

CHAPTER

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Thrombolysis in Ischemic Stroke

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Introduction

The December of 1995 was unlike any other month for stroke research ; and not without reason. National Institute of Neurological Disorders and Stroke (NINDS) in United States of America had just 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.¹ Twelve years down the line, rtPA is the most effective treatment in a subset of ischemic stroke patients both in academic centers and community hospitals. However, there are still some barriers in delivering thrombolytic therapy to ischemic stroke patients. This article will review the major studies bringing rtPA into routine practice of stroke and will address the associated issues with special reference to India.

What triggered the thrombolysis movement?

Although stroke thrombolysis research has been going on since the last three decades, it was the publication of NINDS rtPA trial, which made stroke thrombolysis seem possible in real practice. The NINDS trial randomized 624 patients (312 each placebo and intravenous rtPA) within a time window of 3 h after stroke symptom onset. Half of the patients were treated within 0-90 min and the other half within 91-180 min. A good outcome was

defined as a National Institute of Health Stroke Scale (NIHSS) Score < 1, Glasgow Outcome Score (GOS) = 1, Barthel Index (BI) > 95, and modified Rankin Score (mRS) < 1. The median baseline NIHSS Score was 14 (rtPA group) versus 15 (placebo group). There was no significant difference between the drug treatment and placebo group in the percentages patients with neurological improvement at 24 h (rtPA 47% vs placebo 57%; relative risk (RR) 1.2, p = 0.21), although a post hoc analysis comparing the median NIHSS at 24 h showed a median of 8 in the rtPA treated group versus 12 in the placebo group (p < 0.02). Furthermore , the proportion of rtPA patients achieving a favorable outcome (minimal or no disability) at 3 months on each of the four scales was 1.7 times greater than patients in the placebo group. The long-term clinical benefit of rtPA was confirmed in all single scores as well as in the global test : BI (50% vs 38%; OR 1.6 (95% C.I 1.1-2.5), p = 0.026); mRS (39% vs 26%; OR 1.7(95% CI 1.1-2.5), p = 0.019); GOS (44% vs 32%; OR 1.6(95% CI 1.0-2.8), p = 0.033); and combined end point (OR 1.7 (95% CI 1.0-2.8), p = 0.008). Thus, for every 100 patients treated with recombinant plasminogen activator (rtPA) according to the NINDS protocol, at least 11 more patients are expected to achieve a favorable outcome. More recently, NINDS rtPA Study Group reported that the 1-year follow up of

patients closely matched the results reported at 3 months. Thus evidence exists of a sustained benefit from rtPA at 1 year.⁴ Furthermore, the outcome did not vary by stroke subtype at baseline, meaning that patients with small vessel disease benefited as well as patients with, for instance, cardioembolic stroke. Tissue plasminogen Activator got a prompt approval by FDA within a record time of 6 months. Following close on heels, the American Academy of Neurology and American Stroke Association also issued the guidelines for rtPA administration to patients with acute ischemic stroke,^{2,3} which are basically based on the protocol followed in the NINDS study (Table 1). Some people felt that it was premature for FDA to approve rtPA based on just one positive study, but others held the view that the evidence of efficacy was so compelling, that one could not deny the benefit to the eligible patients.

Predictors of hemorrhage

Thrombolytic therapy with rtPA is not without risk. Symptomatic intracranial hemorrhage (ICH) occurred in 6.4% of patients treated with rtPA in the study sponsored by the NINDS. Those suffering a symptomatic ICH had a high mean NIHSS score of 20. Overall those with the most severe strokes (NIHSS score greater than 20) had a 17% rate of ICH. In short, cases of severe ischemia caused by volume of infarct or duration of infarct), have a high likelihood of hemorrhagic transformation by thrombolysis.

