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Patterns and outcomes of stroke thrombolysis in a tertiary care hospital in North East India

Abstract

Introduction: Intravenous thrombolysis with alteplase (tissue plasminogen activator -tPA) has been approved as the standard of care for the treatment of acute ischemic stroke (AIS) since 1995. Although there have been sporadic reports of hyperacute stroke thrombolysis coming from North-East India, a well-structured study from this resource poor area is lacking in this regard.

Objective: To study the efficacy and safety of intravenous thrombolysis with tPA in AIS.

Materials and methods: All patients of acute Ischemic stroke who were thrombolysed using the 4.5 hour window period, between Dec 2017 to April 2021 were enrolled and studied. We analyzed differences in age, gender, time from onset to start IVT, door to needle time (DNT), pretreatment NIHSS score, postoperative NIHSS score, and so on. They were followed up for a period of 3 months for the determination of outcome. The death rate at 90 days and incidence of SICH were used for assessment of safety.

Results: A total of 30 patients were thrombolysed. 37% of patients were thrombolysed during the covid-19 pandemic. Hypertension was the most common risk factor. The mean Door to needle(DTN) time was 74.1 minutes with the shortest being 25 minutes. The mean NIHSS score at the point of hospitalization was 12.42 and after 24 hours was 9.27. In 57.69% of patients, the primary outcome (≥4 increment in NIHSS score) was achieved. 14.8% of patients suffered from adverse outcomes (death and SICH).

Conclusion: This study re-affirms the safety and efficacy of IV tPA for hyperacute stroke thrombolysis in our set-up.

Keywords: Acute ischemic stroke, alteplase, IV rtPA, thrombolysis, North-east India

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Introduction

Stroke is the second leading cause of death worldwide and the fourth leading cause of death among the low-income countries.[1] None the less it is also a leading preventable causes of disability in the world. WHO had defined stroke 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."[2] AIS is one of the few areas in Neurology which have undergone a radical shift in management and prognosis in the last 2 decades. Trials like NINDS, ECASS III, DEFUSE and DAWN have ushered us into a new era of therapeutics and interventions wherein stroke is no longer just a preventable disease but also a treatable condition. Following these path-breaking trials there have been myriad of publications from the developed world replicating the success of this new therapy. On the other hand the developing nations have somewhat lagging behind in this regard. Among the various causes responsible for the lag, prominent would be higher treatment costs, short treatment window, poor communication, lack of awareness and delay in identification of the symptoms. Even if the patient may reach the healthcare facility in time the process of establishing the diagnosis and ruling out intracerebral hemorrhage (ICH) many a times throws the patient out of the Window period. In-spite of these hurdles hyper acute thrombolysis for stroke started in the year 1995 in India and 2002 at AIIMS.[3] Following this there have been quite a good number of publications from various parts of the country sharing their experience with this procedure. Although there have been sporadic reports of patients being thrombolysed from North east India, but a systematic study in this regard as of now is missing. A stroke unit was formally established in our tertiary care center in 2018, although thrombolysis treatment was already offered prior to that. Here, we report our experience on thrombolysis in acute ischemic stroke from Dec 2017 to April 2021. We presume that this report is the first of its kind from the North eastern part of the country, Assam, India. In this study we have attempted at sharing our experience with this therapy.

Material & methods

This prospective observational study was conducted from Dec 2017 to April 2021 at a tertiary care centre in Guwahati. The center is equipped with a well-established Stroke Unit, stroke treatment protocol, 24 h on-call neurologist and neurosurgeon, neuroimaging (computed tomography [CT] and magnetic resonance imaging), and thrombolysis facility. Hospital electronic database captures patient arrival time and imaging time. tPA bolus and infusion time were noted from nurses chart. Onset time was noted as the time when the patient was last seen normal. O-D time was the time taken to arrive in the emergency department (ED), D-CT was the time taken to initiate CT scan, and D-N was the time taken to initiate tPA bolus dose. Intracranial hemorrhage (ICH) was defined as CT documented hemorrhage with deterioration in NIHSS of ≥4 within 36 h of thrombolysis. During this period a total of 30 patients of ischemic stroke were thrombolysed with Alteplase. Three of the patients were excluded from this study due to lack of sufficient follow up data. The study was approved by the institutional ethical committee and informed consent was obtained from all the participants.

