

Factors influencing nonadministration of thrombolytic therapy in early arrival strokes in a university hospital in Hyderabad, India

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Abstract

Background: It is a well-known fact that very few patients of stroke arrive at the hospital within the window period of thrombolysis. Even among those who do, not all receive thrombolytic therapy. **Objective:** The objectives of this study were to determine the proportion of early arrival ischemic strokes (within 6 h of stroke onset) in our hospital and to evaluate the causes of nonadministration of intravenous and/or intraarterial thrombolysis in them. **Materials and Methods:** Data of all early arrival acute stroke patients between January 2010 and January 2015 were included. Factors determining nonadministration of intravenous and/or intraarterial thrombolysis in early arrival strokes were analyzed. **Results:** Out of 2,593 stroke patients, only 145 (5.6%) patients presented within 6 h of stroke onset and among them 118 (81.4%) patients had ischemic stroke and 27 (18.6%) patients had hemorrhagic stroke. A total of 89/118 (75.4%) patients were thrombolized. The reasons for nonadministration of thrombolysis in the remaining 29 patients were analyzed, which included unavoidable factors in 8/29 patients [massive infarct ($N = 4$), hemorrhagic infarct ($N = 1$), gastrointestinal bleed ($N = 1$), oral anticoagulant usage with prolonged international normalized ratio (INR) ($N = 1$), and recent cataract surgery ($N = 1$)]. Avoidable factors were found for 21/29 patients, include nonaffordability ($N = 7$), fear of bleed ($N = 4$), rapidly improving symptoms ($N = 4$), mild stroke ($N = 2$), delayed neurologist referral within the hospital ($N = 2$), and logistic difficulty in organizing endovascular treatment ($N = 2$). **Conclusion:** One-fourth of early ischemic stroke patients in our study were not thrombolized even though they arrived within the window period. The majority of the reasons for nonadministration of thrombolysis were potentially preventable, such as nonaffordability, intrahospital delay, and nonavailability of newer endovascular interventions.

Key Words

Avoidable factors, recombinant tissue plasminogen activator (rt-PA), stroke, thrombolysis, unavoidable factors

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Introduction

The National Institute of Neurologic Disorders and Stroke (NINDS) trial showed that the patients treated with recombinant tissue plasminogen activator (rt-PA) had 11-13% absolute increase in independent survival at 3 months compared to placebo.^[1] The benefit to the community was an additional 110-130 independent survivors at 3 months per 1,000 patients treated with rt-PA. It is a well-known fact that very few patients

with ischemic stroke arrive at the hospital within the window period of thrombolysis. In various studies, the median time taken to reach the hospital by patients with ischemic stroke ranged from 4 h to >24 h.^[2-4] However, even after reaching the hospital within the window period, some patients do not receive thrombolysis, or only receive it after a delay. Previous

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studies showed that only 1-7% of acute ischemic stroke patients received intravenous rt-PA.^[5,6] In one study, 16.8% of patients with ischemic stroke who reached the hospital within 3 h did not receive rt-PA because of avoidable reasons such as intrahospital delay, patient refusal, and clinical indecision.^[7] The most common reasons for not administering rt-PA in acute ischemic stroke patients include delay in rapidly receiving specialized neurologic care; time consumed in conducting investigations; patient refusal of thrombolysis due to various reasons such as ignorance about the treatment, fear regarding complications, financial status, and protocol exclusions.^[7-10]

In a previous study from South India, it was observed that 10% of stroke patients arrived within 4.5 h and 7.8% of them received thrombolysis. The authors found that the main barriers for thrombolytic therapy were lack of awareness of thrombolytic therapy for ischemic stroke among both patients and referring physicians, affordability, and lack of awareness of stroke symptoms.^[11] Socioeconomic factors also influence thrombolysis in early arrival strokes, hence factors influencing nonadministration of rt-PA are highly variable across countries. In India, till date there are very few studies that have observed the factors leading to nonadministration of rt-PA in early arrival ischemic stroke patients.

Objective

The present study was conducted to determine the proportion of early arrival ischemic strokes (within 6 h of stroke onset) in our hospital and to evaluate the causes of nonadministration of intravenous and/or intraarterial thrombolysis in them.

