

Stumbling Blocks to Stroke Thrombolysis: An Indian Perspective

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Received on: 07 July 2023; Accepted on: 26 July 2023; Published on: 31 August 2023

ABSTRACT

Background and purpose: Stroke is a leading cause of morbidity and mortality worldwide. Developing countries, however, still lag behind in providing timely thrombolytic therapy (TLT) to many eligible patients owing to various reasons. This study aims to identify such factors.

Materials and methods: This was a descriptive observational study undertaken over a period of 18 months at a tertiary care teaching hospital and included 252 acute ischemic stroke patients of which 200 were not thrombolysed. The reasons for nonthrombolysis were recorded and analyzed.

Results: The study included 252 acute ischemic stroke patients of which only 20% were thrombolysed. Of the 200 nonthrombolysed patients, 55% arrived out of the window period while patient-related factors were the second biggest factor preventing thrombolysis. Hospital factors at 14% and financial constraints at 4.5% contributed significantly. Delayed consent emerged as an important factor making 6% of the delays.

Conclusions: Stroke thrombolysis still faces various pre- and intrahospital barriers in India. There is an urgent need to improve infrastructure and organizational streamlining to enable eligible patients to receive prompt treatment.

Keywords: Acute ischemic stroke, Barriers, Intravenous thrombolytic therapy, Stroke thrombolysis, Tissue plasminogen activator, Window period. *Indian Journal of Critical Care Medicine* (2023): 10.5005/jp-journals-10071-24517

HIGHLIGHTS

Stroke thrombolysis in India still faces a myriad of challenges. Despite advances in treatment, numerous factors impede the availability of timely intervention for a majority of stroke patients. Identifying such factors is imperative to improve the proportion of patients receiving thrombolytic therapy.

INTRODUCTION

Stroke is the second leading cause of death worldwide in the adult population, and the fourth leading cause of disease burden.^{1,2} Over the past six decades, age-adjusted stroke incidence rates have more than doubled in low- to middle-income countries, according to a systematic review by Feigin et al.³ A 2008 study⁴ had estimated the prevalence of young strokes in India to account for 18–32% of all cases, while Joshi et al. found it to be the cause of death in 13% of the patients.^{5,6} Other studies discovered a higher age-adjusted incidence of stroke in India with a larger proportion of young strokes.^{7,8}

All these studies have collectively shown the socioeconomic burden that stroke has on society, particularly with a larger young population being affected. This makes it imperative to identify and correct the difficulties in providing thrombolytic therapy (TLT) to eligible patients in the ideal time frame. However, a dearth of extensive stroke studies in India and a lack of proper documentation and stroke registry have precluded us from having the needed information regarding Indian demographic differences and the barriers in stroke management. Our study aims to identify such obstacles that prevent TLT to be received by ischemic stroke patients and throw light on the prevailing problems in a developing country.

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How to cite this article: Shah A, Diwan A. Stumbling Blocks to Stroke Thrombolysis: An Indian Perspective. *Indian J Crit Care Med* 2023;27(9):616–619.

Source of support: Nil

Conflict of interest: None

MATERIALS AND METHODS

The study was a descriptive observational study undertaken over a period of 18 months at a tertiary care teaching hospital and included all the acute ischemic stroke patients who presented to the hospital, diagnosed by neuroimaging, including CT scan and MRI diffusion scans of the brain. This study, undertaken in a tertiary teaching medical institute in Western India, aimed at identifying the reasons for acute ischemic stroke patients not getting thrombolysed. The study was approved by the Institutional Ethics Committee, and an informed consent was taken from all included patients and their relatives. Detailed history was taken, and clinical examination was done to determine the severity of stroke as per the NIHSS score and Glasgow coma scale (GCS). Patient's vital signs were recorded, and previous medical history, including any ongoing medications, enquired. The time of onset of symptoms, time of arrival to the

Table 1: Demographic characteristics of nonthrombolized patients

Age (years)	
Range	18–95
Mean (± SD)	60.36 (±15.41)
Sex	
Male	121 (60.5%)
Female	79 (39.5%)
Sex ratio	1.53
NIHSS score	
Range	33 (1–34)
Mean	11.35

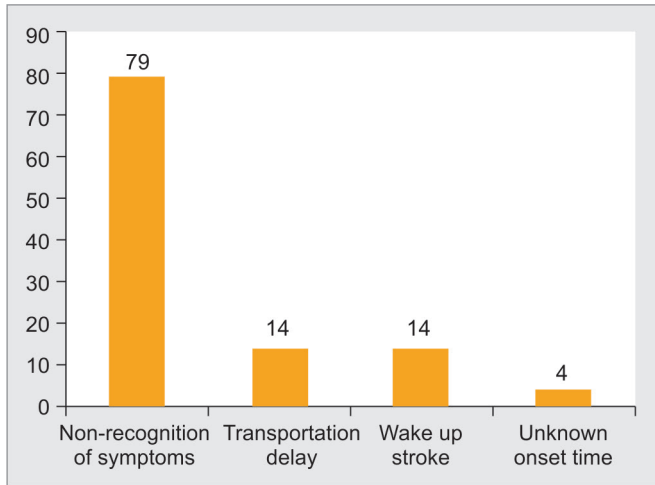


Fig. 1: Reasons for delayed presentation (out of window period)

