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Original Article

Internal Medicine Section

# Outcome Analysis of Intravenous Thrombolytic Therapy in Patients with Acute Ischaemic Stroke and its Association with Critical Time Intervals: An Ambispective Study

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## ABSTRACT

**Introduction:** Intravenous thrombolytic therapy has become the standard of care in patients with acute ischaemic stroke. The success of this therapy depends on achieving the shortest time between the onset of stroke and reperfusion. Many clinical tasks like neurological assessment, imaging and its interpretation, exclusion of contraindications and informed consent must be taken care of, prior to administration of thrombolytic therapy. As this is a time sensitive intervention, it may have variable outcomes in different settings.

**Aim:** To evaluate the immediate and 90-day neurological outcome of the patients who had received intravenous thrombolytic therapy in acute ischaemic stroke and to evaluate its association with stipulated critical time intervals.

**Materials and Methods:** This was an ambispective observational study conducted for a period of 18 months (April 2018-October 2019) in the Emergency Department of Pushpagiri Institute of Medical Sciences, Thiruvalla, a tertiary care hospital in central Kerala, India. For the prospective arm of the study, data were collected from the patients who came to the Emergency Department with acute ischaemic stroke in the window period (three hours) or in the extended window period (3-4.5 hours). Onset to door time, door-to-imaging time, door-to-needle time and onset-to-needle time were assessed and recorded. National Institute of Health Stroke Scale (NIHSS) score at presentation and at 24 hours post-thrombolysis was noted. Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) brain report 24 hours post-thrombolysis was followed-up. The functional outcome at 90 days was assessed using Modified Rankin Scale (MRS) score. For the retrospective arm of the study, the relevant data were collected from the hospital records and the patients were followed-up. The association between the stipulated critical time intervals and 24 hours post-thrombolysis NIHSS score, as well as MRS score at 90 days were calculated using the statistical analysis tool STATA v.14. Statistical comparisons were performed between subgroups using the Chi-square ($\chi^2$) test, Fischer's-exact test, Wilcoxon signed-rank test, and Mann-Whitney U-test as indicated for dichotomous or continuous variables. For all statistical analyses, a p-value of <0.05 was taken as statistically significant.

**Results:** Of the total 110 patients, 105 patients (95.5%) reached the hospital within three hours (window period), and five patients (4.5%) reached within 4.5 hours (extended window period). A total of 58 patients (52.7%) received thrombolytic treatment within three hours and 52 patients (47.3%) within 4.5 hours. After 24 hours of thrombolysis, improvement in neurological function, as defined by an improvement in NIHSS score by 4 or more was found in 73 patients (66.4%). At 90 days follow-up, 76 patients (69.1%) became functionally independent with an MRS score of 0-2. There was a significant association between NIHSS score 24-hours post-thrombolysis and the functional outcome at 90 days. Of the various stipulated critical time intervals, a significant association was seen only with onset-to-door time and NIHSS score 24 hours post-thrombolysis.

**Conclusion:** A total of 69.1% of the patients who have received intravenous thrombolytic therapy for acute ischaemic stroke in this study have shown favourable functional outcome at 90 days. The NIHSS score 24 hours post-thrombolysis compared to baseline is a good predictor of the neurological outcome at 90 days.


**Keywords:** Door-to-imaging time, Door-to-needle time, Modified rankin scale, National institute of health stroke scale, Window period

