

Rapid Thrombolysis Protocol: Results from a Before-and-after Study

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ABSTRACT

Objective: Intravenous thrombolysis within 4.5 hours from time of onset has proven benefit in stroke. Universal standard for the door-to-needle (DTN) time is within 60 minutes from the time of arrival of patients to the emergency department. Our rapid thrombolysis protocol (RTPr) was developed with an aim to reduce the DTN time to a minimum by modifying our stroke post-intervention processes.

Methods: This before-and-after study was conducted at a single center on patients who received intravenous thrombolysis in the emergency department. Consecutive patients who were thrombolysed using our RTPr (post-intervention group) were compared to the pre-intervention group who were thrombolysed before the implementation of the protocol. The primary outcomes were DTN time, time to recovery, and modified ranking score (mRS) on discharge. Secondary outcomes were mortality, symptomatic intracerebral hemorrhage, and hospital and intensive care unit length of stay.

Results: Seventy-four patients were enrolled in each group. Mean DTN time in pre- and post-intervention group was 56.15 minutes (95% CI 49.98–62.31) and 34.91 minutes (95% CI 29.64–40.17) ($p < 0.001$), respectively. In pre-intervention and post-intervention groups, 43.24% (95% CI 32.57–54.59) and 41.89% (95% CI 31.32–53.26) patients, respectively, showed neurological recovery in 24 hours. About 36.49% (95% CI 26.44–47.87) in pre-intervention group and 54.05% (95% CI 42.78–64.93) in post-intervention group had discharge mRS 0–2.

Conclusion: The RTPr can be adapted by clinicians and hospitals to bring down the DTN times and improve outcomes for stroke patients.

Keywords: Ischemia, Rapid thrombolysis protocol, Stroke, Thrombolysis, Tissue plasminogen activator.

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HIGHLIGHTS

Our rapid thrombolysis protocol (RTPr) drastically reduces door-to-needle (DTN) times for thrombolysis in patients of acute stroke. Patients with DTN time <30 minutes had favorable outcomes in our study. We recommend clinicians to use our protocol to reduce DTN times for treating acute strokes.

INTRODUCTION

Background

Strokes are the second leading cause of death and third leading cause of disability across the globe.¹ About 1.9 million neurons are lost every minute that an ischemic stroke is left untreated.² Most effective therapy for acute ischemic stroke (AIS) has been intravenous thrombolysis, either as the sole post-intervention or in combination with endovascular thrombectomy.^{3–5} It is recommended that thrombolysis should be initiated within 60 minutes from the time of arrival to the emergency.^{6,7} One in six patients have a better disability outcome and 1 in 35 have a worse outcome when treated with tissue plasminogen activator (TPA) within the 3- to 4.5-hour window period.⁸ Every minute saved in reducing the onset-to-needle time that has been shown to add 1.8 days of extra healthy life to stroke patients.⁹ We developed our RTPr to reduce our DTN times to the minimum possible to attempt to provide the maximum benefit to patients suffering from acute ischemic stroke. The aim of our study was to investigate the impact of our RTPr on DTN times for thrombolysis and correlate it with neurological recovery. We also aimed to study the incidence of complications like mortality and symptomatic intracerebral

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hemorrhage (sICH). Limited data can be found regarding the impact of a stroke protocol in India.

METHODS

Study Design

This was an electronic health records (EHRs)-based before-and-after study which was approved by our institutional ethics committee. Consecutive patients with acute stroke were enrolled into the study and divided into groups. The pre-intervention group comprised of the patients who had presented with acute stroke and were subsequently thrombolysed in the emergency department (ED) before our RTPr was implemented. The post-intervention group

comprised of patients who presented to the ED with acute stroke within the window period of 4.5 hours and were thrombolysed post-implementation of the RTPr. All patient details were accessed and collected through the hospital's EHR. Time of onset of symptoms to needle time, DTN time of all patients along with National Institute of Health Stroke Scale (NIHSS) at the time of presentation, subsequent neurological recovery, and modified Rankin score (mRS) on discharge were recorded and analyzed. The standard mRS at 90 days was not considered as majority of patients in the both groups did not have follow-up records in the EHR. Secondly, total length of stay (LOS) at the hospital, intensive care unit (ICU) LOS, and incidence of sICH were also studied. sICH was defined as any deterioration in NIHSS score or death within 7 days combined with intracerebral hemorrhage of any type (including petechial) on any posttreatment imaging after the start of thrombolysis (National Institute of Neurological Disorders and Stroke definition).¹⁰

Setting

The study was conducted in the emergency department of a 400-bedded Indian urban tertiary care center.