Inclusion & exclusion criteria

All patients greater than 18 years of age who were diagnosed to have Acute ischemic stroke (AIS) after ruling out ICH on baseline Non

Contrast Computed Tomography (NCCT) of the head with a duration of onset of less than 4.5 hours were included. Wake up strokes were also included if diffusion-weighted MRI (DWI) and fluid-attenuated inversion recovery (FLAIR) MRI (DWI-FLAIR mismatch) mismatch was found on MRI. Patients with Blood Pressure (BP) > 185/110 were included after controlling blood pressure within the required limits with appropriate Intravenous (IV) anti-hypertensives.

Patients with AIS were excluded if they had a history of stroke or serious head injury within the preceding 3 months; had undergone major surgery within 2 weeks; had rapidly improving or minor symptoms; had symptoms suggestive of Subarachnoid hemorrhage (SAH); had Gastrointestinal haemorrhage or urinary tract haemorrhage within the preceding 3 weeks; had arterial puncture at a non-compressible site within the preceding 1 week. Patients taking anticoagulants (heparin or Oral anticoagulants) were excluded as were patients with glucose concentration below 50 or more than 400 mg per decilitre.

Administration of the thrombolytic drug

Alteplase (Actilyse, Boehringer Ingelheim) was administered IV to the selected patients after obtaining informed consents. The dosage was as used in the NINDS study i.e. 0.9 mg/kg body weight, the maximum being 90 mg with 10% administered as a bolus and the rest 90% as infusion over 60 minutes.[4] No anti platelets or anticoagulants were administered within the next 24 hours after treatment and BP was maintained within the required limits.

Post thrombolysis assessment

Patients with symptoms suggestive of Stroke presenting within the window period were initially assessed by an emergency physician. After obtaining adequate history clinical examination with assessment of NIHSS score was done and blood samples drawn for standard laboratory tests. A NCCT scan of the brain was obtained and interpreted by the Neurologist in liaison with the radiologist to rule out ICH. Patients fulfilling the inclusion and exclusion criteria mentioned above were thrombolysed according to the above mentioned protocol. Patients vitals were continuously monitored for the next 24 h in intensive care unit (ICU). Any patient who had worsening of neurological status post thrombolysis was moved urgently for NCCT brain to rule out ICH. Subsequently all thrombolysed patients were subjected to another NCCT brain 24 h after thrombolysis. NIHSS score re-assessed again after 2 h and 24 h and 48 hour post thrombolysis. Modified Rankin scale (mRS) score was assessed at day 7 or at the time of discharge (whichever was later) and 90 days following thrombolysis.

Outcome

The proportion of patients found to have an improvement of ≥4 in NIHSS score 24 hours post thrombolysis were considered for the assessment of primary outcome, while proportion of patients found to have an mRS score of less than 2 after 90 days were considered for the assessment of secondary outcome. Incidence of symptomatic intracerebral hemorrhage (SICH) and deaths were used for evaluation of safety.[4]

Statistical analysis and variables involved

Demographic data, details of clinical examination including blood investigations and brain imaging details, NIHSS, and mRS scores were recorded. Time variables such as symptom-to-door time, door-to-imaging time, and door-to-needle time were noted. The software used for statistical analysis was "SPSS version 16.0" (SPSS Inc., Chicago, IL, USA).

Results

A total of 410 patients were admitted to our stroke service, including hemorrhagic strokes and stroke mimics between Dec 2017 to April 2021; of these patients, 30 (7.3% of all strokes, and 13.3% of all ischemic strokes) received thrombolysis. Of the 30 patients sufficient data was missing for 3 patients, hence they were excluded from this study. Table 1 shows the baseline characteristics of the patients included in the study. Another patient was excluded as he turned out to be a case of Glioma. Mean age of the patients who underwent the therapy was 66 years. Males outnumbered females by constituting 73% of the study group. Hypertension (76.9%) was the most common risk factor found amongst our patients. The proportion of patients who were found to have (non valvular atrial fibrillation (NVAF) was 30.7%. The middle cerebral artery (MCA) territory was the most commonly afflicted region(73%) followed by posterior cerebral artery (PCA) (19.2%) and anterior cerebral artery (ACA) (7.7%). The mean onset to door time was 100.9 minutes. The mean door to needle time (DNT) was 74.1 minutes with the shortest being 25 minutes. The mean baseline NIHSS score and Glassgow Coma Scale (GCS) at the time of admission were 12.4 and 13.1 respectively. Three of the patients had 'WAKE UP' strokes who were subsequently chosen for thrombolysis after obtaining DWI-FLAIR mismatch. Table 2 showing the outcome characteristics of the cohort.

