situation? Evidence-based medicine and European and American guidelines tell us in a class III recommendation that the availability of IAT should generally not preclude the administration of intravenous rt-PA in eligible patients. From a pathophysiological point of view, however, it makes sense to use IAT. Compared with intravenous rt-PA, IAT almost doubles the chances of recanalization and will likely improve the patient outcomes.

With the aforementioned statement, I have moved into the controversial mythical grounds territory of Alfonso Ciccone et al. Ciccone debunks 7 myths that hamper the realization of randomized controlled trials on IAT for acute ischemic stroke. They have to be congratulated for initiating an Italian multicenter, randomized, controlled, open-label clinical trial, with blind follow-up called SYNTHESIS.

SYNTHESIS intends to answer the question whether patients randomized within 3 hours of symptom onset, to intravenous rt-PA started within 3 hours, or, IA rt-PA infused not later than 6 hours after onset will have a better outcome. Recruitment has been slow for several reasons; 7 myths hampering recruitment are mentioned by the authors.

Intravenous rt-PA certainly improves the outcome of mild or moderate strokes, whereas in severe strokes with a hypodense MCA on CT indicating MCA main stem occlusion the effect of intravenous rt-PA is less or even questionable. However, IAT in PROACT II showed an effect in severe strokes with an NIHSS of $\geq 11$, but no benefit in patients with NIHSS 4 to 10. The questions therefore arise, does the location of the vessel occlusion play a role, and is there a correlation with the clinical severity of the stroke? The answer is an unequivocal yes. Studies of clinical and arteriographic findings in acute stroke have shown a significant association of NIHSS scores with the presence and location of vessel occlusion. With an NIHSS score of $\geq 10$, a vessel occlusion will likely be seen on arteriography, and with a score of $\geq 12$, it will probably be located in the internal carotid arteries, MCA main stem or main branch, or basilar artery. Furthermore, there is a significant correlation in the
location of vessel occlusion and outcome. Knowing this, we suspect that a trial comparing intravenous rt-PA and IAT in a population with mostly mild or moderate strokes occurring in a majority of small vessel and peripheral branch occlusions might favor intravenous rt-PA. A trial with mainly severe strokes will have a better outcome with IAT. A trial with a balanced number of mild to moderate and severe strokes may show only in a subgroup analysis that patients with mild and moderate strokes are better served with intravenous thrombolysis, and patients with severe strokes derive a greater benefit from IAT. If the right patient is selected for intravenous thrombolysis and IAT, a greater absolute benefit may be achieved than the 13% to 15% absolute benefit that resulted in trials comparing intravenous rt-PA and placebo.

This is speculation. However, it reveals how many items have to be considered when designing a randomized trial to compare intravenous thrombolysis and IAT for acute stroke. Things get even more complicated when we consider not only intravenous thrombolysis and IAT but also bridging of intravenous thrombolysis and IAT. Bridging intravenous thrombolysis and IAT seems to be sufficiently safe for a “drip and ship” approach, in which patients are given intravenous rt-PA at a primary center and then transferred to a tertiary stroke center for IAT. Such a bridging approach is used in the North American Interventional Management of Stroke (IMS) III Trial. The primary goal of IMS III is to determine whether ischemic stroke patients with NIHSS ≥10 treated with rt-PA using a combined intravenous/intra-arterial approach for recanalization, started within 3 hours of onset, are more likely to have a better outcome than individuals treated with intravenous rt-PA alone. The endovascular treatment arm includes, infusion of rt-PA through a standard microcatheter at the site of the blood clot, embolectomy with the Merci Retriever, or rt-PA infusion through the EKOS Micro-Infusion Catheter concurrent with delivery of low-intensity ultrasound energy. The study will enroll 900 patients.

In Europe, a multinational group has recently applied to the European Commission for funding a Collaborative European Multi-Center Basic Science and Clinical Approach in the Treatment of Stroke (COMBATSTROKE). COMBATSTROKE includes a basic science section to improve endovascular recanalization techniques, and a trial to compare standard intravenous rt-PA with endovascular recanalization techniques, in patients with internal carotid artery or MCA main stem or main branch occlusions diagnosed with MR or CT angiography.

Our Italian friends have decided to join the European consortium. If funded, their article on debunking myths that hamper the realization of IAT trials will hopefully help to realize COMBATSTROKE in Europe and accelerate the North American IMS III trial. Within a few years we hope to be able to select the ideal patient for intravenous thrombolysis and the ideal patient for other intra-arterial recanalization techniques.

Disclosures

None.

References


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