Selection of Participants

All patients who presented to ED with acute ischemic stroke and were subsequently thrombolysed were included in the study.

Interventions

The study intervention constituted of conceptualization, development, and implementation of our in-house RTPr. Table 1 compares the RTPr with our previous stroke protocol. It focused on a multispecialty approach to reduce the DTN times for stroke patients arriving to our emergency.

Rapid Thrombolysis Protocol

Patients arriving in the triaging area with symptoms of stroke are informed to the senior emergency physician in the ED by triage nurse. If we have prehospital information regarding a stroke patient arriving, a green corridor is established from triage to radiology. Counseling of family members regarding the condition, diagnosis, and probable need for thrombolysis by the doctor is performed in the ambulance, and live locations are shared with

the emergency medicine team. The vital signs of the patient are recorded by our trained triage nurse, while the physicians quickly evaluate the patient in the triage room itself. On confirmation of clinical stroke, a "stroke code" is announced by dialing the emergency code. The calls are received by the neurologist on call, radiology, laboratory, and medical administration. The patient is immediately shifted to radiology for computed tomography (CT) brain or magnetic resonance imaging (MRI) screening (diffusion-weighted and fluid attenuated inversion recovery). MRI is performed for patients who have wake up strokes, and exact time of onset is not known or when symptoms/signs are vague. If MRI is contraindicated and a radiological diagnosis is required, then a CT perfusion study is performed. When the patient is in the CT, the family is re-counseled regarding the clinical diagnosis, condition, and probable need for thrombolysis and consent for the same is obtained. Contraindications are ruled out during the scan. Recombinant tissue plasminogen activator (rTPA) is brought to radiology by the emergency nurse to save time if thrombolysis is indicated. If CT is normal and clinical diagnosis of ischemic stroke established, the patient is delivered the bolus dose followed by the infusion over 1 hour. All stroke blood samples are sent before giving the bolus drug. The neurologist then takes the call for the need for additional CT angiography in which case the infusion is continued in the scanner. The patient is then shifted back to the emergency where the emergency physician and nurse monitor the patient's hemodynamics and neurological recovery/worsening. An emergency physician consultant stays with the patient throughout starting from the triage till the patient gets thrombolysed. This minimizes the risk of any delays that may occur in the thrombolysis of the patient. The neurology team decides the need for mechanical thrombectomy, and the patient is shifted to the stroke ICU.

Measurements

Demographic information of patients who underwent thrombolysis was collected. DTN time was defined as the time difference between arrival at the triage and the time the bolus dose of thrombolytic was delivered. Onset-to-needle time was defined as the time between symptom onset and the initiation of thrombolysis. Time to neurological recovery was the time between initiation of thrombolysis and the improvement in the NIHSS (reduction

Table 1: Rapid thrombolysis protocol (RTPr) versus previous protocol

<i>RTPr</i>	<i>Previous protocol</i>
EMS recognize stroke and inform emergency department (ED). Green corridor prepared.	No strict protocol regarding information to ED by EMS. No green corridor.
Family counseled regarding diagnosis, condition, and need for thrombolysis in the ambulance by EMS team.	No counseling done.
Stroke confirmed by triage nurse/emergency physician and stroke code announced.	Did not have a stroke code.
Vital signs noted, and patient shifted for computed tomography (CT) and magnetic resonance imaging (MRI). CT performed if clear neurological deficit and in window period. MRI (CT perfusion if contraindicated) performed if wake-up stroke, time of onset not known, or vague symptoms.	Patient taken to the ED and examined by the emergency physician. Neurologist called and patient seen by their team. Planned for radiology.
Family counseled regarding thrombolysis during CT/MRI and consent taken. All contraindications ruled out during radiology.	Patient shifted to CT/MRI as indicated.
Post-radiological investigation, stroke samples are collected, thrombolysis started and CT/MR angiography of neck and brain done.	Patient shifted back to ED. CT/MRI read and plan for thrombolysis made.
Patient shifted to ED for observation and other investigations. Patient shifted to stroke ICU post-thrombolysis or cath laboratory if mechanical thrombectomy indicated.	Contraindications ruled out and patient thrombolysed after consent from family.



in deficit) as mentioned in the EHR. mRS at the time of discharge was collected from the EHR of the patients who underwent thrombolysis.

Outcomes

The primary outcomes were DTN time and neurological recovery. Neurological recovery was predefined as improvement of symptoms and NIHSS reduction by at least two points in ≤24 hours, >24 hours, or no recovery at all and mRS at the time of discharge. The predetermined secondary outcomes were mortality, sICH, and hospital and ICU LOS.¹¹

Primary Data Analysis

Statistical analysis was conducted using IBM SPSS version 22. Continuous variables were presented as mean and categorical variables as frequency and percentage. Multivariate analysis techniques have been used to determine the neurological recovery basis and the DTN time. Correlation between DTN time and related outcomes was calculated basis the Chi-square test. Other suitable statistical analysis methods were adopted to calculate the outcomes of the research study.