Table 1 Baseline characteristics of 27 patients thrombolysed with alteplase

Variables	Values
Age(years) mean±SD	66.42±11.41
Gender	
Male	19(73%)
Female	7(27%)
Risk factors	
Hypertension	20(76.9%)
Diabetes mellitus	3(11.5%)
Dyslipidemia	2(7.69%)
Coronary artery disease (CAD)	8(30.7%)
Non valvular atrial fibrillation (NVAF)	1(3.8%)
Rheumatic Heart Disease (RHD)	4(15.3%)
Prior ischemic stroke	1(3.8%)
Prior hemorrhagic stroke	
NIHSS on Admission	
<4	0
4-15	16(61.5%)
>15	10(38.4%)
Cerebral circulation	
Anterior cerebral artery (ACA)	2(7.69%)
Middle cerebral artery(MCA)	19(73.07%)
Posterior cerebral artery(PCA)	5(19.23%)
Admission parameters(mean±SD)	
Blood glucose	138.2±30.35
Systolic Blood Pressure	158.26±26.71
Diastolic Blood Pressure	90.69±11.2
Glassgow Coma Scale (GCS)	13.11±2.14
Onset to door time(mean)	100.91 min(1 hour 40.91 mins)
Door to needle time(mean)	74.14 min(1 hour 14.14 mins)
Wake up stroke	3

NIHSS, national institute of health stroke scale; SD, standard deviation

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Table 2 Outcome characteristics

Variables	Values
NIHSS score (Mean±SD)	
Baseline	12.42±6.07
24 hour	9.27± 8.37
MRS score	
90 days(mean)	1.92±1.74
% less than 2	15(57.7%)
Adverse outcome	
Death	2(8.33%)
SICH[4]	2(8.33%)
Asymtomatic ICH[4]	1(4.16%)

Discussion

Even after 25 years of the availability of published data clearly depicting the benefits of IV t-PA, its usage in developing nations is quite limited. Many papers have been published enumerating the barriers leading to the under-utilization of this procedure. Some of the prominent causes are inability to recognize stroke symptoms, lack of awareness to consider stroke as a medical emergency, unawareness about stroke thrombolysis as a treatment option among patients or their relatives, as well as the primary care physicians. Even if some patients do reach in time, factors like non-affordability, delay in assessment in hospital, patient shifting, and neuroimaging are the other barriers which prevent thrombolysis. Proportion of stroke patients reaching a health care facility in window period stands at a meagre 6% in spite of a high symptom recognition rate (58%) among the bystanders.[5]

Ours is one of the few institutes in the North-East India carrying out thrombolysis for acute ischemic stroke. In the last 3 years (2018 to 2021) 30 patients of AIS were thrombolysed in our institute. The mean age of patients in our study was 66.42 years which is comparable to the mean age in NINDS and ECASS III studies wherein it was 68 years and 64.9 years respectively. Age was not used as a barrier in denying patients of this potential disability-limiting procedure. No upper age limit was set as a contraindication for the proposed procedure in our study. Incidence of hypertension in our study (76.9%) was higher as compared to the NINDS study (66%) and ECASS III (62.4%).[4,6]

The mean baseline NIHSS score in our study was 12.4 while it was 10.7 and 14(median in t-PA group) in the NINDS and ECASS III studies respectively. The average time gap between symptom onset and contact with the health care system was 100.9 minutes. The average Door to needle time was 74.1 minutes. [The NIH consensus guidelines recommend a door to needle time (DTN) of ≤ 60 minutes for acute ischemic stroke. 10 out of the 27 patients (i.e 37%) in our study were treated in COVID era which required an additional COVID RAT to be negative before they could be taken for neuroimaging, which took approximately 15-30 minutes on average. This additional detail needs to be taken into account when judging mean DTN time in our study]. Improvement (≥1 point increment) in NIHSS score after 48 hours of the procedure was observed in 76.9 % of our patients while it was significant (i.e ≥ 4 points increment in NIHSS score) in only 57.7 % of the patients. The secondary outcome (i.e mRS of ≤1 over a period of 90 days) was attained in 57.7% of patients.

