



## DOOR-TO-NEEDLE TIME AND THE FACTORS IMPEDING THROMBOLYSIS OF ACUTE STROKE PATIENTS AT A TERTIARY CARE CENTER IN INDIA

**Dr. Darpan Sohni**

MBBS, Department of General Medicine, Osmania General Hospital, Hyderabad, Telangana, India 500012.

### ABSTRACT

**Background:** Intravenous thrombolysis for acute ischemic stroke is time-sensitive with a narrow window period for treatment initiation. The recommended Door-to-needle (DTN) time of <60 minutes is seldom achieved in Indian centers.

In this study, we aimed to evaluate the DTN time at our hospital and identify the factors that limit thrombolysis of acute stroke patients.

**Materials and Methods:** All patients that presented with signs of stroke from September to December 2019 were studied. Patient's demographics, details of symptoms, time of symptom onset, and contraindications to thrombolysis were recorded. The Symptom-to-Door, Door-to-Physician, Door-to-Imaging and Door-to-Needle times were calculated from key temporal data. The factors that influenced the DTN time were also recorded.

**Results:** Out of the 241 patients that presented with symptoms of stroke, 43 (17.8%) were within the window period. Nine patients were thrombolysed and among these, one (11.1%) was started on rt-PA within 1 hour of arrival. The mean DTN time was 112 minutes (median - 102 minutes).

**Conclusion:** The DTN time in this study was much higher than what is recommended. The major factors that impede thrombolysis are: ignorance among the public, lack of a proper triage system at various levels, and lack of a dedicated stroke protocol/team.

**KEYWORDS :** stroke, thrombolysis, rt-pa, door-to-needle

### INTRODUCTION

Stroke is a major health concern and is one of the leading causes of mortality and morbidity worldwide (1) and the incidence in India can be expected to rise in the future as the population undergoes a transition from a predominance of infectious diseases to that of non-communicable diseases. (2)

Reperfusion therapy through intravenous administration of recombinant tissue plasminogen activator (rt-PA) is the most beneficial proven management strategy for treatment for acute ischemic stroke. (3) However, time is of the essence in intravenous thrombolysis (IVT) because it has to be administered within 4.5 hours of symptom onset, with faster administration resulting in better outcomes. (4)

A considerable amount of time is lost in the prehospital period, the so-called symptom-to-door time. Efforts to reduce this time lag have not shown much benefit since campaigns aimed at raising public awareness of stroke symptoms have only limited impact on behavior. (5) Inside the hospital, the focus should be on decreasing the time interval between arrival to the emergency department and IVT administration, the so-called door-to-needle (DTN) time. It is recommended that eligible patients should ideally receive rt-PA therapy within 60 minutes of arrival to the hospital. (6) However, there are multiple limitations in thrombolysis of acute stroke patients even in tertiary care centers. (7)

This study was undertaken to assess the door-to-needle time at our tertiary hospital and evaluate the number of patients that received rt-PA therapy within 1 hour of arrival to the hospital. We also aimed to identify the factors limiting thrombolysis of acute stroke patients.

### MATERIALS AND METHODS

This cross-sectional study was carried out from September to December 2019 after approval from the Institutional Ethics Committee. All patients who presented to our casualty with symptoms suggestive of stroke and within 4.5 hours of symptom onset were included in the study. The patients were first assessed by the casualty staff, following which a medical resident evaluated them and ordered non-contrast computed tomography (CT) of brain. After reporting by a radiologist, a neuro-physician consultation was obtained to formulate a treatment plan and a decision for thrombolysis was made. Informed consent was obtained from all patients. Risk factors for stroke were recorded and contraindications of thrombolysis were checked. Stroke mimics, patients who had evidence of hemorrhagic stroke, or had contraindications for thrombolytic therapy and those who were unwilling to provide consent were excluded.

A structured proforma was employed to record the patient's demographic profile, details of the patient's symptoms, time of onset of symptoms and the reason for delay, if any, to reach the medical facility.

The time of symptom onset for wake-up strokes was taken as the last time the patient was seen healthy. Patient records were used to obtain the following temporal data:

- Time of arrival to the hospital (Door)
- Time of initial assessment by the medical resident (Physician)
- Time of acquisition of CT scan (Imaging)
- Time of initiation of rt-PA drug therapy (Needle)

Other parameters such as Symptom-to-Door (STD), Door-to-Physician (DTP), Door-to-Imaging (DTI) and Door-to-Needle (DTN) time were calculated from the above data. Furthermore, hour-wise distribution of thrombolysed patients was analysed.