RESULTS

The pre-intervention and post-intervention period recorded data for 74 patients each. Mean age of patients in pre-intervention stage was 62.18 years (95% CI 58.97–65.38), while in post-intervention, it was 63.58 years (95% CI 60.77–66.38). There were 82% males in the pre-intervention stage as compared to 62% males in the post-intervention stage. Table 2 enlists baseline characteristics of the patients in both the stages. In the pre-intervention group, one patient was on factor Xa inhibitor and two patients were on antiplatelet for their atrial fibrillation. In the post-intervention group, four patients were on factor Xa inhibitor and two were on anticoagulant for atrial fibrillation.

The mean DTN time was significantly reduced ($p < 0.001$) to 34.91 minutes (95% CI 29.64–40.17) in the post-intervention arm. In the post-intervention arm, 51.35% patients (95% CI 40.18–62.39) had DTN time of up to 30 minutes, while 17.57% patients (95% CI 10.56–27.77) underwent thrombolysis within 30 minutes of arrival in pre-intervention group. In pre-intervention group, 33.78% (95% CI 24.05–45.12) patients were thrombolysed within 45 minutes of arrival, while 28.38% (95% CI 19.37–39.52) patients were thrombolysed after 60 minutes of arrival. In post-intervention group, 81.08% patients (95% CI 70.71–88.38) were thrombolysed within 45 minutes, while 9.46% (95% CI 4.66–18.26) patients were thrombolysed after 60 minutes. Figure 1 depicts patients

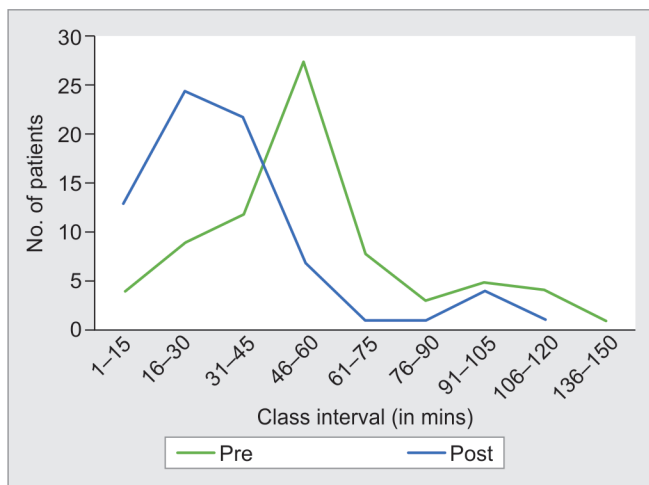


Fig. 1: Patients thrombolysed in various time intervals—pre-intervention versus post-intervention group

thrombolysed at various time intervals in pre-intervention and post-intervention group. The median DTN time reduced from 54.5 minutes in the pre-intervention arm to 30 minutes in the post-intervention arm. Mean time of onset to needle time in pre-intervention group was 150.14 minutes (95% CI 136.09–164.18) (median—140 minutes), and in post-intervention group, it was 123.11 minutes (95% CI 108.62–137.59) (median—113.5 minutes).

Mean NIHSS at time of arrival in pre-intervention and post-intervention groups was 7.82 (95% CI 7.11–8.52) and 7.64 (95% CI 6.69–8.58), respectively. In pre-intervention group, 43.24% (95% CI 32.57–54.59) and 41.89% (95% CI 31.32–53.26) patients in the post-intervention group showed neurological recovery in 24 hours. Out of the patients who were thrombolysed within 30 minutes in pre-intervention group, 75% (95% CI 46.77–91.11) exhibited neurological recovery in 24 hours. Out of the patients who were thrombolysed within 30 minutes of arrival in post-intervention group, 48.65% (95% CI 33.45–64.11) patients showed neurological recovery in 24 hours. In the pre-intervention group, 21.62% (95% CI 13.77–32.27) patients had no neurological recovery at the time of discharge, while 25.68% patients (95% CI 17.10–36.65) in post-intervention group had no neurological recovery at the time of discharge. In pre-intervention group, 87.50% (95% CI 63.98–96.50) patients who had no neurological recovery had DTN of >30 minutes, while 43.75% patients (95% CI 23.10–66.82) had DTN of >60 minutes. In post-intervention group, 57.89% (95% CI 36.28–76.86) patients with no neurological recovery were thrombolysed after 30 minutes, while 15.79% patients (95% CI 5.52–37.57) had DTN of >60 minutes.

