

Hyperacute thrombolysis with IV rtPA of acute ischemic stroke: Efficacy and safety profile of 54 patients at a tertiary referral center in a developing country

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Background: Given the constraints of resources, thrombolysis for acute ischemic stroke (AIS) is under evaluation in developing countries. Prothrombin time (PT), platelet count and activated partial thromboplastin time (aPTT) may not be feasible within the time window. **Aim:** To evaluate the safety and efficacy of thrombolysis in selected patients without the coagulation profile. **Design:** Open, nonrandomized, observational study. **Materials and Methods:** Fifty-four stroke patients were classified using TOAST criteria (large artery atherosclerotic = 13; cardioembolic = 12; small vessel occlusion = 22; other determined etiology = three; undetermined etiology = four). The mean time to reach emergency was 2.4h (1.15-3.4), the mean door to CT, 24 min (10-47) and the door to recombinant tissue plasminogen activator (rtPA) injection, 26.8 min (25-67). The NIHSS scores ranged from 11 to 22 (mean = 15.5 ± 2.7). Patients with history of liver or renal disease or those on anticoagulants were excluded. The PT, aPTT and platelet count were not done. Recombinant tissue plasminogen activator was administered at a dosage of 0.9 mg/Kg. **Results:** Thirty-five patients (65%) significantly improved on NIHSS at 48h (≥4 points) (mean change = 10; range= 4-17). At one month, 43 (79%) improved on Barthel Index (mean change = 45%). One each developed small frontal lobe hemorrhage and recurrent stroke; one died of aspiration; and eight showed no improvement. **Conclusions:** Hyperacute thrombolysis was found useful and safe in selected patients with AIS even without the coagulation studies.

Key words: rtPA, stroke, thrombolysis

Acute ischemic stroke (AIS) is one area in neurological clinical practice that has probably seen the greatest strides as far as an understanding of pathogenesis is concerned.

This has led to advancements made in the treatment options available for patients suffering from ischemic stroke. Plenty of the nihilism that surrounded strokes is gradually being lifted along with the ignorance related to the condition, from both the minds of patients and the treating doctors. Most therapeutic options for AIS have one common feature; they generally have to be administered within a very narrow and specific time window. This is extremely pertinent if the drug-related adverse events have to be minimized and the therapeutic benefits maximized.

The National Institute of Neurological Disorders and Stroke (NINDS) study on the intravenous use of recombinant tissue plasminogen activator (rtPA) within three hours of an AIS has shown the benefit of this form of treatment.^[1] In order to be effective the protocol for institution of rtPA therapy must be strictly followed. The evidence for this form of therapy is of Level I.^[2] When all accumulated evidence for rtPA therapy is considered, the relative risk reduction provided by it is 44%, absolute risk reduction is 13% and the number needed to treat to save one person from death or disability is seven.^[3]

Many countries now routinely thrombolyze all patients of AIS who present within the three-hour time window and do not have any contraindication. However, many stroke units, especially those in the developing nations, are hampered by constraints of resources and lack of awareness. Feasibility of thrombolysis is still being evaluated at these centers. The hyperacute thrombolysis for stroke was started in the year 1995-1996 in India and in March 2002 at the All India Institute of Medical Center, a tertiary referral center in India. We assessed the outcome of patients treated with intravenous rtPA, including the incidence of intracerebral hemorrhage and other adverse events. The overall purpose of this paper is to report the current clinical practice of intravenous thrombolytic

therapy for acute stroke in a tertiary referral center from a developing country.

Materials and Methods

We present the detailed data of the 54 patients treated at AIIMS in whom an adequate follow-up of six months is available. All of these patients were studied prospectively.

The variables that were specifically recorded for each patient treated with rtPA: time of symptom onset, time of arrival in the emergency department, time of CT scan examination and the time of rtPA administration. An extensive neurological examination including the baseline NIH Stroke scale (NIHSS) was performed in all patients. Other parameters noted were the demographic profile, stroke risk factors, baseline CT scan findings and the blood pressure measurements [Table 1].