Continuous variables were described by mean  $\pm$  standard deviation and median based on the results of normality testing. Categorical variables were expressed by counts with percentages. The Statistical Package for Social Sciences (SPSS, v25.0) was used for the statistical analysis of this data.

### RESULTS

Two hundred and forty-one patients presented to the casualty with symptoms of stroke during the study period. Out of these, 198 (82.1%) patients had come more than 4.5 hours from symptom onset and hence, did not satisfy inclusion criteria. Only 43 (17.8%) patients who presented to the hospital within 4.5 hours of symptom onset were included. After the acquisition of CT and laboratory reports, of these forty-three patients, 34 (79.06%) patients were found to have contraindications for IVT. [Table 1].

**Table 1: Distribution of Contraindications for IVT in Acute Stroke Patients**

Contraindications	Number (n)	Percentage (%)
Admission beyond window period (>4.5 h)	198	82.1
Total admitted within window period but contraindicated for thrombolysis	34	
ICH	22	64.7
Refusal to consent	4	11.7
Stroke mimics (Hypoglycemia, Meningitis)	2	5.88
Low hemoglobin (<4 g/dl)	2	5.88
Large MCA infarct	1	2.94
TIA (Improving symptoms)	1	2.94
Recent major surgery	1	2.94
Recent myocardial infarction	1	2.94

ICH: Intracerebral hemorrhage; MCA: Middle cerebral artery; TIA: Transient Ischemic Attack

Total 9 (20.94%) patients with a diagnosis of acute ischemic stroke were treated with rt-PA. Six (66.67%) were male and three (33.33%)

were female. The age range of the subjects was 39 to 78 with a mean age of 60.3 +/- 10.7 years (median - 62 years). Table 2 gives the baseline characteristics of the thrombolysed patients.

**Table 2: Baseline characteristics of thrombolysed patients (n=9)**

Variables	Number (n)	Percentage (%)
Sex		
Male	6	66.67
Female	3	33.33
Age (years), [mean, (median)]		
Male	58.4 (median - 61)	
Female	64.6 (median - 68)	
No comorbidity	2	22.22
Comorbidities		
Hypertension	5	55.55
Diabetes Mellitus	5	55.55
Dyslipidemia	2	22.22
IHD	1	11.11
History of previous TIA/CVA	1	11.11
More than 1 comorbidity	5	55.55
Lifestyle		
Smokers	4	44.44
Alcoholics	3	33.33

IHD: Ischemic Heart Disease; TIA: Transient Ischemic Attack; CVA: Cerebrovascular accident

The mean time interval from the onset of symptoms to presentation to the hospital (Symptom-to-Door time) was 91.3 (SD - 46.4) minutes. The mean door-to-physician (DTP) time was 38.23 (SD - 26.4) minutes. The mean door-to-imaging (DTI) time was 64.05 (SD - 36.25) minutes. The mean door-to-needle (DTN) time was 112.36 (+/- 44.79) minutes. [Table 3]

**Table 3: Comparison of the study intervals with AHA guideline intervals**

Time intervals	AHA recommended time (minutes)	Study time (minutes)
		Mean +/- SD (Median)
Door-to-Physician (DTP) time	15	38 +/- 26 (24)
Door-to-Imaging (DTI) time	45	64 +/- 36 (58)
Door-to-Needle (DTN) time	<60	112 +/- 51 (102)

AHA: American Heart Association; SD: Standard deviation

There was no statistically significant difference in the time delay among the subjects based on sex ( $p=0.091$ ) or age ( $p=0.16$ )

Of the nine patients that were thrombolysed, only one (11.11%) patient was started on rt-PA therapy within 1 hour of arrival to the hospital. Five (55.56%) were thrombolysed between 1 and 2 hours of arrival to the hospital. The remaining three (33.33%) patients were started on rt-PA between 2 and 3 hours of presentation to the hospital.

## DISCUSSION

Saver (2006) proved that "Time is Brain" by showing that even a few minutes saved in delivering rt-PA translates to significant benefits over a patient's lifetime. (8) Therefore, timely arrival of the patient and prompt treatment in the hospital is critical.