Predictors of efficacy

Overall, no difference in mortality occurred despite a higher risk of symptomatic ICH (6.4%) for patients treated with rtPA. Following the original NINDS report, several additional analyses of the cohort were examined. In an attempt to identify patients who would be most or least likely to respond to rtPA, an analysis of baseline variables did not find any pretreatment characteristic that might influence a patient's response to rtPA.⁵ If a 3-hour window of treatment can be met,

thrombolytic therapy with intravenous rtPA can be beneficial for each of the major categories of ischemic stroke: atherothrombotic, cardioembolic, and lacunar stroke. However, follow-up analysis found a relationship between the chance of a favorable outcome and the time from symptom onset to initiation of treatment. The chance of a favorable outcome diminishes the closer one gets to the 3-hour time point. This highlights the fact that ultra-rapid treatment is critical for therapeutic success.⁶

Cost – effectiveness

A post-hoc analysis of cost-effectiveness in the NINDS rtPA Study Group found that treatment with rtPA significantly reduced the cost of care, accomplished by reducing hospital length of stay and increasing the percentage of patients discharged home versus to nursing home or a rehabilitation setting.⁷

Are NINDS results applicable to routine practice ?

Since the FDA approval of rtPA for acute ischemic stroke, several groups have reported the results of treatment in the clinical setting. Tanne and colleagues (1999) published a retrospective series of 189 consecutively treated patients in 13 hospitals who were not involved in the original NINDS study.⁸ The rate of symptomatic ICH was 5.8%. Thus the risk of ICH did not exceed that found in the NINDS study. Even more important was the finding that deviating from the treatment and management guidelines of NINDS trial increased the risk of ICH to 11% versus 4% for patients whose treatment was within the guideline parameters. The most common deviations noted were initiation of treatment beyond 3 hours from symptom onset or use of heparin or aspirin in the first 24 hours. The first large prospective study after the FDA approval of rtPA for acute ischemic stroke was the Standard Treatment with Alteplase to Reverse Stroke (STARS) study.⁹ Three hundred eighty-nine patients were enrolled in 57 medical

Table 1 : TPA Stroke Study Group : Protocol Guidelines for the administration of rt-PA to patients with Acute Ischemic Stroke

