

Thrombolysis in Stroke - Experience In India

Apratim Chatterjee, Subhdeep Gupta,
Bhaskar Ghosh, Biman Kanti Ray

INTRODUCTION

Stroke is a major health problem worldwide and is associated with high mortality and dependence.¹ Stroke was defined by the WHO more than 40 years ago as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.” Acute ischemic stroke (AIS) is an area in neurological clinical practice, which has probably seen the greatest strides as far as an understanding of pathogenesis is concerned. In the December of 1995 there came a paradigm shift in acute ischemic stroke management. National Institute of Neurological Disorders and Stroke (NINDS) in United States of America reported its success in significantly improving the outcome of ischemic stroke by using intravenous recombinant tissue-type plasminogen activator (rtPA), if administered within 3 hours.²

Even after 21 years, rtPA is the most effective treatment in a subset of ischemic stroke patients.

SUMMARY OF THE TRIALS

NINDS Trial 1 and NINDS Trial 2 together randomized 624 subjects within 3 hours of stroke onset to receive 0.9 mg/kg of intravenous tPA or placebo and found that patients treated with tPA within 3 hours of onset had a substantially better chance of functional independence with minimal or no disability 3 months after treatment. The proportion of patients with minimal or no disability increased from 38% with placebo to 50% with tPA, a 12% absolute improvement. The number needed to treat for 1 more patient to have a normal or near normal outcome was 8, and the number needed to treat for 1 more patient to have an improved outcome was 3.1.³ Brain hemorrhages related to tPA caused severe worsened final outcome in 1% of patients.⁴ Overall, for every 100 patients treated within the first 3 hours, 32 had a better outcome as a result and 3 had a worse outcome.

An independent reanalysis of the NINDS trials demonstrated a robust treatment effect in favor of tPA.⁵ Four other phase 3 IV tPA trials, ECASS 1, ECASS 2, ATLANTIS A, and ATLANTIS B, have enrolled small subsets of patients in the under 3-hour time window. The degree of benefit of lytic therapy in the under 3-hour period observed in these trials was concordant with that found in the 2 NINDS trials.^{6,7} The use of tPA for acute ischemic stroke was approved by the US Food and Drug

Administration (FDA) in 1996 and subsequently by regulatory agencies in Canada, Europe, South America, and Asia.

The European Cooperative Acute Stroke Study 3 (ECASS 3) trial was performed to confirm or disconfirm the findings from initial trials suggesting benefit of IV tPA therapy in the 3- to 4.5-hour window. In ECASS 3, 821 patients were randomized to IV tPA or placebo. Major symptomatic hemorrhages occurred in 2.4% of the tPA group versus 0.2% of the placebo group, with no increase in mortality. Patients treated with tPA had a substantially better chance of functional independence with minimal or no disability 3 months after treatment. The proportion of patients with minimal or no disability increased from 45% with placebo to 52% with tPA, a 7% absolute improvement. The number needed to treat for 1 more patient to have a normal or near normal outcome was 14, and the number needed to treat for 1 more patient to have an improved outcome was 8. Overall, for every 100 patients treated within the 3- to 4.5-hour window, 16 had a better outcome as a result and 3 had a worse outcome.⁸

The favorable results of the pooled and ECASS 3 trials in the 3- to 4.5-hour window have been duplicated in a large phase 4 study examining the use of intravenous tPA in routine clinical practice. The international Safe Implementation of Treatment in Stroke (SITS) prospective registry identified 2376 patients treated in the 3- to 4.5-hour window in regular practice at 650 centers from more than 25 countries. The rates of complications and of favorable outcomes were similar to those in ECASS 3. These findings confirm tPA as effective in clinical practice as it is efficacious in clinical trials in the 3- to 4.5-hour window when inclusion and exclusion guidelines are followed.⁹

THROMBOLYSIS GUIDELINES

The American Heart Association/American Stroke Association (AHA/ASA) inclusion guidelines for the administration of rt-PA in under 3 hours are as follows⁶:

- Diagnosis of ischemic stroke causing measurable neurologic deficit
- Neurologic signs not clearing spontaneously
- Neurologic signs not minor and isolated
- Symptoms not suggestive of subarachnoid hemorrhage

