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# INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHEMIC STROKE: A TERTIARY CARE CENTRE EXPERIENCE

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**ABSTRACT** **Objective:** To study the outcome of thrombolysis in acute ischemic stroke in our institution over one year period.
**Methods:** A retrospective descriptive study with details taken from cases with acute ischemic stroke who had received IV thrombolysis with rtPA-alteplase and the details were analysed.
**Results:** Out of 41 cases, 28 were males and 13 were females. Mean age was 59, The Mean NIHSS score at admission was 11. The Mean time delay from the onset of symptoms to needle time was 3.5 hours. 22 subjects (53.65%) had achieved primary outcome in this study. 2 (4.87%) patients had significant symptomatic intracranial hemorrhage. Out of 8 total deaths, 5 deaths were due to direct neurological cause including 2 significant bleed. The mean NIHSS at the time of discharge was 9. Among the 33 survived patients 24 (72.72 %) had favorable MRS outcome (0-2) at the end of 3 months.
**Discussion:** There was a significant treatment effect in terms of the primary out come and secondary outcomes along with slightly lesser hemorrhagic complications were consistent with the case studies in the literature. The pharmacogenomics variations in metabolization of rtPA should also be considered.
**Conclusion:** Acute Stroke management should be given priority and due consideration for earlier management. Alteplase significantly improves the overall likelihood of a good stroke outcome at 3–6 months. The proportional benefit increases with earlier treatment.

**KEYWORDS :** Stroke thrombolysis, RTPA, Tissue plasminogen-activator

## INTRODUCTION

Stroke is one of the leading causes of death and disability in India and It represents 1.2% of total deaths in India. During the last decade, the age-adjusted prevalence rate of stroke was between 250 -350/100,000 and annual incidence was 105/100,000 in urban community and 262/100,000 in the rural community. The ratio of cerebral infarct to haemorrhage was 2.21.Over the years, the utilization of rtPA has increased all across the country, but the use is restricted only to urban centres.

## OBJECTIVE

To study the outcome of thrombolysis in acute ischemic stroke in our institution over one year period and to assess the follow up after thrombolysis.

## METHODS

This is a retrospective descriptive study done at Institute of Neurology, Madras Medical College, Chennai a tertiary care referral hospital in South India. Data about patients who received IV thrombolysis for acute ischemic stroke were collected from the medical records section for one year period and analysed.All patient who received IV thrombolysis with rtPA-alteplase for acute ischemic stroke were included for the study.

Patient with symptoms of stroke initially present to emergency room, Clinical assessment -vitals (Pulse Rate, Blood Pressure, Respiratory Rate, Temperature, Oxygen Saturation, pupils), date, time of onset of symptoms were recorded and detailed Neurological assessment with NIHSS were done. All patients were subjected for CT scan to rule out intra cerebral hemorrhage and to confirm ischemic stroke and ECG, CBG, Coagulation profile were done before starting thrombolysis. Patients with high blood pressure were treated with IV Labetalol and titrated according to blood pressure. After controlling blood pressure and excluding exclusion criteria, As per protocol eligible patients were given IV rtPA-alteplase 0.9 mg/kg weight (10% of total dose as bolus and remaining 90% as infusion over 1 hour). Hyperglycemia was managed with insulin sliding scale. Patient was observed in ICU for 24 hours and vitals are continuously monitored. Repeat CT brain was done after 24 hours and early imaging whenever required.

After conforming no bleed on CT brain after 24 hrs. Patients were started on Aspirin 150 mg od. Subjects were discharged based on clinical status of improvement. Patients were reassessed after 3 months with MRS (Modified Rankin Score).

Out of 2500 Ischemic stroke patients we were able to thrombolysis 41 cases who fit into eligible criteria and their data were obtained and analyzed

### Measurements of outcome

***Primary outcome:***

It is defined as the reduction in NIHSS (National Institute of Health Stroke Scale) score by at least 4 points 24 hours after thrombolysis with IV rtPA.

***Secondary outcome:***

It is assessed after 3 months with MRS (Modified Rankin score). MRS score of 0 to 2 is considered as favorable outcome.