Eligibility for IV treatment with rt-PA	Post rt-PA care
<ul style="list-style-type: none"> Age 18 years or older Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit Time of symptom onset less than 3 hours before treatment would begin 	<ul style="list-style-type: none"> Do not administer heparin, warfarin, or aspirin during the first 24 hours after symptom onset. Monitor neurologic status. Appearance of headache, vomiting, decreased level of consciousness, pupillary asymmetry or any other new neurodeficit necessitates CT Scan and neurosurgical consultation. Monitor for bleeding tendencies
<p>Patient selection : contraindications and warnings</p>	<p>Blood pressure control</p>
<ul style="list-style-type: none"> Evidence of intracranial hemorrhage on pretreatment CT Scan Only minor or rapidly improving stroke symptoms Clinical suspicion of subarachnoid hemorrhage, even with normal CT findings Active internal bleeding Known bleeding diathesis , including but not limited to : platelet count < 100,000/mm³ Receipt of heparin within 48 hours and an elevated activated partial thromboplastin time(aPTT) (greater than upper limit of normal for laboratory) Current use of oral anticoagulants or recent use with an elevated prothrombin time (PT) > 15 seconds Major surgery or serious trauma excluding head trauma in previous 14 days Intracranial surgery, serious head trauma, or previous stroke within 3 months History of gastrointestinal or urinary tract hemorrhage within 21 days Recent arterial puncture at a noncompressible site Recent lumbar puncture On repeated measurements, systolic blood pressure > 185 mm Hg or diastolic blood pressure > 110 mmHg at the time treatment is to begin, and aggressive treatment required to reduce blood pressure to within these limits History of intracranial hemorrhage Abnormal blood glucose level (< 50 or > 400 mg/dl) Post-myocardial infarction pericarditis Seizure observed at the same time the onset of stroke symptoms was observed Known arteriovenous malformation or aneurysm 	<ul style="list-style-type: none"> Monitor blood pressure for the first 24 hours after starting treatment: Every 15 minutes for 2 hours after starting the infusion, then Every 30 minutes for 6 hours, then Every hour for 18 hours If diastolic blood pressure is > 140 mmHg , start an intravenous infusion of sodium Nitroprusside (0.5 to 10 µg/kg/min) If systolic blood pressure is > 230 mmHg and/or diastolic blood pressure is 121 to 140 mmHg , give labetalol 20 mg intravenously over 1 or 2 minutes. The dose may be repeated and /or doubled every 10 minutes, repeated upto 150 mg. If systolic blood pressure is 180 to 230 mm Hg and/or diastolic blood pressure is 105 to 120 mm Hg on two readings 5 to 10 mm Hg apart, give labetalol 10 mg intravenously over 1-2 minutes. The dose may be repeated or doubled every 10 to 20 minutes, upto 150 mg. Monitor blood pressure every 15 minutes during the antihypertensive therapy. Observe the hypotension.
<p>Treatment</p>	<p>Management of Intracranial hemorrhage</p>
<ul style="list-style-type: none"> rt-PA 0.9 mg/kg (maximum of 90 mg) infused over 60 minutes with 10% of the total dose administered as an initial IV bolus over 1 minute. 	<ul style="list-style-type: none"> Suspect the occurrence of intracranial hemorrhage after the start of rt-PA infusion if there is any acute neurologic deterioration, new headache, acute hypertension, or nausea and vomiting. Discontinue rt-PA infusion. Perform immediate CT scan If intracranial hemorrhage is present, do the following : Check PT, aPTT, platelet count and fibrinogen Give 6-8 units of cryoprecipitate containing factor 8 to raise the fibrinogen level to > 150 mg/dl Give 6-8 units of platelets Recheck the fibrinogen level every 4 hours and transfuse with cryoprecipitate to maintain fibrinogen level > 150 mg/dl Take urgent neurosurgical consultation

centers in the United States (24 academic and 33 community). The most important finding of this study was that the symptomatic ICH rate was 3.3%

at 3 days, which is lower than the rate observed in the NINDS study. Protocol violations were noted in 32.6 % of patients and most commonly included

treatment with rtPA more than 3 hours after symptom onset, use of anticoagulants within 24 hours of rtPA administration, rtPA administration despite systolic blood pressure exceeding 185 mm Hg, or elevated partial thromboplastin time. Despite the protocol violations, the STARS study suggested that a favorable outcome and a lower rate of symptomatic ICH could be achieved in clinical practice at multiple medical centers across the United States.

In a smaller retrospective study of in-hospital patient outcomes throughout a large urban community, Katzan and colleagues (2000) reported the results of a chart review at 29 hospitals in the Cleveland, Ohio, metropolitan area from July 1997 to June 1998.¹⁰ IV rtPA was administered to 70 patients (1.8% of ischemic strokes) at 16 hospitals. Symptomatic ICH occurred in 11 (16%) of these patients. Protocol violations were noted in 54.5% of patients with symptomatic ICH and 49.1% of patients without symptomatic hemorrhage. The most common protocol violations were the use of antiplatelet or anticoagulant medications within the first 24 hours, elevated blood pressure, and treatment initiation beyond 3 hours from symptom onset. Although the investigators reported no statistically significant association between the presence or type of protocol deviations and symptomatic ICH, a greater percentage of patients in the symptomatic ICH subgroup had elevated blood pressure or received rtPA beyond 3 hours. Patients with symptomatic ICH tended to be older and had a higher blood glucose level than patients without symptomatic ICH. The Cleveland-area experience provides the only evidence that community rtPA use may not achieve the same robust outcomes as the NINDS study. However, this study was small and did not adequately document the stroke severity, a factor that has been clearly linked to the risk of ICH. According to a comprehensive review of published case series comprising 1714 patients with acute ischemic stroke who have been treated with IV rtPA since the FDA approval in 1996, the overall rate of symptomatic hemorrhage has been 5%.¹¹

Intravenous thrombolysis beyond 3 hours; what do the trials say?