- Onset of symptoms less than 3 hours before beginning treatment
- No head trauma or prior stroke in past 3 months
- No MI in prior 3 months
- No GI/GU hemorrhage in previous 21 days
- No arterial puncture in noncompressible site during prior 7 days
- No major surgery in prior 14 days
- No history of prior intracranial bleed
- Systolic blood pressure under 185 mm Hg, diastolic blood pressure under 110 mm Hg
- No evidence of acute trauma or bleeding
- Not taking an oral anticoagulant, or if so, INR under 1.7
- If taking heparin within 48 hours, a normal activated prothrombin time (aPT)
- Platelet count of more than 100,000/ μ L
- Blood glucose greater than 50 mg/dL (2.7 mmol)
- No seizure at onset with residual postictal impairments
- CT scan does not show evidence of multilobar infarction (hypodensity over one-third hemisphere)
- The patient and family understand the potential risks and benefits of therapy

In May 2009, and again in March 2013, the AHA/ASA guidelines for the administration of rt-PA following acute stroke were revised to expand the window of treatment from 3 hours to 4.5 hours to provide more patients with an opportunity to receive benefit from this effective therapy.^{3,7,10} Eligible patients should receive rtPA therapy as soon as possible, ideally within 60 minutes of hospital arrival. IV fibrinolysis can be considered in patients with rapidly improving symptoms, mild stroke deficits, major surgery within the past 3 months, and recent myocardial infarction; risks should be weighed against benefits.^{19]}

Eligibility criteria for treatment in the 3 to 4.5 hours after acute stroke are similar to those for treatment at earlier time periods, with any 1 of the following additional exclusion criteria:

- Patients older than 80 years
- All patients taking oral anticoagulants are excluded regardless of the international normalized ratio (INR)
- Patients with baseline NIHSS score > 25
- Patients with a history of stroke and diabetes
- Patients with imaging evidence of ischemic damage to more than one third of the middle cerebral artery (MCA) territory¹⁰

CURRENT STATUS IN INDIA

Thrombolytic therapy made a late and slow entry in India, for obvious reasons. These include lack of awareness among public and, among the referring physicians about the existence and usefulness of rtPA treatment. It is found that 8% to 25 % of stroke patients arrived in the hospital within 3 hours.¹¹ All of them were not eligible according to NINDS criteria. Others find the cost very high. But the most important reason which discourages the neurologists to use rtPA is the uncertainty of response and potential for fatal brain hemorrhage.

Several Government run institutes in India have reported good outcome with use of rtPA. All India Institute of Medical Sciences, New Delhi, published their experience of 40 thrombolysed patients within a 3h onset between March 2002 and June 2005.¹² The mean age was 66 years (range 32 - 82 years, male : female ratio = 3:2). The mean time to reach the emergency department was 27 min (25 - 45 min). The NIHSS score at admission ranged from 11 to 22 (mean 14.5 minutes). Twenty -six patients (65%) significantly improved on NIHSS at 48 h (> 4 points) (mean change = 10; range 40 - 17). At one month, 32 (79%) improved on Barthel Index (mean change = 45).¹²

Thirty seven patients were treated with rtPA in a Nizam Institute of Medical Sciences, Hyderabad over 53 months. Twenty -nine (78%) patients had a good outcome at 1 year. 33 Intra-arterial thrombolysis therapy is being used in approximately 10 centers in India. In a tertiary referral center from Kerala, South India, intra-arterial Urokinase (IA UK) was given in 5 patients. In two patients, there was complete recanalization with excellent recovery. In the remaining three patients, the recanalization rate varied from 0% to 50%, with partial recovery in two and no recovery in one patient.¹³

BIN EXPERIENCE

First to start thrombolysis in govt. sector in West Bengal

- Thrombolysis started in Aug 2015,
- Total cases till now 31
- Mean time to reach EMERGENCY: 4.14 hours (30 min - 4.5 hrs.)
- Average NIHSS at presentation – 13
- Early CT changes prior to thrombolysis : 4
- MRI done prior to thrombolysis: 27
- Stroke mimic thrombolysed : 0
- Average door to needle time : 78 minutes
- Average NIHSS reduction at discharge – 4.2
- Complications : reperfusion edema-2, intracranial bleeding-1, cardiac arrhythmia -2
- Special cases thrombolysed: HIV positive, CKD not on HD----good outcome
- Total no. of deaths – 4 (2 due to reperfusion edema, 2 due to cardiac arrhythmia)