hospital, and time of thrombolysis were noted.⁹ NIHSS scores below 3 and more than 25 were considered contraindications to thrombolysis. The reasons for delay in presentation and further in-hospital delays preventing thrombolysis were recorded. Descriptive statistics of nonthrombolized patients and of the most common reasons for non-thrombolysis were calculated. All statistical analyses were done by using SPSS Software Version 25.0.

RESULTS

This study included 252 acute ischemic stroke patients who presented to our institute, out of which 50 patients were thrombolized with Alteplase.⁹ In total, 200 patients, accounting for over 79% of the stroke patients, were not given TLT owing to various reasons as 121 (60.5%) of these were males, while 79 (39.5%) were females. The mean age of patients included in the study was 60.36 years (range 18–95) with a standard deviation of ± 15.41, as shown in Table 1.

The most common factor for nonthrombolysis was found to be being a delay in arrival to the hospital. Among these “out of window period” patients, nonrecognition of symptoms was the most common reason (71.17%, *n* = 79). Wake-up strokes and transportation delays had a similar 12.61% share (*n* = 14) each in the data observed, as depicted in Figure 1.

Table 2 highlights the major reasons contributing to nonthrombolysis in patients arriving within the window period

Table 2: Reasons for nonthrombolysis in patients arriving within window period

Reasons for nonthrombolysis	N (%)
Hospital-related factors	
Bed unavailability	3 (1.5%)
Imaging delay	11 (5.5%)
Diagnosis delay by treating doctor	4 (2%)
Intrahospital delay	1 (0.5%)
Unavailable neuroimaging/TLT at primary center	9 (4.5%)
NIHSS score	
Low (≤3)	16 (8%)
High (≥25)	6 (3%)
Patient-related factors	
Uncontrolled blood pressure	4 (2%)
Anticoagulation	5 (2.5%)
Age	8 (4%)
Recent myocardial infarction	1 (0.5%)
Consent	
No consent by relatives	10 (5%)
Delay in consent	2 (1%)
Financial reasons	9 (4.5%)

(*n* = 89, 44.5%). Hospital-related factors overall contributed the biggest share of them. Unavailability of bed, delay in neuroimaging, and delay in intrahospital transportation of the patient contributed to this subset. Lack of neuroimaging or thrombolysis facilities and a delay in recognition of symptoms by treating doctors at healthcare centers and hospitals where the patient presented prior to reporting to our institute.

The most common patient-related factor that prevented the use of TLT was advanced age, followed by ongoing anticoagulation therapy. Five patients were on daily warfarin use for valvular heart disease and arrhythmias. Consistently high systolic blood pressure of ≥200 mm Hg contributed to a delay and eventual nonthrombolysis of four patients while 11% of the patients were not thrombolized owing to either very low or very high NIHSS. In total, 16 patients had an NIHSS score ≤ 3, while 6 patients had it ≥25. One patient had a history of myocardial infarction 1 month prior.

Nonaffordability of the treatment, including cost of hospitalization and thrombolytic agent, prevented 9 patients from being thrombolized while consent also played a part in the time-bound treatment of patients, making 6% of the nonthrombolized sample.

DISCUSSION

Cerebrovascular accidents constitute a serious public health problem and are one of the leading causes of morbidity and mortality among adults, affecting the victim, their family, and the society as a whole. But despite new advances in technology and better availability of thrombolysis facilities across the country, a large proportion of patients still remain nonthrombolized owing to numerous factors.¹⁰

A recent study found that only 14.7% stroke patients in India reached the hospital within a 3-hour period.¹¹ Systematic reviews of

various studies across the world have identified major pre-hospital factors negatively influencing the timely arrival to the hospital and thrombolysis.^{12,13} Global studies enlisted factors causing an in-hospital delay in thrombolysis, including delays in neurologist's assessment, neuroimaging, obtaining consent for thrombolysis, and uncertainty on the part of the treating doctor regarding diagnosis or initiation of thrombolysis.^{14,15} Similarly, a 2015 study by Badachi et al. found the major reason for nonthrombolysis to be a failure of patients to recognize the symptoms followed by a lack of neuroimaging facilities, nonaffordability, failure of relatives to recognize stroke, failure of the physician to recognize symptoms, and transportation-related problems.¹⁶

Nonrecognition of stroke symptoms was the most common reason in our study. Over 71% of the nonthrombolized patients did not recognize the symptoms either themselves or there was a delay on part of the relatives, particularly in the elderly. A survey by Chhabra M et al. found 46% of the participants to be unaware of the warning signs of stroke,¹⁷ similar to other studies showing the lack of medical education among the general population and inadequate training of paramedical staff hampering the timely treatment of patients.¹⁸⁻²¹ A 2015 study by Ashraf VV et al. underlined the correlation of educational status and hospital arrival,²² while Kulkarni et al. found over 60% patients unaware of any stroke symptoms and only 4% being aware of thrombolysis.²³ Raising awareness among the public regarding signs and symptoms, risk factors, treatment of stroke, and the time-sensitive nature of its outcome is a crucial step to improve stroke treatment.