Majority of the stroke patients in our study presented outside the window period which made them ineligible for thrombolysis. The mean symptom-to-door time for the thrombolysed patients was 91.3 minutes. A number of factors were identified that were responsible for the prolonged time lapse between symptom onset and presentation to the hospital. There is a clear lack of awareness among the public regarding the warning signs of stroke, thus leading to the symptoms being perceived as "not serious". This was one of the major risk factors for delayed presentation of stroke patients to the hospital. Another important reason for the late arrival was a lack of transportation. Many of the patients arrived from far flung areas and emergency medical services in this country are seriously lacking. (9) Financial constraints and poor socio-economic status also contributed to the prolonged symptom-to-door time. These findings are in accordance with those of a number of studies carried out in India to identify factors associated with prehospital delay in stroke patients. (10,11)

Among the 43 patients who presented within the window period, only one (2.32%) was thrombolysed within the recommended 60 minutes of arrival to the hospital. Analysis of our study clearly shows that the Door-to-Needle time at our center is significantly higher than what is recommended. The mean DTI and DTN times were 64 minutes and 112 minutes respectively. These increased time intervals could be linked to a variety of reasons; the crucial one being a lack of triaging at various levels. Stroke patients were not handled with high priority in the casualty. This resulted in them having to wait for quite some time till they were seen by the medical resident/physician. Educating the emergency personnel about stroke symptoms will help to triage and handle stroke patients with higher priority. (12) Stroke patients were not given precedence over non-emergent cases at the radiology department either. Thus again, prioritizing the stroke patient at the radiology unit will help us to improve our time lag between hospital arrival and acquisition of CT brain. (13)

Post-imaging, there was variable delay in reaching the neuro-physician for consultation due to other emergency calls. Kobayashi *et al.* recommended the concept of having a second on-call physician that takes care of only acute stroke patients (14). At our center, the neuro-physician was not looped in till all the reports were available. Having a dedicated stroke team along with a single-step notification of the entire team can help redress this issue.

The DTN time was also influenced by a few patient factors. Two patients required labetalol infusion for uncontrolled hypertension causing delay in treatment initiation. A considerable amount of time had passed before the relatives of two patients agreed and gave their consent for thrombolysis. There was some difficulty in obtaining intravenous access in one of the patients that resulted in a more-than-usual delay.

While many centers around the world are already down to <30 minutes from arrival to treatment (15), there is a lot of scope for improvement in developing countries. The proportion of patients receiving thrombolytic therapy for acute stroke is pathetically low in India. (16) Hence, there is a dire need for the development and implementation of a Stroke Protocol in the tertiary care centers in India. Ideally, such a protocol is activated and set in motion the moment a suspected stroke patient arrives at the hospital. For it to function smoothly, a stroke protocol requires the formation of a multi-disciplinary stroke team/unit comprising of different types of health care personnel working in unison to achieve a DTN time of <60 minutes. Gurav *et al.* (2018) implemented one such "Stroke Code" at their center and proved its significant benefits. (17) Similar, if not better, modifications must be attempted at all major hospitals in the country to reduce the DTN times in the care of acute ischemic stroke patients.

## CONCLUSION

This study's mean Door-to-Needle time of 112 minutes is much more than what is recommended. Only one (11.1%) patient was thrombolysed within 1 hour of arrival to the hospital. The major factors impeding intravenous thrombolysis of acute stroke patients in our study were:

### Pre-hospital:

- Ignorance of stroke symptoms among the public
- Inadequacy of and inaccessible emergency medical services

### In-hospital:

- Lack of a proper triage system for stroke patients
- Lack of a dedicated stroke protocol and stroke team

## REFERENCES

1. Warlow, C., Sudlow, C., Dennis, M., Wardlaw, J., & Sandercock, P. (2003). Stroke. *Lancet (London, England)*, 362(9391), 1211-1224. [https://doi.org/10.1016/S0140-6736\(03\)14544-8](https://doi.org/10.1016/S0140-6736(03)14544-8)
2. Reed, D. M. (1990). The paradox of high risk of stroke in populations with low risk of coronary heart disease. *American Journal of Epidemiology*, 131(4), 579-588. <https://doi.org/10.1093/oxfordjournals.aje.a115542>
3. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. (1995). Tissue plasminogen activator for acute ischemic stroke. *The New England Journal of Medicine*, 333(24), 1581-1587. <https://doi.org/10.1056/NEJM.1995.1214.3332401>
4. Lees, K. R., Bluhmki, E., von Kummer, R., Brodt, T. G., Toni, D., Grotta, J. C., Albers, G. W., Kaste, M., Marler, J. R., Hamilton, S. A., Tilley, B. C., Davis, S. M., Donnan, G. A., Hacke, W., ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group, Allen, K., Mau, J., Meier, D., del Zoppo, G., ... Byrnes, G. (2010). Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet (London, England)*, 375(9727), 1695-1703. [https://doi.org/10.1016/S0140-6736\(10\)60491-6](https://doi.org/10.1016/S0140-6736(10)60491-6)
5. Dirks, M., Niessen, L. W., van Wijngaarden, J. D. H., Koudstaal, P. J., Franke, C. L., van