Mean discharge mRS in pre-intervention and post-intervention groups was 2.69 (95% CI 2.36–3.01) and 2.5 (95% CI 2.11–2.88), respectively. At discharge, 36.49% (OR 3.54, 95% CI 26.44–47.87) in the pre-intervention group had an mRS of 0–2, while 54.05% (OR 1.11, 95% CI 42.78–64.93) in the post-intervention arm had an mRS of 0–2. In the post-intervention group, 52.50% (95% CI 37.50–67.06) patients who had a discharge mRS of 0–2 were thrombolysed within 30 minutes, while 29.63% (95% CI 15.85–48.48) patients with mRS of 0–2 in the pre-intervention group were thrombolysed within 30 minutes.

Three patients (4.05%, 95% CI 1.39–11.25) suffered mortality in pre-intervention group, while two patients (2.70%, 95% CI 0.74–9.33) had mortality in post-intervention group. One patient in each group suffered sICH.

Table 2: Demographic and baseline characteristics of patients

	Pre-intervention group (n = 74)	Post-intervention group (n = 74)
Age (years) mean ± SD	62.18 ± 13.84	63.58 ± 12.09
Males (%)	81.08	61.16
Hypertension (%)	56.76	29.72
Diabetes mellitus (%)	39.18	33.78
Coronary artery disease (%)	18.91	17.56
Atrial fibrillation (%)	4.05	8.10
Cerebrovascular accident (%)	12.16	10.81

Mean ICU LOS was 4.71 days (95% CI 3.66–5.75) and 4.74 days (95% CI 3.73–6.10) in pre-intervention and post-intervention groups, respectively. Average hospital LOS was 9.42 days (95% CI 7.60–11.23) and 10.15 days (95% CI 7.99–12.30) in pre-intervention and post-intervention arms, respectively. In pre-intervention group, 10.81% (95% CI 5.58–19.91) of patients underwent endovascular mechanical thrombectomy (EVT), while 9.46% (95% CI 4.66–18.26) of patients underwent thrombectomy in the post-intervention group. Reasons for prolonged DTN of >60 minutes in post-intervention group are listed in Table 3. All outcomes are tabulated in Table 4.

DISCUSSION

It is well known that the benefit of intravenous thrombolysis in acute stroke is time-dependent. A DTN time of ≤60 minutes is the internationally recognized guideline.¹² Studies have shown that despite guidelines, only one in three stroke patients receive intravenous thrombolysis. There have been strategies implemented in different healthcare settings across the world to shorten DTN times well below the recommended 60 minutes. Heikkilä et al. demonstrated that the DTN time could be brought down to a median time of 20 minutes.¹³ Similarly, Zinkstok et al. brought down the average DTN time to less than 30 minutes after implementing their ABC protocol.¹¹ Our study found that by using our protocol, the mean DTN time was reduced by 22 minutes with the fastest DTN being 6 minutes. Reducing the DTN times have been shown to improve outcomes (mRS ≤2) in

more patients than otherwise.¹⁴ In our study, more patients were discharged with an mRS of 0–2, when the RTPr was used. Patients who received thrombolysis within 30 minutes had a higher probability of a favorable outcome (mRS ≤2) at discharge than those thrombolysed beyond 30 minutes. Kim et al., in their study, did not find any changes in the mRS of patients discharged, but DTN times were significantly reduced.¹⁵ There was no difference in the number of patients who had neurological recovery within 24 hours of thrombolysis between the two groups. But, in both the groups, majority of patients who had neurological recovery within 24 hours had a DTN ≤30 minutes. On the other hand, most of the patients who did not have neurological recovery were thrombolysed beyond 30 minutes. There was no statistical difference in the ICU and hospital LOS and incidence of sICH in both the groups. Traditionally, the onset of symptom to treatment time was 3 hours. This window has now been extended up to 4.5 hours. The European Cooperative Acute Stroke Study (ECASS) group demonstrated in their study that intravenous alteplase can be safely administered to patients with an extended window period of 4.5 hours.¹⁶ In our study, the median onset-to-treatment times was reduced from 150 to 113.5 minutes.