## INTRODUCTION

Stroke is the second leading cause of death in adults globally. Ischaemic stroke accounts for about 62.4% of all strokes [1]. Acute ischaemic strokes are caused by thrombotic or embolic occlusion of cerebral blood vessels. Thrombolytic therapy has added a new dimension in acute stroke care. When administered early (within 4.5 hours of onset), intravenous thrombolytic therapy with alteplase improves outcome in patients with stroke as shown by the National Institute of Neurological Disorders and Stroke (NINDS) trial [2] and the European Cooperative Acute Stroke Study III (ECASS III) trial [3]. However, this is a time sensitive intervention because giving this therapy after the window period is associated with increased risk [4]. It is imperative that no time should be wasted from the onset of stroke to thrombolysis. To ensure this, NINDS has established critical in-hospital time goals for the assessment and management of patients with suspected stroke [5,6]. Implementing an Institutional Stroke management protocol is a good strategy to ensure adherence to these time-sensitive clinical goals [7-9]. This requires a well-coordinated plan from Emergency Medicine, Neurology, and Radiology departments with a focus on rapid identification, response and intervention. The real-life implementation of a stroke protocol is fraught with many difficulties. In a developing country like India the challenges may be more pronounced [10]. There is limited data from India regarding the implementation of thrombolytic therapy and the challenges involved in adhering to the time sensitive goals and its influence on clinical outcomes. In this context, the aim of the study was to ascertain the outcome of thrombolytic therapy with regard to critical time intervals. The primary objective of the study was to assess the immediate (at 24 hours) and 90 days neurological outcome of the patients who received intravenous thrombolytic therapy for

acute ischaemic stroke. The secondary objectives were to find the association between the stipulated critical time intervals namely onset-to-door time, door-to-imaging time, door-to-needle time and onset-to-needle time with the neurological status at 24 hours post-thrombolysis and the functional outcome at 90 days.

## MATERIALS AND METHODS

The study was conducted as an ambispective observational study with prospective and retrospective arms. It was conducted in the Department of Emergency Medicine, Pushpagiri Institute of Medical Sciences, Thiruvalla, Kerala, India. The study was conducted for a period of 18 months from April 2018-October 2019. The study protocol was approved by the Institutional Ethics committee (PIMSRC/E1/388A/11/2018).

**Inclusion criteria:** Patients in the age group between 18-90 years with acute ischaemic stroke who were eligible [6] for thrombolysis were included in the study.

**Exclusion criteria:** Patients with symptom duration more than four and half hours (past window period), those with contraindications [6] for thrombolytic treatment, patients <18 years or >90 years old, patients whose data were not available (in case of retrospective study), and patients not consenting to the study were excluded from the study.

**Sample size calculation:** Sample size was calculated assuming the confidence interval of 95%, proportion of outcome as 78.5% [11] and error as 10% of P, using the formula:

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} P(1-P)}{d^2}$$

Total sample size was calculated as 110. For the prospective arm of the study, informed consent was taken from the patient or the legally authorised representative if the patient was not able to give consent. For the retrospective arm of the study, consent was waived off by the Ethical committee.

### Study Procedure

A total of 32 patients were recruited for the retrospective arm of the study and for the prospective arm 78 patients were recruited. For the prospective arm, data was collected from the patients who came to the Emergency Department with acute stroke in the window period (three hours) or in the extended window period (4.5 hours). NIHSS score [12] at presentation was documented for each patient. All the eligible patients received thrombolytic therapy with alteplase at a dose of 0.9 mg/kg (10% as a bolus and the rest as an infusion over 1 hour) [2,6]. Onset-to-door time, door-to-imaging time, door-to-needle time, and onset-to-needle time were assessed. CT/MRI report after 24 hours of thrombolysis was followed-up. Neurological outcome at 24 hours post-thrombolysis was assessed using NIHSS score. Functional outcome at 90 days was assessed using MRS score [Table/Fig-1] [13,14].

| Score | Description |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance |
| 3 | Moderate disability: requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

**[Table/Fig-1]:** Modified Rankin scale score (Adapted from Van Sweiten et al., [13,14].

The retrospective study collected the required data from the hospital records, and the patients were followed-up. NIHSS score decreasing by ≥4 points were defined as an improvement in neurologic status; increasing by ≥4 points as worsening of neurologic status [12]. Those patients who had an MRS score of 0-2 at 90 days were classified as having "Favourable outcome" and those patients whose MRS score was between 3-6 were classified as having "Unfavourable outcome" [13,14].

