

Editorial

Current Status and Future of Acute Stroke Thrombolysis with Tissue Plasminogen Activator

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Submitted: 22 July 2013

Accepted: 22 July 2013

Published: 24 July 2013

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Timely restoration of cerebral perfusion by systemic thrombolysis is the main goal of treatment of acute ischemic stroke (AIS) and it often results in an improved functional outcome [1]. Since its approval by the Food and Drug Administration in 1996, intravenously administered tissue plasminogen activator (IV-tPA) remains the only evidence based treatment for achieving arterial recanalization and improving outcome in AIS [2]. The pivotal National Institute of Neurological Disorders and Stroke (NINDS) study showed that compared to placebo, IV-tPA, administered within 180 minutes of symptom-onset resulted into an absolute 12% increase in the proportion of patients with no or minimal disability and improved the chances of a good functional recovery at 3 months by about 30% (number needed to treat (NNT) for a favourable outcome= 8). The major side effect of symptomatic intracerebral haemorrhage (SICH) was significantly higher in the IV-tPA group (6.4% versus 0.6% in the placebo group). However, the mortality rates at 90 days were similar in the IV-tPA treated patients (17%) and placebo group (20%).

A pooled analysis of the initial clinical trials with IV-tPA conducted in North America and Europe revealed that treatment initiation within 90 minutes of symptom-onset improved outcomes [Odds ratio (OR) 2.8, 95% Confidence interval (CI) 1.8–4.5] and predicted that benefit could be achieved even beyond 3 hours (OR 1.4, 95% CI 1.05–1.85 for 180–270 minutes) [3]. This was later proven in the European Cooperative Acute Stroke Study [4]. Furthermore, the safety and efficacy of IV-tPA has been reinforced in the real world settings by the postmarketing multicentre studies conducted across USA (Standard treatment with Alteplase to reverse stroke-STARS) [5] and in Europe by the Safe Implementation of Thrombolysis in Stroke monitoring Study (SITS-MOST) registry [6]. The efficacy of IV-tPA in AIS patients older than 80 years of age was established in the recent International Stroke Trial III (IST-III) [7].

A narrow therapeutic window and relatively poor rates of recanalization with IV-tPA alone prompted various combined therapeutic approaches (intra-arterial thrombolysis or endovascular therapy). Although, higher rates of recanalization have been reported in some of the studies with endovascular

stroke therapy and/or bridging therapies, these have not translated into improved functional recovery [8]. Interestingly, the recently published Interventional Management of Stroke (IMS-III) trial showed no significant difference in functional independence with endovascular therapy after IV-tPA as compared with IV-tPA alone [9].

Some of the ongoing clinical trials for AIS thrombolysis with IV-tPA are worth mentioning. First, in a proposed sample size of 400 patients from Australia and New Zealand, the EXTEND (EXtending the time for Thrombolysis in Emergency Neurological Deficits) trial is evaluating the efficacy and safety of IV-tPA use in an extended (3-9 hours) time window for patients with significant penumbral mismatch on magnetic resonance imaging [10]. Second, encouraged by the findings of the CLOTBUST trial (that showed significantly higher rates of complete recanalization or dramatic clinical recovery within first 2 hours (49%) in the tPA+ continuous exposure of the intracranial clot by diagnostic 2-MHz transcranial Doppler ultrasound group as compared to IV-tPA alone (30%; p=0.03) [11], a phase 3, clinical multinational randomised trial (CLOTBUST-ER) was initiated recently. It aims to recruit 830 AIS patients (1:1 randomization) to evaluate the efficacy and safety of transcranial ultrasound (2-MHz delivered to the brain continuously by an operator-independent head frame (Cerevast Technologies, US) as an adjunctive therapy to IV-tPA as compared to the standard thrombolysis with IV-tPA alone [12]. Lastly, the dose of IV-tPA remains controversial, especially in Asia. Compared to the standard-dose of 0.9mg/Kg body-weight (maximum dose 90mg, 10% as bolus and rest as an infusion over 1 hour) [2] used in North America and Europe, Japanese study demonstrated the safety and efficacy of a lower-dose of IV-tPA (0.6mg/Kg body-weight; maximum 60mg, 10% as bolus and remaining as IV infusion over 60 minutes) that were comparable to thrombolysis with the standard dose [13]. In a recent systematic review, we found no significant differences in the functional outcome and SICH rates between AIS thrombolysis with low- versus the standard-dose IV-tPA in Asia [14]. The ongoing multinational ENCHANTED (ENhanced Control of Hypertension ANd Thrombolysis stroke stuDy) trial is a quasi-factorial randomised controlled trial that aims to evaluate the non-inferiority of low-dose IV-tPA compared to the standard-dose as well the superiority of early intensive blood

pressure control in AIS [15]. In conclusion, IV-tPA remains the only approved drug for IV thrombolysis in AIS and the ongoing clinical trials are expected to add some interesting tools to the future armamentarium of stroke neurologists.

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Cite this article

Sharma VK, Batra A (2013) Current Status and Future of Acute Stroke Thrombolysis with Tissue Plasminogen Activator. *J Neurol Transl Neurosci* 1: 1011.