About 10.81 and 9.46% patients in the pre-intervention and post-intervention groups, respectively, underwent endovascular mechanical thrombectomy post-thrombolysis. Studies have shown EVT in addition to thrombolysis to have beneficial effects on patients when onset-to-treatment times are minimized.¹⁷ Through multiple randomized controlled trials, it has been established that the combination of medical thrombolysis and EVT for large vessel occlusions is a superior treatment regimen as compared to thrombolysis alone when initiated within 6 hours of symptom onset.¹⁸ Patients who go to sleep with no neurological symptoms and wake up with deficits pose a unique dilemma in the management strategies. The “wake-up strokes” have an incidence rate of about 15–25% of all AIS patients.¹⁹ Recent studies have established that the window period for EVT can be extended up to 16–24 hours. The selection is based on imaging which shows a salvageable penumbra or a mismatch between neurological deficit and size of infarct. This is beneficial for patients who suffer from “wake-up” strokes and may not be a candidate for thrombolytic therapy.^{20,21}

Table 3: Reason for prolonged (>60 minutes) door-to-needle (DTN) time in the post-intervention group

<i>Reason for prolonged DTN time >60 minutes</i>	<i>Post-intervention group (n = 11)</i>
Unstable patients requiring stabilization	2 (18.2)
Delayed decision by physician	1 (9.1)
Delayed consent from family	2 (18.2)
Unclear symptoms	4 (36.3)
Wait for coagulation profile	1 (9.1)
Asymptomatic patient who developed symptoms after arrival to ED	1 (9.1)

Table 4: Study outcomes

	<i>Study outcomes</i>	
	<i>Pre-intervention (95% CI)</i>	<i>Post-intervention (95% CI)</i>
Mean DTN (minutes)	56.15 (49.98–62.31)	34.91 (29.64–40.17)
Mean onset-to-needle time (minutes)	150.14 (136.09–164.18)	123.11 (108.62–137.59)
DTN ≤30 minutes (%)	17.57 (10.56–27.77)	51.35 (40.18–62.39)
DTN ≤45 minutes (%)	33.78 (24.05–45.12)	81.08 (70.71–88.38)
DTN >60 minutes (%)	28.38 (19.37–39.52)	9.46 (4.66–18.26)
Neurological recovery ≤24 hours (%)	43.24 (32.57–54.59)	41.89 (31.32–53.26)
No recovery (%)	21.62 (13.77–32.27)	25.68 (17.10–36.65)
Mean mRS at discharge	2.69 (2.36–3.01)	2.5 (2.11–2.88)
Patients with mRS 0–2 at discharge (%)	36.49 (26.44–47.87)	54.05 (42.78–64.93)
Patients with mRS 0–2 thrombolysed ≤30 minutes (%)	29.63 (15.85–48.48)	52.50 (37.50–67.06)
Mortality (%)	4.05 (1.39–11.25)	2.70 (0.74–9.33)
sICH (%)	1.35 (0.24–7.83)	1.35 (0.24–7.83)
Mean ICU LOS (days)	4.71 (3.66–5.75)	4.74 (3.73–6.10)
Mean hospital LOS (days)	9.42 (7.60–11.23)	10.15 (7.99–12.30)

“Stroke codes” globally have shown to maximize the number of patients receiving thrombolysis and shortening the DTN times.^{13,22–24} Our protocol incorporated the code stroke concept and factored in the EMS, triage nurse/physician, ancillary specialties, and administration. Since the lead was with the ED, all staff members were educated and trained regarding importance of stroke, early initiation, and ownership of the patient. Radiology department was primed that code stroke patients would be the top priority and no other patient should be taken into the scanner before the stroke patient. Work space optimization, education, training, cooperation, reorganizing processes, and protocols can help improve the capacity efficiency of the ED to provide the best standard of care to patients suffering from acute ischemic strokes.^{25–28} We took all these factors into consideration while preparing our protocol.

LIMITATIONS

The major limitation of our study was the sample size. Our electronic health records were introduced in 2017 and the RTPr in 2018. Thus, we had only few electronic records of patients before the implementation of RTPr. To avoid confounding, we selected the same number of consecutive patients who were thrombolysed post the implementation of our protocol. If we would have taken all the patients thrombolysed since our new protocol, the results may have been different. Another limitation was that this was a single center study and our protocol will need validation in bigger multicentric studies. Since our study was quasi-experimental, there was risk of unidentified confounding and bias.

CONCLUSION

In our study, we found that patients who were thrombolysed within 30 minutes had better and favorable outcomes. We recommend clinicians to aspire to achieve a DTN of ≤ 30 minutes than the much accepted 60 minutes for acute stroke patients. The RTPr brings down the DTN time substantially for patients of acute ischemic stroke safely. This study showed better outcomes for patients who were thrombolysed using our protocol. The RTPr is a useful tool which can be adapted to bring down the DTN time and improve outcomes for stroke patients. We do recommend larger multicentric studies to validate the RTPr.

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