Potential benefits and significant risks, specifically the fourfold greater risk of symptomatic intracerebral hemorrhage^[4] after thrombolytic treatment were discussed with all patients and/or their families and informed consent obtained. The rtPA protocol was based on protocols published by the American Heart Association and the American Academy of Neurology.^[5,6] Inclusion and exclusion criteria are shown in Table 2. All patients had pretreatment CT scans that were read by the attending neurologist together with the radiologist. Each of our patients received 0.9 mg/Kg of intravenous rtPA up to a maximum of 90 mg, based on the estimated or actual body weight. Ten per cent of this calculated dose was injected as a bolus and the remainder infused over an hour. Heparin and aspirin were withheld for the first 24h after rtPA administration in all our patients. Hypertension was treated using intravenous labetolol or intravenous enalapril. Occasionally, injection nitroglycerine or nitroprusside was required.

Results of follow-up CT scans or MRI scans were recorded in all patients thrombolysed. The use of aspirin, clopidogrel, heparin, acitrom and antihypertensives

Table 1: Pretreatment characteristics

Age	66 years (32-82)
Sex	31:23
Hypertension	35 (65%)
Diabetes mellitus	22 (41.2%)
Hypercholesterolemia	8 (14.7%)
AF	11 (20.6%)
CHF	8 (14.7%)
CAD	6 (11.8%)
Prior stroke	9 (17.7%)
Smoking	17 (32.4%)
Mean admission Blood pressure	156/88 mmHg
Mean maximum Pretreatment Blood pressure	166/90 mmHg
NIHSS	15.5 ± 2.7 (11-22)

Table 2: Criteria for use of tissue plasminogen activator (rtPA) in treating acute ischemic stroke at All India Institute of Medical Sciences

Clinical inclusion criteria

- Patient/caregiver able to give informed consent before study procedure.
- Age ≥ 18 years.
- Onset of symptoms of ischemic stroke within 0-3h.
- Measurable neurological deficit defined as impairment of language, motor function, cognition and/or gaze, vision or neglect.
- Score for stroke severity ≥ 4 on the National Health Stroke Scale (NIHSS).

Clinical exclusion criteria

- Severe symptoms (coma or severe obtundation with fixed eye deviation and complete hemiplegia or NIHSS score > 22).
- Minor stroke symptoms (NIHSS score < 4) or those that are rapidly improving.
- History of stroke in previous six weeks.
- Seizure at onset unless the treating physician is convinced that the neurological deficit is due to stroke and not seizure.
- Previous known intracranial hemorrhage.
- Hemorrhage in pretreatment CT scan of the brain.
- Uncontrolled baseline hypertension (> 185/110 mmHg).
- Myocardial infarction in past 30 days.
- Recent (< 15 days) surgery, major arterial puncture, trauma or ulcerative wounds.
- Known and clinical evidence of chronic or acute hepatic or renal disease.
- Known bleeding diathesis/ coagulopathies.
- Patients on anticoagulants.
- Pregnancy, lactation or parturition within the previous 30 days.
- Hypoglycemia, hyperglycemia (baseline serum glucose level must be between 50 mg% - 400 mg%).

Computed tomography (CT) exclusion criteria

- Evidence of acute or chronic intracranial bleeding on CT.
- Likely etiology other than acute brain ischemia.
- Early signs indicating infarct of more than a third of the territory of the middle cerebral artery.

during the hospital stay was noted. The peak blood pressure during rtPA administration as well as during the first 24h after the infusion was recorded. Using the TOAST criteria, stroke subtype was determined by the following classification: 1). Large artery atherosclerosis, 2). Cardio-embolic, 3). Small-vessel occlusion, 4). Stroke of other determined etiology, 5). Stroke of undetermined etiology. We obtained telephone or clinic follow-up with the patient and caregiver in all 54 cases and assessed the Barthel Activities of Daily Living Index. For analysis, we defined a good outcome as an improved NIHSS of ≥ 4 and a Barthel Index of ≥ 75%. At AIIMS, due to constraints of time and resources we deviated from the recommended NINDS protocol in excluding patients with a history of liver or renal disease and in not obtaining results of platelet counts, prothrombin time and activated partial thromboplastin time in patients prior to thrombolysis.