- Oostenbrugge, R. J., Huijsman, R., Lingsma, H. F., Minkman, M. M. N., Dippel, D. W. J., & PRomoting ACute Thrombolysis in Ischemic Stroke (PRACTISE) Investigators. (2011). Promoting thrombolysis in acute ischemic stroke. *Stroke*, 42(5), 1325–1330. <https://doi.org/10.1161/STROKEAHA.110.596940>
6. Jauch, E. C., Saver, J. L., Adams, H. P., Bruno, A., Connors, J. J. B., Demaerschalk, B. M., Khatri, P., McMullan, P. W., Qureshi, A. I., Rosenfield, K., Scott, P. A., Summers, D. R., Wang, D. Z., Wintermark, M., Yonas, H., American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, & Council on Clinical Cardiology. (2013). Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 44(3), 870–947. <https://doi.org/10.1161/STR.0b013e318284056a>
  7. Gurav, S. K., Zirpe, K. G., Wadia, R. S., Pathak, M. K., Deshmukh, A. M., Sonawane, R. V., & Goli, N. (2015). Problems and limitations in thrombolysis of acute stroke patients at a tertiary care center. *Indian Journal of Critical Care Medicine: Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine*, 19(5), 265–269. <https://doi.org/10.4103/0972-5229.156468>
  8. Saver, J. L. (2006). Time is brain—Quantified. *Stroke*, 37(1), 263–266. <https://doi.org/10.1161/01.STR.0000196957.55928.ab>
  9. Murthy, J. M. K. (2007). Thrombolysis for stroke in India: Miles to go.. *Neurology India*, 55(1), 3–5. <https://doi.org/10.4103/0028-3886.30415>
  10. Srivastava, A. K., & Prasad, K. (2001). A study of factors delaying hospital arrival of patients with acute stroke. *Neurology India*, 49(3), 272–276.
  11. Nandigam, K., Narayan, S. K., Elangovan, S., Dutta, T. K., Sethuraman, K. R., & Das, A. K. (2003). Feasibility of acute thrombolytic therapy for stroke. *Neurology India*, 51(4), 470–473.
  12. Kocak, S., Dogan, E., Kokcam, M., Girisgin, A. S., & Bodur, S. (2012). Limitations in thrombolytic therapy in acute ischemic stroke. *Pak J Med Sci*, 28(4), 586–590.
  13. Yu, R. F., San Jose, M. C. Z., Manzanilla, B. M., Oris, M. Y., & Gan, R. (2002). Sources and reasons for delays in the care of acute stroke patients. *Journal of the Neurological Sciences*, 199(1–2), 49–54. [https://doi.org/10.1016/s0022-510x\(02\)00103-x](https://doi.org/10.1016/s0022-510x(02)00103-x)
  14. Kobayashi, A., Skowronska, M., Litwin, T., & Czlonkowska, A. (2007). Lack of experience of intravenous thrombolysis for acute ischaemic stroke does not influence the proportion of patients treated. *Emergency Medicine Journal: EMJ*, 24(2), 96–99. <https://doi.org/10.1136/emj.2006.040204>
  15. Meretoja, A., Strbian, D., Mustanoja, S., Tatlisumak, T., Lindberg, P. J., & Kaste, M. (2012). Reducing in-hospital delay to 20 minutes in stroke thrombolysis. *Neurology*, 79(4), 306–313. <https://doi.org/10.1212/WNL.0b013e31825d6011>
  16. Durai Pandian, J., Padma, V., Vijaya, P., Sylaja, P. N., & Murthy, J. M. K. (2007). Stroke and thrombolysis in developing countries. *International Journal of Stroke: Official Journal of the International Stroke Society*, 2(1), 17–26. <https://doi.org/10.1111/j.1747-4949.2007.00089.x>
  17. Gurav, S. K., Zirpe, K. G., Wadia, R. S., Naniwadekar, A., Pote, P. U., Tungenwar, A., Deshmukh, A. M., Mohapatra, S., Nimavat, B., & Surywanshi, P. (2018). Impact of “stroke code”-rapid response team: An attempt to improve intravenous thrombolysis rate and to shorten door-to-needle time in acute ischemic stroke. *Indian Journal of Critical Care Medicine: Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine*, 22(4), 243–248. [https://doi.org/10.4103/ijccm.IJCCM\\_504\\_17](https://doi.org/10.4103/ijccm.IJCCM_504_17)