Materials and Methods

This is a prospective, observational study that was done between January 2010 and January 2015 at Nizam's Institute of Medical Sciences (NIMS), Hyderabad, which is a tertiary care university hospital in South India. Approval was obtained from the Institutional Ethics Committee. All stroke patients who arrived within 6 h of stroke onset were included in this study and informed consent was taken from all patients/their legally authorized representatives.

In our hospital, there are physicians in the Emergency department who are trained to identify patients with acute stroke, and in such cases they inform the neurologist immediately. One neurologist is always available throughout the day for emergency services. Evaluation starts with history regarding the onset of time of neurological deficit, rapid assessment of vital data, and neurological deficits using the National Institutes of Health Stroke Scale (NIHSS). History of any vascular risk factors, and history related to contraindications for thrombolysis, is also obtained. Meanwhile, blood investigations including coagulation profile and arrangements regarding brain imaging, either computed tomography (CT) scan or diffusion-weighted imaging-magnetic resonance imaging (DWI-MRI) are done.

Time of stroke onset was defined as the time at which the patient or a witness first noted a definite neurologic abnormality. If the symptoms were first noted on awakening or if not witnessed, the time of onset was recorded as when the patient was last seen

well. Hypertension (HTN) was defined as per the Joint National Committee (JNC) VII classification.^[12] Diabetes mellitus (DM) was diagnosed by the American Diabetes Association criteria.^[13] Dyslipidemia was defined as per the National Cholesterol Education Programme-Adult Treatment Panel III (NCEP-ATP III) criteria.^[14] Transient ischemic attack (TIA) was defined according to the American Heart Association/American Stroke Association (AHA/ASA) Stroke Council definition in 2009.^[15] A patient having a NIHSS score less than 4 was taken as having suffered a minor stroke.

The patient's demographic characteristics, earning and employment status, education level, distance from the hospital, knowledge of stroke symptoms, and awareness of thrombolysis were asked about with the standard questionnaire. Time taken from the onset of stroke to reach the hospital, from onset of the stroke to performing CT/DWI-MRI, from onset of stroke to admission in the stroke unit, and door-to-needle time were recorded from the nurse's records. Patients with ischemic stroke who were eligible and gave consent for thrombolysis were thrombolysed by intravenous and/or intraarterial routes according to established guidelines. Factors responsible for nonadministration of thrombolytic therapy in patients with ischemic stroke who presented within the window period were also identified and analyzed. Factors responsible for nonadministration of thrombolytic therapy were classified as unavoidable and avoidable factors. Factors that made patients ineligible for thrombolysis based on the decision of the treating neurologist were considered as unavoidable factors. Avoidable factors included hospital-related and patient-related factors. All data were collected in a predesigned *pro forma* and entered into a Microsoft Excel 2007 (Microsoft Corp, Redmond, WA, USA) database.

Statistical analysis

The present study was an observational study. For demographic data and descriptive statistics of scores, we used the mean \pm standard deviation (SD) or median (interquartile range) values.

Results

During the study period of 5 years (from January 2010 to January 2015), 2,593 patients with stroke got admitted in NIMS Hyderabad, a tertiary care university hospital in South India. Out of 2,593 patients, only 145 (5.6%) patients presented within 6 h of stroke onset. The mean age of patients who presented within 6 h of stroke onset was 55.0 ± 15.2 years. Males accounted for 71.0%. Mean time from stroke onset to arrival was 152.7 ± 76.6 min and mean door-to-image time was 31.0 ± 25.6 min. At presentation, mean blood sugar and mean arterial pressure were 144.0 ± 63.1 mg/dL and 108.2 ± 16.9 mmHg, respectively. Stroke severity as measured by baseline NIHSS at presentation was 11.8 ± 5.7 . Out of all vascular risk factors, HTN ($N = 85$; 58.6%) was found to be the most common risk factor, followed by DM in 37 (25.5%) patients [Table 1]. Among 145 patients presented within 6 h of stroke onset, 118 (81.4%) patients had ischemic stroke and 27 (18.6%) patients had intracerebral hemorrhage. Out of 118 patients with ischemic stroke, 89 (75.4%) patients were thrombolysed (88 patients by intravenous route and 1 patient by intraarterial route). The remaining 29 (24.6%) patients were not thrombolysed due to various reasons [Figure 1].