Results

Fifty-four patients received IV rtPA for AIS between March 2002 and March 2006. The stroke team was notified of 1096 patients suspected of having an acute

stroke during this period. The most common reasons for disqualification from thrombolytic therapy were, exceeding the window period (38%), intracerebral hemorrhage (20%), minor or rapidly resolving symptoms (20%) and a nonstroke diagnosis (12%). Of the patients who could qualify to receive thrombolysis, 26% could not be thrombolized since they could not afford rtPA.

The mean age of our patients was 66 years, ranging from 32 to 82. Out of the 54 patients who were thrombolysed, 31 were males. Co-morbid illnesses in the form of hypertension, diabetes and hypercholesterolemia were present in 44 (64.7%), 22 (41.2%) and eight (14.7%) patients respectively. Additionally, atrial fibrillation was present in 11(20.6%), congestive heart failure in eight (14.7%) and coronary artery disease in six (11.8%). There was a history of prior stroke in 10 (17.7%). The mean blood pressure at admission was 156/88 mmHg and the mean maximum pretreatment blood pressure was 166/90 mmHg. Eighteen of the 54 (32.4%) patients were smokers [Table 3].

The mean baseline NIHSS was 14 ± 2 (range 8-22). Using TOAST criteria, patients were classified into: large artery atherosclerotic = 13; cardioembolic = 12; small vessel occlusion = 22; other determined etiology = three; undetermined etiology = four. The mean time to reach emergency was 2.4h (1.15-3.4h). The mean door to CT time was 24 min (10-47 min). The mean door to rtPA injection time was 26.8 min (25-67 min). The NIHSS scores ranged from 11 to 22 min (mean = 15.5 ± 2.7). Patients with history of liver or renal disease or those on anticoagulants were excluded. The PT, aPTT and platelet count results were not obtained prior to thrombolysis. Early signs of infarction on CT were seen in 25/54 (46.3%) patients. These were sulcal effacement in 11, insular ribbon sign in six and loss of gray white matter definition in eight. Am infarct in the follow-up CT or MRI was present in 53 of our 54 patients (97.1%).

Mean length of hospitalization in our patients was nine days. During hospital stay, antihypertensive therapy had to be given to 44 (82.4%) patients. Antiplatelet drugs were given to all 54 patients while 10 (17.7%) received anticoagulants. No patient was given blood transfusion. Hemorrhagic conversion was noted in five (8.8%). Symptomatic intracranial hemorrhage or fatal hemorrhage did not occur in any of our patients.

Table 3: Clinical characteristics of the study popular

Received antihypertensive treatment	44 (82.4%)
Received anticoagulation	10 (17.7%)
Received antiplatelets	54 (100%)
Received transfusion	None
Length of hospitalization	9 ± 9 days
Infarct of follow-up CT/MRI	52 (97.1%)
Hemorrhagic conversion	5 (9%)
Symptomatic intracerebral hemorrhage	None
Fatal ntracerebral hemorrhage	None
Mean length of follow-up	9.5 ± 3 months

Thirty-five patients (65%) significantly improved on NIHSS at 48h (≥ 4 points) (mean change = 10; range = 4-17). At one month, 43 (79%) improved on Barthel Index (mean change = 45%). Of these, 19 (44% of the 43 patients improved; 35% of total number[54]), achieved $\geq 95\%$ scores on Barthel Index indicating near normal functional status. Of the stroke subtypes, cardioembolic and small vessel occlusions did better than others. Of the eight patients who showed no improvement, six were lacunar strokes. One developed small frontal lobe hemorrhage and recurrent stroke; one died of aspiration and eight showed no improvement. The mean length of follow-up after discharge was 9.5 ± 3 months. Although not part of the study protocol, modified Rankin Score (mRS) was administered at the end of three months to 48 (88%) patients (the rest could not be directly observed). The average mRS was 1.4 (0-2). One patient developed deep venous thrombosis of the saphenous vein and had to be hospitalized for treatment. One patient developed pneumonia and recovered with therapy.