## STATISTICAL ANALYSIS

Data were entered using Microsoft excel 2016 and STATA v.14 was used for statistical analysis. Continuous variables with skewed distribution were presented as median (range) while categorical variables were presented as count (percentages). Statistical comparisons were performed between subgroups using the $\chi^2$ test, Fischer's-exact test, Wilcoxon signed-rank test, and Mann-Whitney U-test as indicated for dichotomous or continuous variables. For all statistical analyses, a p-value of <0.05 was taken as statistically significant.

## RESULTS

The study included 110 subjects who fulfilled the inclusion criteria. The median age of the study population was 65 years. The minimum age included in the study was 32 years and the maximum age was 89 years. There were 78 (70.90%) males and 32 (29.10%) females in the study group. The age and gender distribution is given in [Table/Fig-2].

| Age group (years) | Male, n (%) | Female, n (%) | Total, n (%) |
|---|---|---|---|
| 31-40 | 3 (2.7) | 1 (0.9) | 4 (3.6) |
| 41-50 | 2 (1.8) | 3 (2.7) | 5 (4.5) |
| 51-60 | 19 (17.3) | 2 (1.8) | 21 (19.1) |
| 61-70 | 27 (24.5) | 18 (16.4) | 45 (40.9) |
| 71-80 | 21 (19.1) | 8 (7.3) | 29 (26.4) |
| 81-90 | 6 (5.5) | -- | 6 (5.5) |
| Total | 78 (70.90%) | 32 (29.10%) | 110 (100%) |

**[Table/Fig-2]:** Age and sex distribution in the study sample.

**Critical time intervals:** NINDS has established critical in-hospital time goals for the assessment and management of patients with suspected stroke [5,6]. This includes onset-to-door time, door-to-imaging time, door-to-needle time, and onset-to-needle time. Onset-to-door time implies how fast the patient reaches the hospital from the time of onset of symptoms. Door-to-imaging time should preferably be within 25 minutes of arrival. Initiation of fibrinolytic therapy, if appropriate, within one hour of arrival to the hospital is the ideal door-to-needle time. Onset-to-needle time which is defined as the time from the onset of symptoms to the initiation of thrombolytic therapy should be within 4.5 hours [6]. Various critical time intervals as observed in the study are shown in [Table/Fig-3].

| Time | n (%) |
|---|---|
| **Onset-Door time** | |
| <3 hours | 105 (95.5) |
| ≥3 hours | 5 (4.5) |
| **Door-to-imaging time** | |
| <25 minutes | 46 (41.8) |
| ≥25 minutes | 64 (58.2) |
| **Door-to-needle time** | |
| <1 hour | 39 (35.5) |
| ≥1 hour | 71 (64.5) |
| **Onset-to-needle time** | |
| <3 hours | 58 (52.7) |
| 3-4.5 hours | 52 (47.3) |

**[Table/Fig-3]:** Critical time intervals in study population.

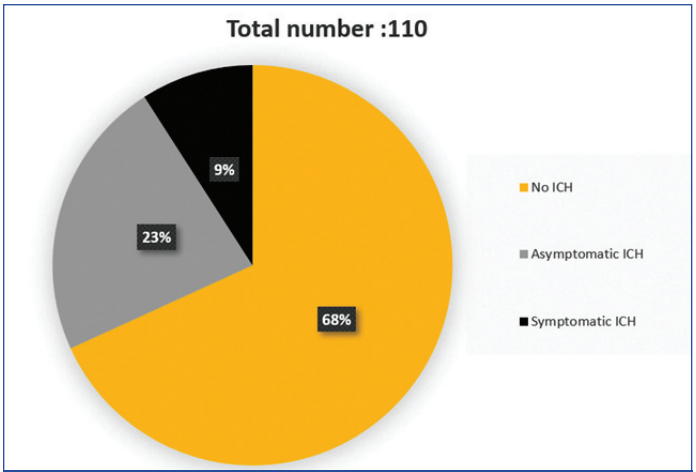
**NIHSS score at presentation:** The median NIHSS score on presentation was 11, with a range from 5-27.