Three large, randomized, double blind, placebo controlled trials evaluating cardiac doses of intravenous Streptokinase given upto 6 hours after the onset of stroke symptoms failed to demonstrate a benefit of treatment with the drug and were terminated prematurely because of increased rates of intra cerebral hemorrhage (ICH) and mortality in the treated groups.^{12,13,14} Potential contributors to the hazards included severe strokes in one trial and the high doses of streptokinase administered in all the three studies. Even though, streptokinase has been given up as a treatment option, its potential in treating patients within 6 hours is possible, if dose is reduced and strict selection criteria are met. Clearly, there is a scope for further clinical trials in this direction.

So far three major double blind placebo controlled trials of treatment with intravenous rtPA beyond the 3-hour window have been carried out. The first among these was the European Acute Stroke Study (ECASS) trial, which was a multicenter, randomized, double-blind, placebo controlled study of 620 patients with acute hemispheric stroke who presented within 6 hours of symptom onset.¹⁵ Patients were randomized to receive either rtPA (1.1 mg/kg, maximum dose 100 mg) or placebo. Primary end points were scored on the Barthel Index (BI) and the Modified Rankin Scale (mRS) 3 months after stroke. No significant benefit was seen with therapy in the intention to treat population as measured by the primary end points. Of the 620 patients enrolled, 109 (17.4%) were considered to have had major protocol violations. When these patients were excluded from analysis, a statistically significant benefit to treatment with rtPA was seen on the mRS at 3 months in the remaining target population.¹⁶

To further evaluate the role of dose and timing of thrombolytic therapy, two additional trials were undertaken: the European Cooperative Acute Stroke Study II (ECASS II) and the Alteplase

Thrombolysis for Acute Non Interventional Therapy in Ischemic Stroke (ATLANTIS).^{17,18} ECASS II, like the ECASS I trial, included patients who presented within 6 hours of stroke onset, but used the NINDS dosing regimen of 0.9 mg/kg. The primary endpoint was a favorable outcome on the mRS, using the dichotomized method of the NINDS trial. Eight hundred patients were enrolled, with only 158 treated within 3 hours. Seventy-two protocol violations were reported ; most were violations of the CT criteria. A favorable outcome (mRS 0-1) was seen in 40.3% of the rt-PA group and 36.6% of the placebo group, which was not a statistically significant difference ($p = 0.277$). Post-hoc analysis based on the dichotomized mRS of independence (mRS 0 - 2) did reveal a statistically significant benefit to treatment with rtPA, with 54.3% of treated patients returning to independence versus 46% of placebo patients ($p = 0.024$). The ECASS II trial showed that the use of rtPA in acute ischemic stroke within 6 hours of symptom onset was not supported by the trial, although there might be a trend toward better outcome with treatment. The investigators also recommended conservative interpretation of the 0 to 3 hour results, because the number of patients treated within that time window was small.

The Alteplase Thrombolysis for Non Interventional Therapy in Ischemic Stroke (ATLANTIS) was similar in design to the NINDS study and was undertaken to determine whether the benefits of rtPA demonstrated within 3 hours of symptom onset could be extended to a longer time window (3-5 hours). The primary outcome was percentage of patients with a good outcome (NIHSS 0-1) at 90 days. The trial was terminated prematurely in July 1998, when the Data Monitoring and Safety Board analysis found "treatment was unlikely to prove beneficial"; however, no difference in mortality was seen between the treatment and placebo groups, suggesting that treatment within 5 hours of symptom onset was safe.