Discussion

Despite the demonstration of benefit from thrombolytic treatment with intravenous rtPA by the NINDS trial as early as in 1995, this form of therapy has been relatively underused in developing countries. The reluctance to aggressively thrombolysed patients of acute ischemic stroke has been attributed to several factors including delay in the arrival of the patients to stroke units, limited resources, ignorance or disbelief amongst neurologists as to the efficacy of this form of treatment and a fear of serious rtPA-related complications.

We succeeded in treating 54 patients of acute ischemic stroke with IV rtPA over a period of four years. Importantly, we were unable to thrombolysed 38% of otherwise eligible patients due to delay in evaluation and treatment. Several studies have tried to analyze the causes of such delays but they have all been conducted in developed countries under very different circumstances.^[7-12]

The mean age of patients in our study was 66 years, whereas the mean age of patients in the NINDS trial was 67 years. Advanced age increases the odds of a poor outcome after thrombolysis.^[13,14] However, post hoc analysis of the NINDS data showed rtPA to be beneficial for patients in all strata of age. As stroke increases with age, it becomes important to decide if older patients should be denied this potentially disability-avoiding therapy.

Our patients had a mean baseline NIHSS of 14 which is similar to that of patients in the NINDS rtPA trial. The stroke subtype by final diagnosis was most often, in 35.3% patients, small vessel disease. The NINDS trial and a few subsequent studies have shown that intravenous thrombolysis within the three-hour time window is similar between different stroke subtypes.^[1] It has

therefore been recommended that extensive diagnostic evaluation to determine stroke subtypes before thrombolysis is neither required nor justified.

Patients arrived in the emergency department at an average of 150 min after the symptom onset. A CT scan was performed within 22 min and intravenous rtPA was administered within an average of 27 min from the time of arrival to the emergency department respectively. A significant difference between our experience and the NINDS trial is that half of the patients randomized in the NINDS study were treated within 90 min of stroke onset. However, the response to treatment observed in the NINDS trial between patients treated under 90 min and between 90 and 180 min did not differ. This underlines the importance of not withholding treatment from patients even if they present beyond 90 min of symptom onset. We were able to treat patients within an average of 27 min from their time of arrival at the emergency department. This is contrary to the popular perception that it is generally not possible to treat patients within the time window of 180 min in busy and constrained hospitals of developing countries unless they arrive early. Recent NIH consensus guidelines recommend a “door-to-needle” time of 60 min or less for acute stroke patients.

An improvement of four points or more on the NIHSS at 48h was seen in 65% of our patients while a Barthel Index of 75 or more at one month was present in 79% patients. It is important to note here that the long-term benefit as observed from the Barthel Index is significantly more impressive than the immediate benefit as reflected from the 48h NIHSS. The reluctance of many neurologists to treat patients is based on this premise of insufficient immediate improvement in outcome. However, it is equally important not to lose sight of the delayed benefits, especially considering the tremendous impact that stroke morbidity has on the individual, caregivers and society as a whole.

This preliminary data from a tertiary care center from a developing country shows that hyperacute thrombolysis in acute ischemic stroke is both feasible and useful. It also emphasizes the importance of increasing awareness about stroke and its acute management. More significantly, till such time that patients start presenting more promptly for treatment, it needs to be understood that thrombolysis can still be provided in hospitals if a dedicated stroke team endeavors to reduce the “door-to-needle” time to the minimum possible.

The limitation of the present study is the lack of a control group which will impede with the assessment of the efficacy of thrombolysis. However, since the study is strictly observational, it may be taken as a pilot project to evaluate essentially the feasibility and safety. The other limitation is the sample size. We concede that this is a

small number to draw any definite conclusions. However, the observation does reveal that in this small number of patients, hyperacute thrombolysis can be undertaken in spite of not obtaining coagulation results in carefully screened patients of AIS. A future trial needs to be undertaken with a blinded, controlled and randomized design to substantiate the above findings.

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