**NIHSS score 24 hours post-thrombolysis:** The median NIHSS score at 24 hours was 6, with a range from 0-32. Improvement in neurological function, as defined by an improvement in NIHSS score (NIHSS Score reduction by 4 or more) was found in 73 patients (66.4%). Worsening of neurological function, defined by an increase in NIHSS score by 4 or more was present in 12 patients (10.9%). No significant difference in NIHSS score (from -3 to +3 difference) was seen in 25 patients (22.7%) [Table/Fig-4].

| Change in NIHSS score | n (%) |
|---|---|
| Worsening (≥4) | 12 (10.9) |
| No remarkable difference (-3 to 3) | 25 (22.7) |
| Improvement (≤4) | 73 (66.4) |

**[Table/Fig-4]:** Change in NIHSS Score after 24 hours of receiving thrombolytic therapy in study population.

**Imaging results after 24 hours post-thrombolysis:** Imaging (MRI Brain/CT Brain) done after 24 hours revealed that 35 patients (32%) had intracerebral haemorrhage/haemorrhagic transformation of infarct following thrombolysis. Symptomatic intracerebral haemorrhage as defined by haemorrhage associated with worsening of NIHSS over 4 points was seen in 10 patients (9%) in the study population [Table/Fig-5].




**[Table/Fig-5]:** Intracranial haemorrhage post-thrombolysis in the study population (ICH-intracranial haemorrhage).

**Modified Rankin scale score at 90 days:** At 90 days follow-up, 76 patients (69.1%) became functionally independent with an MRS score of 0-2 (favourable outcome), 34 patients (30.9%) had an MRS score between 3-6 (unfavourable outcome). Seven patients (6.4%) died during the three-month period. This is shown in [Table/Fig-6].

| Modified Rankin score | n (%) |
|---|---|
| Favourable (0-2) | 76 (69.1%) |
| Unfavourable (3-6) | 34 (30.9%) |

**[Table/Fig-6]:** Modified Rankin Score at 90 days in the study population.

**Outcome analysis in terms of NIHSS score at 24 hours and functional outcome at 90 days:** The median NIHSS scores at baseline and at 24 hours were 11 (range: 5-27) and 6 (range: 0-32), respectively. There was a significant difference between the NIHSS scores at baseline and at 24 hours in patients who had received intravenous thrombolysis therapy (p-value <0.001) [Table/Fig-7].

| NIHSS score | Median (range) | Significance of difference from baseline (p-value) |
|---|---|---|
| Baseline | 11 (5-27) | <0.001* |
| 24 hours | 6 (0-32) | |

**[Table/Fig-7]:** Outcome analysis in patients with acute stroke who underwent thrombolysis in terms of NIHSS score at 24 hours.
*Wilcoxon signed rank test

Among the 73 patients who had improvement in NIHSS score after 24 hours, 59 patients (80.8%) had MRS score less than or equal to 2 (favourable outcome) and 14 patients (19.2%) had MRS Score more than 2 (Unfavourable outcome). All the 12 patients who had worsening in NIHSS score after 24 hours, were found to have MRS score more than 2 at 90 days. Among the 25 patients who didn't have much difference in their NIHSS score after 24 hours, 17 patients (68%) had favourable outcomes and 8 patients (19.2%) had unfavourable outcomes. A significant association was observed in this study between NIHSS score after 24 hours -post-thrombolysis and 90 days functional outcome (p-value <0.001) [Table/Fig-8].