***Symptomatic intracranial hemorrhage***

It is defined as any intracranial hemorrhage with neurologic deterioration, as indicated by an NIHSS score that was higher by 4 points or more than the value at baseline or any hemorrhage leading to death.

***Asymptomatic intracranial hemorrhage***

It includes all intracranial hemorrhages that do not meet the definition of symptomatic intracranial hemorrhage.

## RESULTS

Total number of patients received thrombolysis were 41, among them 28 were males and 13 were females.33 (80.5%) cases were due to anterior circulation stroke and 8 cases (19.5%) were due to posterior circulation stroke.

Age distribution**:** Mean age was 59 ,age distribution shown below

| Age range | No. of patients | Percent of Total |
|---|---|---|
| 20 to 40 | 5 | 12.19 |
| 41 to 60 | 19 | 46.3 |
| 61 to 80 | 16 | 36.02 |
| >80 | 1 | 0.24 |

The Mean NIHSS score at admission was 11 and their distribution as mentioned below

**National institute of health stroke scale Score (NIHSS) at admission.**

| Score | No. of patients | Percent of Total |
|---|---|---|
| 5-9 | 3 | 7.3% |
| 10-15 | 23 | 56.09% |
| 16-20 | 11 | 26.82% |
| 21-25 | 4 | 9.75% |
| >25 | 1 | 2.43% |

**Time from the onset of symptoms to needle time:**

The Mean time delay from the onset of symptoms to needle time was 3.5 hours Majority of patients received thrombolysis after 3 hours .The delay is due to late arrival to hospital after stroke symptoms.

| Time (symptom onset to needle ) | No. of patients | percent |
|---|---|---|
| <3 hours | 7 | 17.08% |
| 3-4.5 hours | 34 | 82.92% |

The Primary outcome is defined as NIHSS reduction by at least 4 points, 24 hours after thrombolysis. 22 patients (53.65%) had achieved primary outcome in this study.

| Primary outcome | No. of patients | percent |
|---|---|---|
| present | 22 | 53.65 |
| Not obtained | 19 | 46.34 |

Regarding hemorrhagic complication, 2 (4.87%) patients had significant symptomatic intracranial hemorrhage and subsequently underwent decompressive craniotomy. Despite these measures these 2 patients had expired. Also 10 patients had subtle asymptomatic hemorrhagic transformation, but all these patients had shown clinical improvement at the time of discharge.

| Haemorrhage complication | No. of patients | percent |
|---|---|---|
| symptomatic intracranial hemorrhage | 2 | 4.87% |
| asymptomatic hemorrhagic transformation | 10 | 24.39% |

**Regarding larger size of infarct** about 10 patients had developed significant size of infarct with mass effect warranting decompressive craniotomy and among them 3 had expired .Most of these patient had a relatively higher NIHSS score

**Regarding death outcome**, there were 8 deaths. 5 deaths were due to direct neurological cause (2 patients Hemorrhagic complications, 3 patients had larger infarct and mass effect). Among the remaining 3 non neurological deaths, 2 deaths were related to ventilator related events and 1 was due to sepsis.

Regarding outcome at the time of discharge, the mean NIHSS at discharge was 9 Most of the patient noted to have improving trend in Neurological deficit at the time of discharge

| Score at discharge | No. of patients | Percent of Total |
|---|---|---|
| 5-9 | 17 | 41.46 |
| 10-15 | 12 | 29.26 |
| 16-20 | 4 | 9.75 |
| >20 | 0 | 0 |
| Death | 8 | 19.51 |

The Secondary outcome was measured with MRS Score after 3 months of thrombolysis. MRS Score of 0 to 2 is considered as favorable outcome. Among the 33 survived patients 24 (72.72 %) had favorable MRS outcome (0-2) at the end of 3 months.

| MRS score | No. of patients | Percent |
|---|---|---|
| 0 | 3 | 9.09 |
| 1 | 9 | 27.27 |
| 2 | 12 | 36.36 |
| 3 | 5 | 15.15 |
| 4 | 3 | 9.09 |
| 5 | 1 | 3.03 |
| 6 | 0 | 0 |

## DISCUSSION

Thrombolysis with intravenous tissue-type plasminogen activator (IV tPA) is the approved treatment for patients with acute ischemic stroke (AIS) within window period of 4.5 hours. Although the proportion of patients treated with IV tPA has steadily increasing since it was approved in 1996, the treatment rate is still lower.

