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Review Article

Thrombolytic Therapy in Acute Stroke: Outcome, Barriers & How to Overcome

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Introduction

Stroke is the leading cause of disability among adults globally. Despite advances in preventive strategies and initial therapy for stroke, nearly 800,000strokes occur per year in the United States and 87% of all strokes worldwide areischemic in origin.[1] As recently as less than 10 years ago, management of acute ischemic stroke consisted of diagnosis, medical support & rehabilitation after acute event. There are now interventions for acute revascularization, either pharmacological or mechanical, that allow blood follow to be restored promptly to the ischemic brain tissue.[2,3]

It is also one of the leading cause of death in our country. But there has been limited progress in management of patientswith stroke in developing countries and data on stroke care inthese countries are sparse.[4,5,6] Guidelines are continuouslydeveloped and updated in the developed world but theirpracticality for use in developing regions is unrealistic [6].The number of stroke patients receiving r-tPA in the thirdworld is extremely low. In Stroke thrombolysis is currentlyused in few developing countries like Brazil, Argentina,Senegal, Iran, Pakistan, China, Thailand, and India.[7]

Sadly, thrombolysis is still underused in our country. Purpose of this review is to highlight the positive results of thromblytic therapy in acute stroke which willencourage our physician to offer this therapy to an increasing number of stroke patients, and thereby reduce the considerable socioeconomic burden of stroke.

Role of Thrombolytic therapy

Ischemic stroke results from vascular occlusion that reduces cerebral blood flowto the area of brain perfused by the occluded artery. In either thrombotic or embolicstroke, such occlusion is caused by obstruction of the artery by thrombus.If the reduction in blood flow is sufficiently severe, a series of events occurs atthe cellular level that leads to infarction.Tissue plasminogen activator (t-PA) is a serineprotease that acts by enhancing the conversionof inactive plasminogen to active plasmin. Plasminacts on fibrin clots, causing dissolution andlysis. The activity of t-PA is greatly enhanced inthe presence of fibrin, increasing fibrinolysisspecifically at the site of thrombosis[8].This theoretically result in revascularization of a previously occluded blood vessel well and reversal of brain ischemia. In vivo,t-PA is released by endothelial cells; in contrast,exogenously administered t-PA is derived fromthe application of recombinant DNA technologyand is thus designated recombinant t-PA (rt-PA).Unlike first-generation plasminogen activatorssuch as streptokinase and urokinase, rt-PA is fibrin-selective and preferentially activates fibrinboundplasminogen.

Thrombolytic medications in acute stroke became a significant part of stroke treatment after the publications of the National Institute of Neurological Disorders And stroke t-PA Stroke Study Group Trial(NINDS) in 1995.In thisNINDS trial, the rate of a favorable outcome wassignificantly greater with intravenous rt-PA thanwith placebo (odds ratio, 1.7; 95% CI, 1.2 to 2.6;P = 0.008). This benefit was sustained at 6 monthsand at 1 year.[9]

In the subsequent ECASS III, 821 patients whopresented between 3 and 4.5 hours after the onsetof stroke were randomly assigned to intravenousrt-PA or placebo.[10]At 90 days, significantly more patientstreated with rt-PA had favorable outcomes, as com-pared with those given placebo (52.4% vs. 45.2%;odds ratio, 1.34; 95% CI, 1.02 to 1.76; P = 0.04).

Clinical Use of Fibrinolytic Therapy

Intravenous administration of t-PA within 3 hoursafter the onset of stroke increases the probability of a favorable outcome. Recommended protocolsfor selecting patients for treatment with intravenousrt-PA are adapted from the inclusionand exclusion criteria from the NINDSrt-PA trial . On the basis of results of ECASS III,[10]some stroke centers

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now treat patients who presentfrom 3 to 4.5 hours after stroke onset; however, at present, the FDA has approved only rt-PAtreatment delivered within 3 hours after strokeonset.