| NIHSS score | MRS ≤2 n (%) | MRS >2 n (%) | p-value |
|---|---|---|---|
| Worsening | 0 | 12 (100.0) | <0.001* |
| No remarkable difference | 17 (68.0) | 8 (32.0) | |
| Improvement | 59 (80.8) | 14 (19.2) | |

**[Table/Fig-8]:** Association between 90 days post-thrombolysis outcome and NIHSS score at 24-hour post-thrombolysis.
*Fisher exact test

**Association between critical time intervals and NIHSS score 24 hours post-thrombolysis:** Of the various critical time intervals, a statistically significant association was observed only with Onset-to-door time and 24 hours post-thrombolysis NIHSS score (p-value 0.031) [Table/Fig-9]. It was observed that those who presented within three hours of symptom onset had a significant improvement in NIHSS score at 24 hours compared to those who presented after 3 hours but within 4.5 hours.

| Time | NIHSS worsening n (%) | NIHSS No difference n (%) | NIHSS improvement n (%) | p-value |
|---|---|---|---|---|
| **Onset-to-door time** | | | | |
| <3 hours | 10 (9.5) | 23 (21.9) | 72 (68.6) | 0.031* |
| ≥3 hours | 2 (40.0) | 2 (40.0) | 1 (20.0) | |
| **Door-to-imaging time** | | | | |
| <25 minutes | 2 (4.3) | 12 (26.1) | 32 (69.6) | 0.155* |
| ≥25 minutes | 10 (15.6) | 13 (20.3) | 41 (64.1) | |
| **Door-to-needle time** | | | | |
| <1 hour | 4 (10.3) | 10 (25.6) | 25 (64.1) | 0.909* |
| ≥1 hour | 8 (11.3) | 15 (21.1) | 48 (67.6) | |
| **Onset-to-needle time** | | | | |
| <3 hours | 6 (10.3) | 12 (20.7) | 40 (69.0) | 0.825** |
| 3-4.5 hours | 6 (11.5) | 13 (25.0) | 33 (66.5) | |

**[Table/Fig-9]:** Association between various time intervals and change in NIHSS at 24 hours post-thrombolysis.
*Fisher exact p-value, **Chi-Square test

**Association between critical time intervals and 90 days functional outcome as per Modified Rankin scale score:** The Onset-to-door time, door-to-imaging time, door-to-needle time, and onset-to-needle time were compared between the groups with favourable and unfavourable outcomes. None of the parameters differed significantly between the groups [Table/Fig-10].

| Time | MRS ≤2 | MRS >2 | p-value |
|---|---|---|---|
| **Onset-to-door time** | | | |
| <3 hours | 73 (69.5) | 32 (30.5) | 0.644* |
| ≥3 hours | 3 (60.0) | 2 (40.0) | |
| **Door-to-imaging time** | | | |
| <25 minutes | 32 (69.6) | 14 (30.4) | 0.927** |
| ≥25 minutes | 44 (68.7) | 20 (31.3) | |
| **Door-to-needle time** | | | |
| <1 hour | 25 (64.1) | 14 (35.9) | 0.401** |
| ≥1 hour | 51 (71.8) | 20 (28.2) | |

| Onset-to-needle time | | | |
|---|---|---|---|
| <3 hours | 39 (67.2) | 19 (32.8) | 0.658** |
| 3-4.5 hours | 37 (71.2) | 15 (28.8) | |

**[Table/Fig-10]:** Association between critical time intervals and MRS score at 90 days. *Fisher exact test, **Chi-square test

## DISCUSSION

Thrombolytic therapy is the standard of care in acute ischaemic stroke. However, this therapy must be given in the first 4.5 hours after the onset of symptoms to be effective. A series of clinical tasks, including initial assessment, imaging, neurology consultation, image interpretation, excluding contraindications, procurement of medications, informed consent, etc must be done before administration of thrombolytic therapy. Accomplishing these clinical tasks within the limited window period is challenging. Compliance to the critical in hospital time goals set by NINDS may help in overcoming the constraints [5]. These critical time intervals are door-to-imaging time (<25 minutes), door-to-needle time (<60 minutes) and onset-to-needle time (<4.5 hours). In this study, adherence to the time sensitive goals and its relationship with immediate and 90 days neurological outcome were analysed.