R.G. KAR MEDICAL COLLEGE EXPERIENCE

- Thrombolysis started in May'16
- Thrombolysis done in General Medicine Ward and emergency room by General medicine residents under supervision of neurologist.
- Total no of cases thrombolysed: 20
- Average time to reach emergency : 3.10 hrs (45 mins to 4 hours)
- Average NIHSS at presentation – 15.6
- Early CT changes prior to thrombolysis : 6
- MRI done prior to thrombolysis: 7
- Stroke mimic thrombolysed : 2
- Average door to needle time : 40 mins (only 25 for last 10 cases, least being 15 mins)
- Average NIHSS reduction at discharge – 8.1 (n=17)
- Complications : 1 ICH (NIHSS at presentation was 25), 3 Extracranial bleeding
- Total no of deaths – 3 (2 due to aspiration pneumonitis, 1 due to ICH)

COST EFFECTIVENESS OF THE THERAPY

Initially before starting thrombolysis in govt. sector in West Bengal in BIN in AUG 2015, thrombolysis was only available to select few in private sector where quite a huge cost of therapy was there which was not within the reach of poor people. However after successfully initiating thrombolysis in BIN, IPGMER with a success in the first 12 cases, a plea was made to the state government to make the drug free and make it available in the essential drug list. After a brief wait, luckily enough the government like many other drugs has made it completely free and available in other government institutes as well after which there has been a huge surge of the rate of thrombolysis in Bengal which is widely available to people of all economic background.

Even before it was made free it was seen that the use of the drug correctly limited the duration of hospital stay and mortality and morbidity of the patient and thus reduced the overall cost of therapy (compared to ischemic strokes which are not thrombolysed) coupled with productive numbers of working days lost for the patient. Thus the balance was in any way better cost effective for thrombolysis even if the patient had to buy the drug.

BARRIERS TO THROMBOLYSIS IN INDIA AND WAYS TO OVERCOME

A study was recently conducted (yet in the process of publication) in BIN to find out the barriers to thrombolysis by Chatterjee et al and his colleagues. Out of a total of 147 consecutive patients of acute ischemic stroke 18 could be thrombolysed (12.24%). Out of the 129 patients who could not be thrombolysed 51 patients got enrolled in the ER within 4.5 hours but lost time after emergency entry at various steps. The mean time of onset of stroke

to ER entry, attending by ER physician, ER to imaging and attending by neurophysician was 4.14 hours, 23.43 min, 41.90 min and 11.91 min respectively. Rest 78 patients could not be thrombolysed because of 51.4 % had economic constraints, 28.4% of patients relatives did not give consent, 2.4% had refractory high blood pressure, 4.8% had logistic problems, 5.4% had fluctuating NIHSS scores, seizure at onset was present in 2% of patients, other causes were upper GI bleed 0.7%, lower GI bleed 0.7%, recent surgery in 1.4%, oral anticoagulant intake in 0.7%, taking loading dose of antiplatelet in 0.7%, superficial bleed and respiratory distress after tpa starting in 0.7% and recent AMI in 0.7%.

Leaving apart the economic part which we have already overcome much still remains to be done. The most important is the knowledge barrier, the concept that we really do not have any time left even within the window period and the dictum the sooner the better should be emphasized in the ER. A separate triage should be made for the acute ischemic stroke patients in the ER to reduce the waiting time. Separate imaging facility should be made available for the acute ischemic stroke patients so that they will not have to wait at imaging. On call residents should be primed to leave all work apart and attend the ischemic stroke patients as soon as possible. A code should be made with availability of pager system or some alarm to inform the members of the stroke team once an ischemic stroke comes within the window period. This stroke team should constitute of ER physician, neurologist, radiologist, nurse adept with stroke care, ward boys skilled for stroke care. A definite stroke care pathway should exist for every institute to give the best possible care in the simplest and fastest way in their institute.