On analyzing the factors for nonadministration of thrombolysis, we found unavoidable factors in 8/29 (27.6%) patients. These included massive infarct ($N = 4$), gastrointestinal bleed ($N = 1$), recent cataract surgery ($N = 1$), hemorrhagic infarct ($N = 1$), and oral anticoagulant usage with prolonged INR ($N = 1$) [Table 2].

We found avoidable factors for nonadministration of thrombolysis in 21/29 (72.4%) patients.^[16] These included nonaffordability ($N = 7$), fear of bleed ($N = 4$), rapidly improving symptoms ($N = 4$), mild stroke ($N = 2$), delayed neurologist referral within the hospital ($N = 2$), and logistic difficulty in organizing the endovascular treatment during nighttime ($N = 2$) [Table 2].

Discussion

In our study, early arrival strokes accounted for 5.6% of all stroke patients. Previous studies showed that early arrival strokes accounted for 1-7% of all strokes.^[4] One study from India evaluated the reasons for delay in arrival and found that the distance from hospital, time lapsed in contact with a

local doctor, and lack of knowledge of the symptoms of stroke were independent factors associated with delay in arrival.^[12] Public education programs to increase awareness of warning signs, stroke risk factors, availability and effectiveness of treatment, improvements in transport methods, and educating local practitioners regarding thrombolysis can increase the proportion of early arrival strokes, leading to increased benefit of thrombolysis.^[17] Where transport distances are too long, telemedicine may allow greater accessibility to treatment.^[18,19] Two-thirds of the subjects in our study were young (<60 years), which may be due to genetic predisposition as well as the high prevalence of young-onset HTN and DM in the Asian population.^[20]

In our study, thrombolysis was done in 75.4% of early arrival ischemic strokes. Although thrombolysis in three-fourth of early arrival ischemic strokes is a relatively high proportion compared to several other studies; at the same time, one-fourth were not thrombolitized despite being within the hospital during the window period. The narrow therapeutic window, a rapid improvement in neurologic dysfunction, mild symptoms, age, and CT findings are the reasons for exclusion from thrombolysis most frequently reported in the literature. In our study, we classified the factors of nonadministration of thrombolysis as unavoidable (8 patients) and avoidable (21 patients) factors.

The most common unavoidable factor was massive infarct ($N = 4$). According to the AHA/ASA stroke guidelines 2013, if frank hypodensity on non-contrast-enhanced CT involves more than one-third of the middle cerebral artery territory, intravenous rt-PA treatment should be withheld (Class III; Level of Evidence A).^[21] The ECASS study (6 h window period) showed that early ischemic changes involving more than one-third of the middle cerebral artery territory was associated with increased risk of intracerebral hemorrhage in thrombolitized patients.^[22] However, a systematic review of the CT scans in the NINDS (3 h window period), and some other studies found that early ischemic changes involving more than one-third of the middle cerebral artery territory were not independently associated with increased risk of adverse outcome in thrombolitized patients, and hence, thrombolysis may be beneficial in some subset of patients with large infarct size.^[23-26]

Table 1: Demographic characteristics of early arrival (<6 h) stroke patients

Variables	Values
Number of patients	145
Age (mean±SD [*])	55.0±15.2 years
>60 years	54 (37.2%)
Male:Female	2:5
Female	42 (29.0%)
Time from stroke onset to arrival (mean±SD [*])	152.7±76.6 min
Door-to-imaging time (mean±SD [*])	31.1±25.6 min
Blood sugar at presentation (mean±SD [*])	144.0±63.1 mg/dL
Mean arterial pressure at presentation (mean±SD [*])	108.2±16.9 mmHg
NIHSS at presentation (mean±SD [*])	11.8±5.7
HTN	85 (58.6%)
DM	37 (25.5%)
Previous strokes	15 (10.4%)
Previous TIA	6 (4.1%)
Coronary artery disease	24 (16.6%)
Atrial fibrillation	3 (2.1%)
Hyperlipidemia	14 (9.7%)
Hyperhomocystinemia	22 (15.2%)
Smoking	23 (15.9%)
Alcoholism	14 (9.7%)

