

Acute ischemic Stroke - Is Thrombolysis need of the hour? A Clinical debate

Vijay K. Dixit

Consultant Neuroradiologist, VIMHANS, Nehru Nagar, New Delhi, India

Abstract : *Thrombolytic treatment of stroke patients remains a controversial topic in clinical medicine .Contemporary acute ischemic stroke therapy protocols opt for time and ignore specificity. Therapeutic decisions regarding whether to use thrombolytics are complex and depend on more than simply the time that has expired since stroke symptom onset and findings on CT scan. There is considerable current interest in new MRI techniques and vascular imaging studies like diffusion -perfusion MRI, MRA , CTA and Doppler .These are capable of identifying the ischemic penumbra representing the tissue that may be salvaged if perfusion can be restored quickly enough , a key concept in stroke physiology in a clinically relevant manner. A good radiological selection of patients for thrombolysis may increase the number of potential patients who are actually treated for acute ischemic stroke . A number which is currently disappointingly low.*

Interventions in acute ischemic stroke should aim to minimize mortality, impairment, and disability and reduce the complications of stroke such as deep vein thrombosis. Therapies to reduce brain damage may act by restoring blood flow thus reducing infarction within the penumbra (thrombolysis), preventing thrombus extension (by giving antiplatelets), and increasing cerebral resistance to ischemia. (neuroprotective drugs).

Thrombolysis aims at reducing the volume of infarcted brain by recanalizing the occluded vessel and restoring blood flow. Although this may seem of obvious benefit thrombolysis is not currently routinely used owing to the uncertainty of the risk-benefit ratio. It may, however, prove to be appropriate in certain selected patients. At present the criteria for such a selection are unclear but the overall aim would be to identify cases of major ischemic stroke in which little spontaneous recovery is likely and in which the hemorrhagic transformation of infarct with thrombolysis is low. In addition patients in whom spontaneous recanalization of occluded vessel had occurred would need to be excluded.

There are various **Thrombolytic agents** available including tissue plasminogen activator (tPA), urokinase, single chain urokinase plasminogen activator, streptokinase and acylated plasminogen streptokinase activator complex. These agents differ in half life, stability and fibrin selectivity. The relative effectiveness and the most effective doses of the different thrombolytic agents is unclear owing to the lack of data from randomized controlled trials.

Intravenous Thrombolysis by giving recombinant tissue plasminogen activator (tPA) to selected patients within three hours of ictus has become part of emergency care of patients with hyperacute ischemic stroke¹. Unfortunately only 2-3% of the eligible population in a developed country like U.K, receives this treatment. Currently, intravenous thrombolysis appears to result in improved outcome in certain patients but it remains unclear how to select patients who will benefit from the total population of patients with acute ischemic stroke. Shortly after the NINDS trial¹ and ECASS trial² and other studies^{3,4} the FDA approved use of tPA for stroke, and committees of the American heart Association, AHA⁵ and the American academy of Neurology,

AAN⁶ published guidelines endorsing its use. Intravenous thrombolysis is initiated with, a dose of 0.9 mg/kg body weight, tPA (upto a maximum of 90 mg). The dose is divided in to an initial bolus (10 % of total dose) followed by infusion of the rest. (90% of total dose.)