The ECASS authors pointed out that the failure to demonstrate a treatment effect could be attributed to major protocol violations that resulted in the incorporation of patients who did not meet the study's CT inclusion criteria into the final analysis-a group that comprised 17.4% of the entire cohort. The study results were impacted by these widespread protocol violations and the inclusion of patients treated up to 6 hours after symptom onset. Also ECASS-I used a higher dose of IV tPA [1,2].

NINDS trial [2] demonstrated a significant difference for each outcome measure in favor of the IV tPA group. In terms of adverse outcomes, the rate of symptomatic ICH (sICH) was significantly higher in the IV tPA group (6.4% vs 0.6% in placebo group, P < .001).

ECASS-II [3,4] was designed to evaluate whether a lower tPA dose of 0.9 mg/kg would be efficacious in an extended time window of up to 6 hours. ECASS-II also used slightly modified CT exclusion criteria swelling exceeding 33% of the middle cerebral artery territory excluded patients from ECASS-II. With the strokes were less severe with a median NIHSS of 11. There was a significantly higher rate of sICH in the IV tPA group overall (8.8% vs 3.4%), but no significant difference in the mortality rate between the treatment and the placebo groups for the 3- to 6-hour time window.1The results revealed a non-significant odds ratio (OR) of 1.2 (95% confidence interval [CI] 0.8-1.6) favoring the 3- to 6-hour window tPA group. There was a significantly higher rate of sICH in the IV tPA group overall (8.8% vs 3.4%), but no significant difference in the mortality rate between the treatment and the placebo groups for the 3- to 6-hour time window.

The alteplase thrombolysis for acute non interventional therapy in ischemic Stroke (ATLANTIS) trial [5,] there was a significantly higher rate of both asymptomatic ICH and sICH in the tPA group but no difference in mortality rates at 30 or 90 days. The primary outcome measure was excellent neurologic recovery (NIHSS 0 or 1) at 90 days.Secondary outcomes were excellent functional recovery (MRS, BI, and GOS) at 30 and 90 days. There was no significant difference in the primary outcome nor was there any significant treatment effect for any of the secondary outcomes. Of note, as was seen in the NINDS tPA trial, there was a significantly higher rate of both asymptomatic ICH and sICH in the tPA group but no difference in mortality rates at 30 or 90 days.

A pooled analysis 6 of ATLANTIS, ECASS-I, and NINDS was published in 2004. This study showed that while the benefit of tPA, expressed as the OR of a favorable outcome, diminishes over time, a potential treatment benefit could be still seen through the 3- to 4.5-hour window (OR 1.4, 95% CI 1.1-1.9). Furthermore, the adjusted hazard ratio for death was not significantly worse in the extended time window compared to the standard 3-hour time window. These results suggested that extending the time window could safely provide a clinical benefit

Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) [7] in 2008 evaluated the use of IV tPA in the 3- to 6-hour window after symptom onset in select patients with perfusion–diffusion mismatch on magnetic resonance imaging (MRI) . Mean infarct growth trended lower in the treatment group and reperfusion was significantly higher in the IV tPA group. Although there was a nonsignificant trend toward good neurological and functional outcomes in the treatment group, achieving reperfusion was associated with good neurological and functional outcomes. It suggested that in carefully selected patients, reperfusion after 3 hours might offer good neurological and functional outcomes

The third ECASS ECASS III [8] trial aimed to definitively answer the question of whether IV tPA in the 3- to 4.5-hour window was safe and effective. IV tPA in the extended time window is efficacious. The rate of sICH was significantly higher in the IV tPA group even when all commonly used definitions of sICH were applied there was no difference in the mortality rate, which suggested that IV tPA in the extended time window was safe.

The SITS-International Stroke Treatment Registry (SITS-ISTR)[9] they reported no significant difference in rates of sICH, mortality, and functional independence (MRS < 2) at 3 months in patients treated within the 3-hour and the 3- to 4.5-hour time windows.