A subsequent meta analysis of all thrombolytic trials revealed thrombolytic therapy to be effective

in improving outcome at the risk of increased intra and extracranial hemorrhage. Using a dichotomized scale of MRSS of < 0 or $= 2$ versus $>$ or $= 3$, there was a 37% relative chance of improvement. The higher rate of hemorrhage in the 3 - 6 hour versus the 0 - 3 hour window (Odds ratio 3.23 versus 2.68) were not statistically significant.¹⁹

Role of MRI Imaging in extending window

A substantial amount of information is available from diffusion-perfusion magnetic resonance imaging (MRI) studies that potentially salvageable ischemic tissue exists in some patients for many hours after stroke onset. Diffusion-perfusion MRI is an imaging modality now widely available at many centers. Diffusion weighted imaging (DWI) rapidly demonstrates the presence of ischemic regions where failure of energy metabolism has occurred. Perfusion - weighted imaging (PWI) evaluates tissue perfusion in the brain microvasculature and can rapidly determine the presence of hypoperfused regions. The discrepancy of PWI and DWI volumes is called the diffusion-perfusion mismatch and appears to identify potentially salvageable ischemic tissue. The PWI-DWI mismatch thus provides a readily identifiable imaging marker of potentially salvageable ischemic tissue that can be widely used to identify potentially treatable ischemic stroke patients irrespective of time from onset. This was stressed in a recent study where the treatment was based on MRI evidence of a diffusion-perfusion mismatch evidence beyond 3 hours of onset of stroke. Nineteen patients with MRI diffusion-perfusion mismatch were treated with intravenous rt-PA. For comparison, 21 historical controls were chosen. The treated group had better recanalization at day 3 (87% vs 47%), significantly less lesional expansion (14 cc vs 56 cc) and a significantly higher number of patients demonstrating an improvement in the NIHSS of greater than 7 points.²⁰

Meta analysis

With growing experience and better training of emergency medical personnel, internists, and neurologists throughout all stroke services, the efficacy of intravenous thrombolytic therapy with rtPA may even improve and the time window may be routinely extended to 6 h after symptom onset. While rtPA is approved for thrombolytic therapy in the 3h time window, there is level I (positive meta-analyses from large methodologically flawless randomized controlled trials), level II (positive secondary endpoints of large randomized controlled trials, i.e. ECASS I and II), and ample level III and IV evidence that thrombolysis works in the 4.5 - 6 h time window. Accordingly, with the recommendations of the Cochrane Collaboration,²¹ and the European Stroke Initiative,²² intravenous thrombolysis is safe and effective up to 6 h in selected patients, and likely best within 4.5 h after stroke onset. The ideal selection tool may be stroke MRI.²³ The fact that an individual therapy based on advanced knowledge is offered that does not meet the criteria of drug approval institutions and therefore may be associated with a higher risk of hazardous if not fatal side-effects must be stressed when informed consent is obtained. Patients and their relatives should be informed not only about the hazards of thrombolytic therapy within or outside the 3 h time window but also about its potential benefit and the risk of not being treated.

Intra-Arterial Thrombolysis

Anterior Circulation

For ischemic stroke patients who are not candidates for intravenous rtPA, intraarterial (IA) thrombolysis may be a treatment option for carefully selected patients who present up to 6 hours after symptom onset. The PROACT II Study was a multicenter effort to determine whether administering an intra-arterial thrombolytic agent- in this case 2-hour infusion of 9 mg of IA recombinant pro-urokinase (pro-UK)- could improve 3-month functional outcomes in patients with acute middle cerebral artery (MCA) territory stroke.²⁴ One hundred eighty