Appropriately, each organization emphasized the urgency of treatment. When it is effective, tPA forestalls irreversible brain infarction by lysing occlusive thrombi, thus facilitating the reperfusion of ischemic brain. Ischemic brain cells die within hours without perfusion. Unfortunately, thrombolytic drugs sometimes can cause fatal brain hemorrhages. AHA and AAN recommended the intravenous administration of tPA immediately after CT scanning to rule out the intracranial hemorrhage. Strict adherence to this time window and choosing not to suggest test to detect underlying occlusive vascular lesions precludes many patients who might benefit from thrombolytic treatment and includes those who are unlikely to benefit, for example, those with ICA and main trunk MCA (M1) occlusions and those in whom the embolus has already dissipated. Severe strokes (implying a large relatively proximal clot) with little or no collateralization usually do badly with intravenous tPA and risk ICH. (1, 7) Alternative treatment should be considered in these cases. One of the views is that Hyperacute ischemic stroke comprises a heterogeneous group of patients and the time window must vary on an individual basis. The time window and the opportunity for treatment depend upon the site and extent of clot and collaterals. Ideally, management should be individualized following investigation with CT, CT angiography (CTA), and CT perfusion (CTP) studies. (OR MRI, MRA, DWI/PWI studies) to optimize and rationalize therapy. CTA /MRA will demonstrate the site and extent of clot and CTP/DWI/PWI will help to differentiate the already infarcted from ischemic "at risk" but potentially viable tissue i.e. ischemic penumbra. With a more distal branch occlusion and good collaterals, the time window is obviously longer. Conversely, if there is total occlusion of the M1 segment or proximal M2 which include the lenticulostriate arteries the time window may be less. Lenticulostriate are true end arteries, without collateral circulation, supplying the basal ganglia which have a high metabolic rate. Reperfusion after delay is associated with an increased risk of hemorrhage.

Intra-arterial thrombolysis has been proposed as a treatment of acute ischemic stroke since the 1980s, PROACT I 1988^{8,9}.

Follow up clinical efficacy trial was reported in February 1999¹⁰. Intra-arterial thrombolysis involves the direct infusion of thrombolytic agent into the occluding thrombus achieving higher local concentration of drug, lower systemic concentration and fewer hemorrhagic complications¹¹. It allows thrombolysis to be given to only those patients in whom vessel occlusion has been demonstrated. Further the exact site of occlusion can be seen. Recanalization rates appear to be higher than intravenous thrombolysis¹². Additionally, mechanical means may be applied to disrupt the clot using the microguidewire and this may facilitate the action of the thrombolytic agent. Clot retrieval devices are now available (Merci, Bos sci, approved by FDA). Mechanical thrombolysis is obviously invaluable if clot is resistant to intra-arterial tPA. If thrombus is superimposed upon a stenosis, it may be necessary to undertake angioplasty or stent the lesion. Mechanical thrombolysis may also be considered if pharmacological thrombolysis is contraindicated.

Although intra-arterial techniques have distinct advantages there are logistical problems. Intravenous thrombolysis has obvious advantage of ease and rapidity of administration and avoids the disadvantage of intra-arterial treatment which includes the inevitable additional time delays, risk of procedure. In additional intra-arterial treatment requires specialist Neurointerventional training. There are a few small randomized trials^{9,10,13} comparing intra-arterial thrombolysis with placebo, within six hours of the ictus and combined intra-arterial and intravenous treatment¹⁴⁻¹⁶ reporting encouraging results. But there are no randomized trials comparing intravenous and intra-arterial treatment. Current opinion suggests that intra-arterial treatment may be useful for large vessel occlusions and in those presenting after 3 hours window period where DWI/PWI/CTP are favorable.

Vertebrobasilar occlusion is usually associated with a poor prognosis with overall mortality rates of 70-80% there are no randomized studies but many cases of thrombolysis are reported in literature using local intra-arterial infusions of urokinase or tPA¹⁷. The precise time window is uncertain and therapeutic windows of up to 72 hours have been reported. Signs of brain stem infarction on imaging are not always indicative of poor outcome. However, coma or tetraparesis for several hours is indicative of poor prognosis despite recanalization.

The current opinion suggests that immediate intravenous tPA opts for time and ignores specificity. To achieve specificity now requires resources but very little time. We will all agree that

patients are better served by accurate diagnosis and appropriate specific therapy. Intravenous tPA is an important therapeutic option that is appropriate for some occlusive lesions. However, it is not appropriate treatment for some other patients with acute ischemic strokes which might be better treated by other methods.