In this study, only 39 (35.5%) patients received thrombolytic therapy within one hour of hospital arrival. In the remaining 71 patients (64.5%), the recommended door-to-needle time was not achieved. Other studies conducted in India showed that door-to-needle time varied widely from 27-140 minutes [15,16]. This reflects the constraints in providing thrombolytic therapy in a developing country like India. Analysis of the door-to-imaging time in this study showed that this was more than 25 minutes in the majority of the patients (58.2%). This might be a major limiting step that has led to the prolongation of the door-to-needle time as well as the onset-to-needle time. Further studies are needed to look into other factors that may cause delay in thrombolytic therapy. A significant improvement in NIHSS score after 24 hours of thrombolysis was seen in 66.4% of patients. This was slightly more when compared with other studies done in India where an improvement in NIHSS score was observed for 32-64% of the study subjects [16,11].

On analysing the functional outcome and neurological recovery, it was observed that 69.1% of patients who received thrombolysis became functionally independent at 90 days. Previous studies in India reported a similar efficacy for thrombolytic therapy (48-78%) [11,16,17]. Functional independence with an MRS of 0-2 at three months was reported in 84% of patients in the study done by Tsivgoulis G et al., in Greece [18]. In the study by Chao AC et al., in Taiwan, MRS of 0-2 at 90 days was observed in 53.4 % of the study group [19]. Even though in this study, critical time intervals could not be achieved as per the desired targets, the overall outcome is comparable to other studies.

A significant association between onset-to-door time and 24 hours NIHSS score improvement was observed in this study. The patients who reached the hospital in the window period (within 3 hours) had a better improvement in NIHSS score at 24 hours after receiving thrombolytic therapy compared to those who reached the hospital in the extended window period (between 3-4.5 hours). There was no significant change in the functional outcome at 90 days in these two groups. This difference in finding may be attributed to the lower number of patients in the extended window period group compared to the window period (4.5% and 95.5%, respectively).

Similarly, it has been observed that a significant association exists between 24-hour post-thrombolysis NIHSS score and 90 days functional outcome. Those who have demonstrated significant improvement in NIHSS score after 24 hours of receiving thrombolysis are more likely to achieve favourable functional outcomes at 90 days. All the 12 patients who had worsening of their NIHSS score after 24 hours were eventually found to have unfavourable neurological outcomes at 90 days. This finding was in congruence with the results of the previous studies by Rangaraju S et al., and Heitsch L et al., where 24-hour NIHSS score was found to be a strong predictor of 90-day functional outcome in stroke patients [20,21]. The NIHSS score at 24 hours can prove to be a valuable tool to prognosticate the patients with ischaemic stroke who have received thrombolytic therapy.

Further studies are needed to validate the role of post-thrombolytic NIHSS score as a tool to predict outcome of thrombolytic therapy. The real-life constraints in achieving time bound goals for successful implementation of thrombolytic therapy has to be identified and addressed in a resource limited country like India.

### Limitation(s)

The main limitation of the study was that it was a single-centre observational study. The study had included retrospective analysis and relied upon the documented timings and scores which might not be fully accurate.

## CONCLUSION(S)

The favourable functional outcome at 90 days was established following the intravenous thrombolytic therapy for acute ischaemic stroke. In a majority of patients, the recommended door-to-imaging time and door-to-needle time were not met reflecting the barriers in implementing timely thrombolytic therapy. The NIHSS score at 24 hours post-thrombolysis when compared to the baseline was determined as a good predictor of the neurological outcome at 90 days. Also, subjects who presented within three hours of symptom onset had a significant improvement in NIHSS score at 24 hours compared to those who presented after three hours.

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