When a patient is evaluated for any thrombolytic therapy,it is vital to evaluate the patient as soon as practicable.In Acute setting patient should receive as quickly as possible:

- Triage to emergency room
- Airway, Breathing , Circulation & finger stick test to exclude hypoglycaemia
- CT scan of Head to exclude haemorrhage& to look for early signs of infarct.
- Blood Test: Complete blood count,complete metabolic panel and coagulation profile to rule out thrombocytopenia,liver failure and recent use of anticoagulsnts.
- ECG
- Evaluation of blood pressure with control using labetatol or nicarsdipine if systolic blood presssure is 180 or greater.
- Nerological evaluation that includes

- Time of Onset (time the patient was last seen as normal, not time the family thinks stroke occured)
- NIH stroke scale: Many protocols exclude patients who have mild deficits, since their prognosis for recovery is good without thrombolytic therapy.[11, 12]

The **National Institutes of Health Stroke Scale**, or **NIH Stroke Scale** (**NIHSS**) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0.

Score	Stroke Severity
0	No Stroke Symptoms
1-4	Minor Stroke
5-15	Moderate Stroke
16-20	Moderate to Severe Stroke
21-42	Severe Stroke

However, treatment should be initiated on the basis of the assessmentof adisabling deficit rather than on a defined lower limit for the NIHSSscore. For example, isolated aphasia or hemianopia is a disabling deficit despite an NIHSS score of 2 or 3.

Inclusion and Exclusion Criteria for Intravenous t-PA Therapyin Patients with Acute Ischemic Stroke

Inclusion criteria	Exclusion criteria
• Diagnosis of ischemic stroke causing measurable neurologic deficit. • Onset of symptoms <3 hr before start of treatment (or, in selected cases,<4.5 hr) • Age < 18 yr .	• Head trauma or prior stroke within the previous 3 month • Symptoms suggestive of subarachnoid hemorrhage • Arterial puncture at no compressible site within the previous 7 days • History of intracranial hemorrhage· • Elevated blood pressure (systolic, <185 mm Hg, or diastolic, e"110 mm Hg)that has not responded to antihypertensive treatment • Evidence of active bleeding on examination • Acute bleeding diathesis, including but not limited to the following:-Platelet count d"100,000/mm3 -Heparin received within 48 hours, resulting in aPTT > upper limit of normal -Current use of anticoagulant, with INR < 1.7 or PT < 15 sec • Blood glucose concentration d"50 mg/dl (2.7 mmol/liter) • CT evidence of multilobar infarction (hypodensity>one third of the cerebral hemisphere) Relative exclusion criteria, depending on risk:benefit ratio‡ • Only minor or rapidly improving stroke symptoms (clearing spontaneously) • Seizure at onset with post-ictal residual neurologic impairments • Major surgery or serious trauma within the previous 14 days • Gastrointestinal or urinary tract hemorrhage within the previous 21 days • Acute myocardial infarction within the previous 3 month.

The FDA-approved dose of intravenous rt-PA is0.9 mg per kilogram of body weight, with a maximumdose of 90 mg. A bolus of 10% of the doseis given over a period of 1 minute, with the remainderinfused over a period of 60 minutes. Weightshould be determined as reliably as is possible.

Management of post-fibrinolytic period

For the first 24 hours after treatment, patientsreceiving rt-PA should be closely monitored in aspecialized unit so that the patient can be evaluated frequentlyby the nursing staff. Blood pressure shouldbe checked every 15 minutes for the first 2 hours,every 30 minutes for the next 6 hours, and thenevery hour for 16 hours. Antihypertensive therapywith labetalol or, if necessary, intravenous nicardipineshould be administered to maintain blood pressure at a level below 180 mm Hg systolic and105 mm Hg diastolic.[13,14] Neurologic examinationwith the use of the NIHSS should be performedevery 15 minutes for the first 2 hours,every 30 minutes for the next 6 hours, and thenevery hour for 16 hours. If a change in neurologicstatus is noted, the rt-PA infusion should be discontinuedand a CT scan obtained. No anticoagulantor antiplatelet therapy should be given for thefirst 24 hours after treatment with intravenousrt-PA. If a CT scan at 24 hours shows no evidenceof hemorrhage, antithrombotic therapy directed atsecondary stroke prevention and tailored to thepresumed cause of the stroke should be started.