REFERENCES

1. *The National Institute of Neurological Disorders and Stroke rT-PA Stroke Study Group.* Tissue plasminogen activator for acute ischaemic stroke. *N Engl J Med* 1995;333:1581-7
2. *Hacke W et al.* Randomised double-blind placebocontrolled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European – Australasin Acture Stroke Study Investigation (See comments). *The Lancet* 1988 352, 1245-51
3. *Trouillas P et al.* Thrombolysis with intravenous rtPA in a series of 100 cases of acute carotid territory stroke: determination of etiological, topographic, and radiological outcome factors. *Stroke* 1998 29, 2529-40
4. *Hacke W et al.* Thrombolysis in acute ischaemic stroke: controlled trials and clinical experience. *Neurology* 1999 53, S3-S14
5. *Adams HP Jr, Brott TG, Furlan AJ, et al.* Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management for patients with acute ischemic stroke : a statement for healthcare professionals from a special writing group of the Stroke Council, American Association. *Stroke* 1996;27:1711-1718
6. *Practice advisory : thrombolytic therapy for acute ischemic stroke – summary statement :* report of the Quality Standards Subcommittee of the American academy of Neurology. *Neurology* 1996;47:835-839
7. *Albers GW, Bates VE, Clark WM, et al.* Intravenous tissue-type plasminogen activator for treatment of acute stroke. *JAMA* 2000;283:1145-50
8. *del Zoppo GJ et al.* Local intra-arterial fibrinolytic therapy in acute carotid territory stroke. A pilot study. *Stroke* 1998 19, 307-13
9. *del Zoppo GJ and Sasahara AA.* Interventional use of plasminogen activators in central nervous system 1998,19,2/6
10. *Furlan A et al.* Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Prolyse in Acute Cerebral Thromboembolism J. Amer. Med. Assoc.* 1999 282, 2003-11
11. *Katzan IL et al.* Intra-arterial thrombolysis for perioperative stroke after open heart surgery. *Neurology* 1999 52,1081-4
12. *Pessin MS, del Zoppo GJ, Furlan AJ.* Thrombolytic treatment in acute stroke, review and update of selected topics. In: Moskowitz MA & Caplan L, eds, *Cerebrovascular diseases : 19th Princeton Stroke Conference*, 1995 pp 409-18 Butterworth –Heinemann
13. *Lisbaa RC, Jovanovic BD, Albers MJ.* Analysis of the safety and efficacy of intra-arterial thrombolytic therapy in ischaemic stroke. *Stroke* 2002;33:2866-71
14. *Lewandowski CA, Frankel M, Tomsick TA, et al.* Combined intravenous and intra-arterial therapy of acute ischaemic stroke. Emergency management of stroke (EMS) bridging trial. *Stroke* 1999;30:2598-605
15. *Keris V, Rudnicka S, Vorona V, et al.* Combined intra-arterial/intravenous thrombolysis for acute ischaemic stroke. *Am J Neuroradiol* 2001;22:352-8
16. *Surez JI, Zaidat OO, Sunshine JL, et al.* Endovascular administration after intravenous infusion of thrombolytic agents for the treatment of patients with acute ischaemic strokes. *Neurosurgery* 2002;50:251-50
17. *Ng PP, Higashida RT, Cullen SP, et al.* Intraarterial thrombolysis trials in acute ischaemic stroke. *J Vasc Interv Radiology* 2004;15:S77-85

Announcement

International Medical Educator Program Fellowships of CMCL-FAIMER Regional Institute 2007

The CMCL- FAIMER regional Institute's Fellowship is a One-year Fellowship program designed for Indian medical school faculties who have the potential to play a key role in improving medical education. The first session consists of five days of intensive course at Chirstan Medical College, Ludhiana, India during January 2007 followed by an inter session curriculam innovation project at the participant's home institution through internet discussion group; the second will be in January 2008. The program is uniquely designed to teach education methods and leadership skills, as well as to develop strong professional bonds with other medical educators. The CMCL- FAIMER Regional Institute, running in its second year, is sponsored by the Foundation For Advanced of International Medical Education and Research (FAIMER), which is a nonprofit foundation of the Educational Commission for Foreign Medical Graduates (ECFMG), USA. Limited funding is available to support Fellows' travel, local expenses and course fee. The cost of carrying out the project, however, is not included. Fifteen fellowships are on offer this year.

For details visit our site. : <http://cmcl.faimer.googlepages.com/home> or contact Dr Tejinder Singh , Director of the Program and Vice Principal at Christian Medical College, Ludhiana 141008 Tel :01612608617, Mobile 09815400048, e-mail : cmcl.faimer@gmail.com