patients were randomized to receive intra-arterial pro-UK or placebo in a 2:1 randomization scheme. The study design included patients with less than 6 hours of acute ischemic stroke symptoms who were suspected of having MCA occlusion. After a CT scan excluded hemorrhage and showed no evidence of acute hypodensity or sulcal effacement in more than one third of the MCA territory, all patients underwent angiography to identify the site of thrombosis. If occlusion of M1 or M2 segment was found, the patient was randomized to either pro-urokinase or a control group. All patients received a periprocedural IV heparin drip for 4 hours and repeat angiogram at 1 and 2 hours to assess the status of thrombolysis. The results showed that 40% of the treatment group versus 25% of the control group achieved the primary outcome of slight disability or better at 3 months ($p = .043$). This difference represents a 15% absolute benefit and 60% relative benefit for treatment with IA pro-urokinase. Thus, for every six patients treated one additional patient will achieve slight disability or better outcome at 3 months (number needed to treat = 6). The benefit was seen despite a 10% risk of symptomatic ICH. Several other case series have also suggested a benefit of IA thrombolysis in severe posterior circulation stroke even when therapy is delayed out to 24 hours.²⁵ Intra-arterial thrombolytic therapy is not approved by FDA and is considered experimental. Patients and their attendants must be apprised of this.

Posterior circulation

Intra-arterial thrombolysis for acute posterior circulation ischemia differs substantially from intra-arterial thrombolysis of anterior circulation vessels. This includes differences in the proportions of underlying stroke mechanisms, differences in the morbidity and mortality and above all differences in the time window during which ischemia may be successfully reversed.²⁵ Unlike the striatum and cerebral cortex, the brainstem is relatively resistant to ischemia. The practical consequence of this in regard to intra-arterial thrombolysis is that successful recanalization might reverse clinical

deficits as far out as 24 hours from stroke symptom onset in some instances.²⁵

Indian experience

Intravenous Thrombolysis

Thrombolytic therapy made a slow but sure entry into Indian neurological practice, for obvious reasons. These include lack of awareness among public and, among the referring physicians about the existence and usefulness of rtPA treatment. However, as per a survey carried out in various cities in India, it was found that 8% to 25 % of stroke patients arrived in the hospital within 3 hours.²⁶ All of them do not receive rtPA as many do not qualify as per the NINDS criteria. Others find the cost very high. But the most important reason even in the big cities, as anywhere else in world, which discourages the neurologists to use rtPA is the uncertainty of response and potential for fatal brain hemorrhage. Approximately 15 stroke units in India use tPA for acute stroke.²⁷ In a study from a private sector tertiary referral hospital in Northwest India, 489 stroke patients were screened between September 2001 and November 2003.²⁸ Seventy-two of them (14.7%) presented within a 3-h window. Thirty-eight of the 72 patients had had an ischemic stroke. Sixteen out of 38 ischemic stroke patients did not meet the inclusion criteria for thrombolysis therapy. Only five out of the 22 eligible patients received tPA. The remaining 17 eligible patients could not afford the drug.²⁸ In another study from the rural catchment area in India, only 20 (31%) patients out of 64 evaluated reached the hospital within 3 h.²⁹ Seven patients were found eligible for thrombolysis but none of them received the drug. The cost of the drug was a major hinderance, as most of the patients belonged to a lower socioeconomic strata.²⁹

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 between March 2002 and June 2005.³⁰ 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).³⁰

In a private sector hospital from Amritsar, 34 patients were given tPA over 3 years.³¹ In half of the group, MRI DWI/PWI sequences were used to select patients for thrombolysis. Patients in the DWI/PWI group had a better outcome than the patients who received rtPA based on CT scan.³¹ In another private hospital in Chennai, sonothrombolysis was used along with iv rtPA in 42 patients with good recovery.³² 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. The mean age was 41.2 years (range 30 - 65 years, all were men). Digital Subtraction Angiography (DSA) showed distal internal carotid artery occlusion in one patient and occlusion in one patient and occlusion of the middle cerebral artery or its branches in the others. The UK dose ranged from 120 000 to 500 000 U. 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.³⁴

A private sector hospital in Guntur, South India, has successfully implemented IA thrombolysis therapy based on the PROACT-II protocol.²⁴ A neuro-interventional team is available 24 h and patient selection is based on CT scan and four-vessel angiogram. IA thrombolysis was used in 40 patients with ischemic stroke in both anterior and posterior circulation. UK was used in all patients (100,000- 750,000 U), except in one patient , where

tPA (20 mg) was used. The baseline NIHSS ranged from 8 to 25 (median 17) at admission. Twenty-five (62%) patients had good outcome (mRS 0-2) at three months.