Barrier of thrombilytic therapy

Prehospital Barriers :

One of the most important prehospital barriers of thrombolysistherapy in the developing world is nonrecognitionof stroke warning signs by patients at risk, families, thegeneral public and even health workers in some places [15].There is poor recognition of stroke symptoms in developingcountries [16]. The people at the highest risk have the lowestknowledge regarding vascular disease including limitationsto ascertain mild and transient symptoms as stroke[17] .In summary following three types of prehospital barrier is identified in different studies:

- **The patient or family did not recognise symptoms of stroke or seekurgent help**: Several studies identified this as a barrier[18-20, 21-23] .The commonest factors associated with it were: (i) patientliving alone [24], (ii) symptomsnot recognised or not interpreted as stroke (iii) lack of bystander witness when stroke symptomsoccurred (iv) patient or family not seekingmedical help at all (v) patient or family having nosense of urgency to seek help when symptoms started (vi) stroke symptoms started at home and (vii) patient refused to go to hospital .
- **Patient or family did not call an ambulance:** Twenty-threestudies identified this as a barrier.[25-28] These studies foundthat ambulance transfer was associated with a shorter delayto arrival at hospital, whereas first contacting a general practitioner(GP) increased the delay.
- **Paramedical staff did not triage stroke as an emergency:** Wefound seven studies that evaluated delays from calling theemergency services to the time of ambulance arrival, and from ambulance arrival at the patient to reaching the hospital[29]. These studies found that stroke was often not regarded as an emergency by the paramedicalstaff, leading to slower ambulance transfer.

In –Hospital barrier:

- **Emergency department did not triage stroke as an emergency:**several studies have found that examined delay from stroke onset(or arrival at hospital) to first medical assessment, neurologistsassessment, or alerting the acute stroke team[21-23] .The median delay from arrival at hospital to first medicalassessment varied considerably, ranging from 20 minutesto 4 hours [30].
- **Delay in neuroimaging:** Delays occurred in: requesting the scan,transporting the patient to the radiology department, carrying out the scan, and reporting the scan by a neuroradiologist
- **Ineffcient process of in-hospital emergency department:** Reported reasons for delay in wardtransfer included beds being unavailable and delay in obtaininga porter to transport the patient .
- **Diffculties in obtaining informed consent for thrombolysis:** Inthe acute phase, many stroke patients have language impairmentor reduced consciousness, which makes it diffcult to get their consent for treatment. Two studies identified thisbarrier. In one study, 10% of patients did not receive the treatment because they refused consent whereas only0.4% of patients refused in another study ‘
- **Physicians' uncertainty in administering rt-PA:** In the USA,where rt-PA is licensed, one study in 1998 found that only16% of neurologists had ever administered the treatment. In this review, one study showed that some physicianswere reluctant to administer rt-PA because of conflicting trial results and difficulty in starting treatment within3 hours of stroke onset .
- **Other identified barriers:** Five studies reported other barriers:(a) delays in retrieving old medical records, performingphlebotomy, and acquiring the drug from pharmacy (b) delays in transferring the patient from another hospital.

Commonest reasons for being ineligible forthrombolysis using rt-PA,	The proportions of patientswho were ineligible for these reasons(% range)
• Delay to treatment >3 hours, or onsettime unknown	22–94
• CT scan shows haemorrhage or signsof extensive infarction	10–22
• Clinical signs of stroke too mild or resolving rapidly.	9–19
• Medical contraindications to rt-PA	6–10
• Refusal to consent to treatment	0.4–10

Stroke patient is a great burden for a family as well as for the country because of huge cost of treatment and rehabilitation. So, if we give quick recovery of the patient it is beneficial for his family and the country. For this purpose we should try to overcome the barriers of treatment .

Measures to overcomethese in-hospital barriers could include, e.g. training ofemergency department staff to triage stroke as an emergency,improving access to CT scanning and training ofdoctors in administering thrombolysis.

Conclusion

Treatment with intravenous rt-PA can be given any acute ischemic stroke patients whomeet the stated inclusion criteria, including presentationwithin 3 hours after the onset of stroke, and who do not meet any of the stated exclusion criteria.28,67. Both American Heart association and the European Stroke organization have recently updated their guidelines to extend the treatment window to 4.5 hours. So in conclusion intravenous rt-Pa is a reasonable treatment option when used in tertiary care hospital and is administered according to the guideline established by the NINDS study.

Conflict of Interest : None

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