In 2010, the updated pooled analysis [10] of ATLANTIS, ECASS-I, and

NINDS updated with data from ECASS-II, ECASS-III, and EPITHET. The treatment effect size decreased as the time from stroke onset increased. Although the IV tPA group was significantly more likely to have sICH, there was no difference in mortality between the control and IV tPA groups for the 3- to 4.5-hour time window. This analysis suggested that there was some benefit of IV tPA in the extended time window but likely not past 4.5 hours.

In response to the exclusion of older patients in prior stroke trials, the third International Stroke Trial (IST-3) [11] was conducted the study demonstrated a greater benefit for IV tPA in patients older than 80.

Cochrane review [12] suggested after review included data from 27 trials involving 10 187 patients that thrombolytic therapy given up to 6 hours after onset of symptoms significantly reduced the likelihood of death or dependency (mRS 3-6) at 3 to 6 months after stroke and patients older than 80 years of age benefited just as much as younger patients.

Analysis of GWTG data from 32 019 patients who were treated with IV tPA for AIS revealed that patients treated in the extended window were significantly more likely to be ambulatory at discharge and to be discharged home without a significant difference in mortality or sICH when compared to patients treated in the standard time window.[13]

Thomalla G et al "concluded that the outcome of IV-tPA therapy in an expanded time window of 6 hours in MRI selected patients was better than in unselected patients from the pooled rtPA stroke trials".[14]

Schellinger PD et al compared "MRI based thrombolysis" with "CT based thrombolysis".They concluded that "MRI based thrombolysis" was more effective and safer than the "CT based thrombolysis [15] Ogata T et al reviewed data from two studies using alteplase in patients with acute stroke 3-6 hours after its onset in two groups of patients i.e. EPITHET and DEFUSE groups while using the outcome based on MRI. They concluded that alteplase improved the re-perfusion rates significantly. [16]

In our case series for thrombolysis for Ischemic stroke, the mean time interval from the onset of symptoms to needle time for thrombolysis was 3.5 hours (210 minutes). The major portion of this delay is due to late arrival to hospital.

About 53.65 % had obtained the defined primary outcome of significant reduction in NIHSS stroke scale. One patient who was 81 years old also had significant improvement after 3 months.

Regarding complication following thrombolysis two patients (7.69%) had significant symptomatic intra cranial hemorrhage and expired which can be attributed to multi factorial reasons like higher NIHSS and larger infarct size and associated multiple comorbidities. The significant post thrombolytic related bleeding complication was less in this case series when compared to other studies.

The mortality in 3 patients were due to larger infarct size and significant mass effect correlated with the higher NIHSS and the other 2 cases were due to hemorrhagic complication of thrombolytic therapy along with larger infarct size which were not salvageable even with decompressive craniotomy .

About 69 % had improving trend in NIHSS in comparison to admission NIHSS at the time of discharge. In overall about 24 patients (58.53%) had a favorable outcome with MRS scale of 0- 2 at the end of 3 months. These findings were consistent with the previous studies in the literature.

Saposnik G et al had suggested that the "SPAN-100 index could be a simple method for estimating the clinical response and risk of hemorrhagic complications after rtPA for acute ischemic stroke". [17]

The pharmacogenomic variations in metabolization of rtPA should also be considered. (Apo E4 phenotype) while considering the haemorrhagic complication issues with thrombolytic therapy.

A larger cohort is required for better statistical significance to analyse well about the efficacy and other aspects of thrombolytic therapy.

## CONCLUSIONS

Acute Stroke management should be given priority and due consideration for earlier management. Hence sensitisation of earlier acute stroke management to be improved by providing adequate awareness for the public as well as the referring medical professionals so as to refer to appropriate designated stroke care units in time**.**

The efficacy of rtPA had been already well established by various trials is well illustrated in this case series also. Despite some risk of fatal intracranial hemorrhage, alteplase significantly improves the overall likelihood of a good stroke outcome at 3–6 months. The proportional benefit increases with earlier treatment and remains statistically significant up to at least 4·5 h after initial stroke symptoms, irrespective of age or stroke severity. A larger cohort is required for better statistical significance.

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