These preliminary data from India show that hyperacute thrombolysis in acute ischemic stroke is feasible in urban private and public sector tertiary hospitals. It could be widely used if a greater number of dedicated stroke teams /stroke units become available, and the cost of the drug is reduced.

Barriers to thrombolysis in India

Infrastructure

Eighty per cent of population from India lives in rural areas where the health care infrastructure is poor. Many patients having acute ischemic stroke find it difficult to travel in a reasonable time to the centers where there are resources to facilitate tPA. These facilities, which are primarily located in urban areas, become difficult to access mainly due to poor road infrastructure. There are hardly any ambulance services in rural areas.

Socio-cultural factors

People living in India have very little access to information about stroke. A study in northwest India documents that only a third of subjects interviewed, correctly identified the brain as the affected organ in a stroke.³⁵ Low threat perception of stroke was an independent factor for the late arrival of patients at the emergency department in a study from north India.³⁶ Most rural patients having stroke attending a university hospital in south India were not aware of the importance of the time window in stroke management.²⁹

Economics

Most governments in developing countries are not in a position to provide thrombolysis therapy in government hospitals to patients in need. Health insurance systems are limited to a minute section of the community. Patients must cover the costs using their own personal savings or not receive treatment. In a study from south India, all seven

patients eligible for thrombolysis therapy belonged to lower socioeconomic group from rural India and could not afford the therapy.²⁹ In an urban hospital in northwest India of the 23 eligible patients, only five actually received the drug; the remaining patients were unable to afford the high cost of the treatment.²⁸

Low-cost thrombolytic agents

Urokinase is a cheaper alternative to rtPA, and the preliminary results of a Chinese i.v. Urokinase trial are promising.³⁷ The effectiveness of this drug should be evaluated in a multicentered study across other countries. The Asian population may respond to low-dose rt-PA (0.6 mg/kg) based on a study from Japan.³⁸ The reproducibility of the results of the former study should be explored in other Asian countries. If found to be beneficial, it will increase the utilization of rtPA in India

Although written consent is not necessary before administration of rtPA for treatment of stroke, a full discussion of the potential risks and benefits of treatment with rtPA with the family and the patient is recommended.

To conclude, stroke thrombolysis is a reality and stroke thrombolysis works. Unquestionably there is a certain risk involved in terms of intracranial hemorrhage, but considering the devastation and disability a stroke causes, the risk taken is worth it, provided the neurologist is well versed in the thrombolytic therapy. Moreover, with proper selection and strict adherence to NINDS protocol, the chances of intracerebral hemorrhage can be minimized.

Current Recommendations of American Stroke Association for thrombolysis in Adults with Ischemic Stroke

Class I Recommendations

- Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of

ischemic stroke (Class I, Level of Evidence A). Physicians should review the criteria outlined in Table 1 (which are modeled on those used in NINDS trial) to determine the eligibility of the patient.

- Besides bleeding complications, physicians should be aware of the potential side effect of angioedema that may cause partial airway obstruction (Class I, Level of Evidence C).

Class II Recommendations

- A patient whose blood pressure can be lowered safely with antihypertensive agents may be eligible for treatment, and the physician should assess the stability of blood pressure before starting rtPA (Class IIa, Level of Evidence B).
- A patient with a seizure at the time of onset of stroke may be eligible for treatment as long as the physician is convinced that residual impairments are secondary to stroke and not a postictal phenomenon. (Class IIa, Level of Evidence C).

Class III Recommendations

- The intravenous administration of streptokinase for treatment of stroke is not recommended (Class III, Level of Evidence A).
- The intravenous administration of anocrod, tenecteplase, reteplase, desmoteplase, urokinase, or other thrombolytic agents outside the setting of a clinical trial is not recommended (Class III, Level of Evidence C).

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