RECENT ADVANCES IN THROMBOLYSIS AROUND THE GLOBE

Bridging Thrombolysis: Bridging therapy (the combination of intravenous [IV] and intra-arterial [IA] thrombolysis) is part of the therapeutic armamentarium in the daily practice of several stroke centers. As time to recanalization has emerged as a new goal in acute stroke care, combining the speed of IV alteplase administration and the higher recanalization rates of the IA route is a relevant approach. Controlled studies have reported the feasibility and efficacy of bridging therapy in terms of recanalization rates, but a positive clinical impact has only been observed in a select population of IV alteplase nonresponder patients. These findings raise the question of the target population for bridging therapy. It is not yet clear whether it should only be considered for IV alteplase nonresponder patients, or whether the small sample size of the other studies is the main explanation for the absence of any significant clinical benefit. In the study showing a significant favorable outcome at 3 months, higher morbidity and mortality were associated with bridging therapy, with higher symptomatic hemorrhage and death rates.

Beyond recanalization rates, favorable clinical outcomes and safety need to be assessed. Pending the results of an ongoing randomized controlled trial comparing the

410 bridging approach with IV alteplase administration (the unique recommended therapy for patients with acute ischemic stroke), bridging therapy is considered an investigational technique.

Sonothrombolysis: Multiple *in vitro* and animal models have demonstrated the efficacy of ultrasound to enhance fibrinolysis. Mechanical pressure waves produced by ultrasound energy improve the delivery and penetration of alteplase (recombinant tissue plasminogen activator [tPA]) inside the clot. In human stroke, the CLOTBUST phase II trial showed that the combination of alteplase plus 2 hours of continuous transcranial Doppler (TCD) increased recanalization rates, producing a trend toward better functional outcomes compared with alteplase alone. Other small clinical trials also showed an improvement in clot lysis when transcranial color-coded sonography was combined with alteplase. In contrast, low-frequency ultrasound increased the symptomatic intracranial hemorrhage rate in a clinical trial. Administration of microbubbles (MBs) may further enhance the effect of ultrasound on thrombolysis by lowering the ultrasound-energy threshold needed to induce acoustic cavitation. Initial clinical trials have been encouraging, and a multicenter international study, TUCSON, determined a dose of newly developed MBs that can be safely administered with alteplase and TCD. Even in the absence of alteplase, the ultrasound energy, with or without MBs, could increase intrinsic fibrinolysis. The intra-arterial administration of ultrasound with the EKOS NeuroWave® catheter is another ultrasound application for acute stroke that is currently being studied in the IMS III trial. Operator-independent devices, different MB-related techniques, and other ultrasound parameters for improving and spreading sono thrombolysis are being tested.

- **Mechanical thrombolysis:** Mechanical thrombectomy devices specifically for AIS intervention were developed in the 1990s concomitant to the advances in bioengineering devices which produced microcatheters and guide-wires amenable and safe to navigate the extremely complex and tortuous cerebral vasculature. Theoretically, mechanical devices provide several advantages over pharmacological thrombolysis, including revascularizations of large artery occlusions, more complete recanalization under observation, lesser amount of lytics to be used, reduced risk of hemorrhage, and a longer time interval for intervention. Six broad groupings classify neurothrombectomy devices: clot retrievers, aspiration or suction devices, snare-like devices, ultrasonography technologies, or lasers, and now stent retrievers. Potential harms associated with navigating mechanical devices into the intracranial circulation may include direct trauma to the neurovasculature (including vasospasm, vessel dissection, perforation or rupture) and fragmenting thrombi into previously unaffected vessels and cerebral territories.

A total of seven retrieval devices were evaluated for stroke applications. Of which two devices have received FDA approval for use. The success of an application in these devices is gauged by percentage of recanalization of the occluded artery.

- Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 hours when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 hours after symptom onset (Grade A, Level 1a, KSU Grade A). Mechanical thrombectomy should not prevent the initiation of intravenous thrombolysis where this is indicated, and intravenous thrombolysis should not delay mechanical thrombectomy (Grade A, Level 1a, KSU Grade A). Mechanical thrombectomy should be performed as soon as possible after its indication (Grade A, Level 1a, KSU Grade A). For mechanical thrombectomy, stent retrievers approved by local health authorities should be considered (Grade A, Level 1a, KSU Grade A). Other thrombectomy or aspiration devices approved by local health authorities may be used upon the neurointerventionists discretion if rapid, complete and safe revascularisation of the target vessel can be achieved (Grade C, Level 2a, KSU Grade C) If intravenous thrombolysis is contraindicated (e.g. Warfarin-treated with therapeutic INR) mechanical thrombectomy is recommended as first-line treatment in large vessel occlusions (Grade A, Level 1a, KSU Grade A) Patients with acute basilar artery occlusion should be evaluated in centres with multimodal imaging and treated with mechanical thrombectomy in addition to intravenous thrombolysis when indicated (Grade B, Level 2a, KSU Grade C); alternatively they may be treated within a randomized controlled trial for thrombectomy approved by the local ethical committee. The decision to undertake mechanical thrombectomy should be made jointly by a multidisciplinary team comprising at least a stroke physician and a neurointerventionalist and performed in experienced centres providing comprehensive stroke care and expertise in neuroanesthesiology (Grade C, Level 5, GCP, KSU Grade C). Mechanical thrombectomy should be performed by a trained and experienced neurointerventionalist who meets national and/or international requirements (Grade B, Level 2b, KSU Grade B). The choice of anesthesia depends on the individual situation; independently of the method chosen, all efforts should be made to avoid thrombectomy delays (Grade C, Level 2b, KSU Grade C).

PATIENT SELECTION FOR MECHANICAL THROMBOLYSIS

- Intracranial vessel occlusion must be diagnosed with non-invasive imaging whenever possible

before considering treatment with mechanical thrombectomy (Grade A, Level 1a, KSU Grade A).

- If vessel imaging is not available at baseline, a NIHSS score of ≥ 9 within three, and ≥ 7 points within six hours may indicate the presence of large vessel occlusion (Grade B, Level 2a, KSU Grade B).
- Patients with radiological signs of large infarcts (for ex. using the ASPECTS score) may be unsuitable for thrombectomy (Grade B, Level 2a, KSU Grade B).
- Imaging techniques for determining infarct and penumbra sizes can be used for patient selection and correlate with functional outcome after mechanical thrombectomy (Grade B, Level 1b, KSU Grade B).
- High age alone is not a reason to withhold mechanical thrombectomy as an adjunctive treatment (Grade A, Level 1a, KSU Grade A).

At present mechanical thrombectomy is being successfully done at various centres in the country however a definite published statistics of this procedure across the country is still awaited.

CONCLUSION

- “Miles to go “is still the belief in stroke medicine and it is sure that the future has more to offer and that day is not far when a large burden of morbidity and mortality due to ischemic stroke will be just in history.
- The advent of stroke thrombolysis has given rise to a new group of neurointerventionalist across the country specialised in stroke. Thrombolysis care and much hope rests upon their shoulder in taking the country ahead in stroke care.

REFERENCES

1. Warlow C, Sudlow C, Dennis M, Wardlaw J, Sandercock P. Stroke. *Lancet* 2003; 362:1211-24.
2. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rtPA Study Group. *N Engl J Med* 1995; 333:1581-1587.
3. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359:1317-29.
4. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *Stroke* 2002; 33:493-5.
5. The NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333:1581-7.
6. [Guideline] Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007; 38:1655-711.
7. [Guideline] Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke* 2009; 40:2945-8.
8. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet* 1998; 352:1245-51.
9. Diedler J, Ahmed N, Sykora M, Uyttenboogaart M, Overgaard K, Luejckx GJ, et al. Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset. *Stroke* 2010; 41:288-94.
10. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013; 44:870-947.
11. Indian Collaborative Acute Stroke Study (ICASS). Proceeding of Annual Conference of Andhra Pradesh Neuroscientists Association. Tirupati 2003.
12. Padma V, Soni D, Bhatia R, Srivastava A, Singh M. Thrombolysis in ischemic stroke: experience from a tertiary care hospital in India. *J Neurol Sci* 2005; 238:S428.
13. Sylaja PN, Kuruttukulam G, Joseph S, Gupta AK, Radhakrishnan K. Selective intra-arterial thrombolysis in acute carotid territory stroke. *Neurol India* 2001; 49:153-157.