Safety outcomes

Adverse outcome in the form of either deterioration of NIHSS score, SICH or death was found in 23.1% of patients. 8.3% of patients developed SICH during the course of their hospital stay which is higher as compared to the NINDS and ECASS III study. It would be statistically inappropriate to derive a significance out of this percentage considering the small sample size. All 3 of the patients who died during the course of their treatment were septuagenarians and 2 of them had malignant MCA infarct (greater 50% of the MCA territory[7]) and one having top of the basilar syndrome. 2 of them had diabetes along with hypertension. One of the deaths was due to fatal ICH. None of the patients being studied died during the 90 day follow up.

Special situations

Among the patients thrombolysed 1 was COVID positive and another was in the post covid state (10 days after the first negative RT-PCR report). Of the 3 patients who had seizures at onset only 1 turned out to be a stroke mimic and was found to be case of glioma on MRI. Rest of the 2 patients with seizure at onset had MCA territory strokes. These patients were taken up for the procedure as none of them had a previous history of seizures. 3 of the cases were WAKE UP strokes and were thrombolysed on the basis of DWI-FLAIR mismatch. 8(33%) of the patients thrombolysed had severe stroke (i.e NIHSS score 15-25)[8] .One patient of DCM with atrial fibrillation (AF) on Acenocoumarol was thrombolysed because of the availability of her same day INR report at hand. It so happened that she had a cardiology follow up that day and suffered a stroke on her way home.

With the Therapeutic Time Window being extended upto 9 hours[9] and increasing awareness among people, more number of cases of stroke are going to seek care within the Golden period. The reluctance on the part of treating emergency personnel in going ahead with this procedure is based out of 2 main reasons. First is the dread of exposing the patient to the risks of life threatening bleed and second, is the lack of significant improvement in the immediate post procedure period. But trials like NINDS and ECASS III have shown that treatment with t-PA results in more favourable outcome than standard medical care even after taking into account the small risk of intracerebral haemorrhage, and that long term benefits far outweigh the immediate benefits. Our study reaffirms the benefits of alteplase as an effective agent for IV thrombolysis in acute ischemic stroke.

Studies from India

Following these landmark International trials there have been several studies from India too. Studies mentioned in the Table 3 are among the few.

With more data pouring in favour of this therapy from both inside and outside India, it is prudent not to deny patients of AIS of their chance at a meaningful functional life.

The limitations of this study are as follows

1. Sample size is too small to arrive at a definitive statistical significance

2. Non availability of a control group to validate our findings.

Table 3 Comparative studies on IV thrombolysis

Sl. No	Studies	Study period	No.of patients	Age (years)	Most common Risk Factor	DTN (minutes)	SICH	mRS <2	Secondary outcome
1	Our study	2017-2021	26	66 (mean) 67.5(median)	Hypertension	74.14(mean) 77.5(median)	8.3%	57.7%	57.7%

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Table Continued...

Sl. No	Studies	Study period	No.of patients	Age (years)	Most common Risk Factor	DTN (minutes)	SICH	mRS <2	Secondary outcome
2	M v padma et al [3]	2002-2006	54	66 y	-do-	27(mean)	Nil *	65%	79%(barthel index ≥75 after 1 month)#
3	Lalitha pidaparthi et al [10]	2010-2015	89	55 y	-do-				
4	Dheeraj khurana et al[11]	2011-2015	189	60 y(median)	-do-	63(median)	2.65%$		40%^()
5	Madhav rao et al[12]	2017-2018	25	53 y	-do-	73.4(mean)	12%	60%	60%

* 8.8% had Asymptomatic ICH.

#Average mRS at 90 days was 1.4.

$Haemorrhage occured in 13.2%

^ 60% functional independence,10% complete recovery, 40 % had mRS 0-1 at 90 days follow up.

Conclusion

Nevertheless the results of this study do demonstrate that hyperacute stroke thrombolysis is feasible, relatively safe and worth giving a shot. There is a need to educate the general public as to the identification of stroke symptoms, and making them realize that this condition requires emergency medical care. Along with this there is also a need to train our health care professionals in this regard too. With enough motivation it is possible to direct our infrastructure and streamline the emergency staff to have a reasonable door to needle time.

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Conflicts of interest

There are no conflicts of interest.

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