^{*}Standard deviation

Table 2: Factors responsible for nonadministration of thrombolysis in early arrival strokes

Unavoidable factors (number of patients)	Avoidable factors (number of patients)
Massive infarct ^[4]	Lack of affordability ^[7]
Hemorrhagic infarct ^[1]	Fear of bleed ^[4]
Gastrointestinal bleed ^[1]	Rapidly improving symptoms ^[4]
Oral anticoagulant use with prolonged INR ^[1]	Mild stroke ^[2]
Recent cataract surgery ^[1]	Delayed neurology referral ^[2]
	Unavailability of clot retrieval device ^[2]

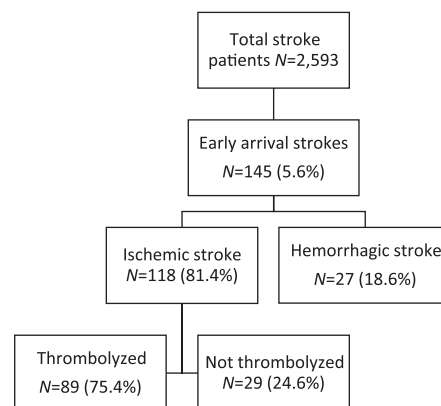


Figure 1: Proportion of early arrival stroke patients and types of strokes

In this study, thrombolysis was deferred in 1 patient due to recent cataract surgery. Although cataract surgery is not a major surgery, a few case reports on thrombolysis for myocardial infarction showed that there is a risk of total hyphema and retro-orbital hemorrhage with loss of vision following streptokinase administration after cataract surgery.^[27-29] Whether to consider cataract surgery as a major surgery with the potential risk of loss of vision is questionable.

A significant ($N = 7$) number of patients refused thrombolysis because of nonaffordability, which means that the patient or family declines thrombolysis due to costs. In developing countries such as India, economic issues play an important role in such decisions and the majority of the population do not have insurance coverage or credit facility. Government health policies and insurance program implementation may address this potentially avoidable reason for nonadministration of thrombolysis. Four patients had fear of bleed, even after proper counseling, and therefore refused thrombolysis. Proper public awareness programs are needed regarding modern strategies of stroke management and the value of emergent arrival to a hospital to overcome these factors. People with more awareness may make more rational and beneficial health care decisions.

Four patients were not thrombolized due to rapidly improving symptoms; however, 3 worsened subsequently. Two other patients had mild stroke with NIHSS less than 4, due to which they were not given rt-PA. As per AHA/ASA guidelines 2013, use of intravenous thrombolysis in minor strokes and rapidly improving strokes should be weighed against benefits (Class II b; Level c), and further studies are required to address these issues.^[21] Some studies showed that around one-third of patients with mild stroke who were not thrombolized worsened subsequently and that thrombolysis in them is efficacious.^[30,31] Future studies are required to clarify this issue. Withholding the treatment to patients with rapidly improving symptoms and patients with mild stroke may not be justified.

Delay in referral to a neurologist by emergency medical personnel within our own hospital prevented 2 patients from getting thrombolized. Education of all emergency department medical personnel, and paramedical staff regarding the importance of urgent referral of suspected strokes to a neurologist is an important, necessary step to avoid these issues. In fact, the existence of a separate, well-trained team for identifying patients with suspected acute ischemic stroke is essential in ensuring a better stroke management.^[32] In our study, 2 patients presented after 4.5 h but within 6 h, who were eligible for endovascular mechanical thrombectomy. Because of technical reasons including nonavailability of clot retrieval device, endovascular intervention was not performed in those 2 patients. An increased number of interventional neurologists and availability of catheter laboratory and clot retrieval devices around the clock are necessary for an effective stroke program.

Conclusion

Our study highlights the fact that about one-fourth of early ischemic stroke patients were not thrombolized, even though they arrived within the window period. Some of the reasons are

potentially preventable, such as nonaffordability, intrahospital delay, and nonavailability of endovascular interventions. Similar studies need to be done in other hospitals to identify the reasons for nonadministration of rt-PA in early arrival strokes.

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Conflicts of interest

There are no conflicts of interest.

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