In our study, hospital and healthcare-associated factors were the second biggest reason. These included a lack of neuroimaging facilities and proper and prompt medical care availability at primary healthcare centers, particularly in rural areas, where the patients first presented. About 13 patients did not get thrombolized due to these factors prior to arrival at our institute. Three patients were not lysed due to the unavailability of beds, while one patient had an intrahospital delay in transportation to the critical care unit from the imaging room due to lack of staff. Being a tertiary care setup with established stroke code, intrahospital delay was significantly less in our study when compared with institutes without established protocols.²⁴

Another factor, common to many developing nations, was of logistics.²⁵ Lack of transportation modalities to and from a primary or tertiary healthcare center, lack of proper roads and connectivity, and financial implications thereof have a significant role to play in India.²¹ About 12.6% patients in our study had transport-related delay in presentation, who could have reached the hospital within the window period otherwise. It may be recommendable to the public to use any vehicle feasible to safely transport the patient to the hospital without unnecessary delay till the ambulance coverage is improved.

Our study also shed light on other patient and related factors, including lack of timely consent. Similar observations were made by Faiz et al.,²⁶ showing a decision delay accounting for 62.3% of the prehospital delays, while the same accounted for 45% prehospital delays in a study by Chang et al.²⁷ Relatives did not give consent for thrombolysis for 10 patients, while there was delayed consent given for 2 patients. Delay on relatives' part to appreciate the patient's condition and understand the consequences, both positive and negative of thrombolysis, and willingness to take a decision on behalf of the patient are important determinants. Studies abroad have identified readiness for decision-making among the next of kin of incapacitated patients as one of the factors; however,

no dedicated study has been done to understand the Indian perspective in this regard.²⁸

Financial constraints were a big contributor, as has been observed in other studies in the country.²⁹⁻³¹ Thrombolytic agents are costly, particularly in private institutions. An Indian study reported 16% stroke patients who were eligible for TLT could not afford the therapy due to its high cost.³²

In our study, 18 patients making 9% of the total nonthrombolized patients, did not receive rtPA owing to NIHSS score guidelines. This nonmodifiable factor included both too low (≤ 3) and too high (≥ 25) NIHSS scores. Five patients were on warfarin therapy. Availability of a portable coagulometer could have helped estimate their INR, but device unavailability prevented TLT to these patients.

Recognition of stroke symptoms heralds the chain of events that may favor a good functional outcome in ischemic stroke patients. Public education, implementing regionally befitting pre- and intrahospital emergency medical systems, promoting medical research, and national policies and guidelines are essential to aid a stroke victim. Learning collaborative and improved training of medical and paramedical staff with a streamlined protocol for action can provide early revascularization opportunities, as has been observed in studies abroad.³³ A delay in neurologist opinion may be overcome by extensive training of emergency physicians and internists to recognize and initiate thrombolysis with confidence. With telemedicine, thrombolysis can be availed at rural and primary healthcare centers under the appropriate guidance of a neurologist, which can save precious time.

Infrastructure improvement to minimize the transfer delay of a patient from a nonstroke center, streamlining the database to prevent delay in obtaining or retrieving prior records or in obtaining drug from the pharmacy must be emphasized. The government and hospital authorities may provide thrombolytic agents at subsidized rates to aid with the financial constraints that a majority of patients face, particularly in private setups.

Establishing expedited stroke triage pathway with close collaboration between emergency personnel, physicians, nurses, neurologists, and radiologists, allocation of beds and staff to cater specifically to stroke patients, and TLT delivery in the CT scan room itself may further reduce the intrahospital delay.³⁴

While the world is advancing in reperfusion strategies with endovascular thrombolysis and mechanical thrombectomy, extending the benefit of treatment to many more patients, most of India still lags behind. Before switching to these novel strategies, there is a dire need to improve the thrombolysis facilities and expand the timely administration to a higher percentage of eligible patients.

Our study had its limitations being a single-center study based on a tertiary-level teaching hospital. The results may not truly reflect the situation in public hospitals where the nonthrombolized proportions may be higher. Also, our study was an observational study without an intervention arm that could have highlighted the factors amenable to modifications.

CONCLUSION

Despite advances in technology and improved community knowledge and literacy, identification and prompt management of ischemic stroke still remain a challenge in India. Our study conducted in a tertiary care teaching institute has highlighted the various factors, both pre- and intrahospital, that impede the availability of thrombolytic therapy to stroke patients in India.

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