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Original Research Article

Acute ischemic stroke thrombolysis- experience from a rural hospital in Kerala, India

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ABSTRACT

Objective: Outcome assessment of thrombolysis with intravenous rt-PA in acute ischemic stroke.
Materials and Methods: All patients with acute ischemic stroke patients who underwent IV thrombolysis with rt-PA from January 2019 to December 2021 were studied retrospectively. Clinical efficacy outcome was the favourable outcome on modified Rankin scale at 90 days defined as a score of ≤2.
Results: During our study period, a total of 50 patients with ischemic stroke thrombolysis underwent intravenous recombinant tissue plasminogen activator (rt-PA). The study consisted of 33 males and 17 females with a mean age of 64.82 (12.21 standard deviation) years. The median time from onset of symptoms to IV rt-PA administration was 120 minutes (interquartile range 90 - 160). The mean door to needle time was 50.1 (21.32 SD) minutes. Favourable outcome (mRS score ≤2) was observed in 38 patients (76%) at three months' follow-up. Poor outcome (mRS score >2) was seen in the remaining 12 patients (24%). Large artery atherosclerosis had the most favourable outcome followed by small vessel occlusive stroke. Factors predicting favourable outcome in our study were age <60 years ($p = 0.03$), female gender ($p < 0.001$) and large vessel occlusion ($p < 0.001$). Factors predicting poor outcome were hypertension ($p < 0.001$), dyslipidemia ($p = 0.01$), prior stroke ($p < 0.001$) and symptomatic haemorrhage ($p = 0.02$).
Conclusion: Ischemic stroke patients can be thrombolysed in a safe and effective even in rural settings if proper institutional protocol is formulated and its implementation is ensured.

1. Introduction

World stroke organization report in 2017 states that stroke is the leading cause of disability and the second leading cause of death globally. Stroke kills about 6 million people per year and non-fatal stroke affects about 11 million people every year. As per the report, 40 to 50 per cent of survivors are permanently disabled.[1]

Administration of intravenous recombinant tissue plasminogen activator(rt-PA) in acute ischemic stroke(AIS) within 3 hours of symptom onset has been known to improve the outcome as per the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke study.[2] The patients thus treated with rt-PA had a 30% relative risk reduction of the death or disability at 90 days follow up. This benefit was observed in small vessel and large vessel strokes as well as cardio-embolic strokes.

Our hospital is a 400-bed multi speciality tertiary care centre in Kozhencherry, a rurally located village in Pathanamthitta district of Kerala State, South India. We started the thrombolytic therapy for acute ischemic stroke in June 2005. Here we review our 2-year experience with thrombolysis in ischemic stroke from January 2019 to December 2021.

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2. Materials and Methods

All patients with AIS within 4.5 hours of symptom onset, who underwent thrombolysis with intravenous rt-PA from January 2019 to December 2021 were studied retrospectively. In total 50 patients were analysed. A neurologist clinically evaluated all patients and non-enhanced Computed Tomography (CT) scan was taken at the time of presentation. Inclusion and exclusion criteria were according to American Stroke Association guidelines. Informed consent was obtained after explaining the potential benefits and risks including the possibility of intracerebral haemorrhage. Labetalol was used to control blood pressure when indicated. All patients were treated with IV rt-PA (Alteplase, Boehringer-Ingelheim, Ingelheim, Germany). The dose used was 50mg in most patients. Patients were admitted in stroke unit and Magnetic Resonance Imaging (MRI) scan brain was taken at 24 hours, before starting antiplatelet agents. All patients who remained stable for 48 hours were shifted to the ward.

The National Institute of Health Stroke Scale (NIHSS) was recorded at presentation, day 1, day 7 and 3 months. The modified Rankin Scale (mRS) score was recorded at discharge and at 3 months. Clinical efficacy outcome was the favourable outcome on modified Rankin scale at 90 days defined as a score of ≤2. Patients were followed up in the outpatient department at 2 weeks and 3 months after discharge.

Data collected include demographic characteristics, presenting symptoms, risk factors, time of symptom onset (the time they were last seen to be well), onset to needle time (the time from symptom onset to rt-PA administration) and door to needle time (the time from presentation to the hospital to initiation of thrombolysis). Patients were sub typed into a large vessel, small vessel and cardio-embolic stokes. Symptomatic intracerebral haemorrhage (ICH) was defined as per NINDs rt-PA stroke study criteria (haemorrhage associated with worsening of one or more points on NIHSS scores).[2]

2.1. Statistical analysis

Baseline characteristics were represented as frequency with percentage for categorical variables; mean ± standard deviation for normally distributed continuous variables and mean with interquartile range for skewed continuous variable. Normality of the data was assessed using skewness, kurtosis and by constructing histogram. Proportions were analysed using chi square test and Fischer exact test if any of cell frequency was < 5. The predictors of outcome were determined by univariate analysis that included the following variables: Demographic (gender, age), risk factors such as hypertension, DM, dyslipidemia, coronary artery disease, atrial fibrillation, old stroke, hypothyroidism, smoking and alcohol use, NIHSS score at admission and discharge, onset to needle time, symptom onset to rt-PA time, symptomatic intracranial haemorrhage and subtypes. Variables with a significant P value (≤0.05) in univariate analysis were considered for multivariate analysis (logistic-regression analysis). Statistical analyses were performed using STATA software Version 15.0.

3. Results

During our study period, a total of 50 patients underwent ischemic stroke thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA). The study consisted of 33 males and 17 females with a mean age of 64.82 (12.21 standard deviation) years. Hypertension was the most common risk factor (60%) followed by diabetes mellitus (54%). Smoking and alcohol intake were the other common risk factors involved (40% each). Among the stroke subtypes large artery stroke atherosclerosis was the most common (58%), followed by small vessel occlusive stroke (24%).The median time from onset of symptoms to IV rt-PA administration was 120 minutes (interquartile range 90 - 160). The mean door to needle time was 50.1 (21.32 SD) minutes. The median NIHSS score at presentation was 8 (interquartile range 6-10) while at discharge the median score was 7 (interquartile range 5-9). The dose of IV rt-PA used was 0.9 mg/kg body weight. The characteristics of the study subjects are depicted in Table 1.

Table 1: Characteristics of study subjects

Age (in years)	**64.82 12.21** *
Sex (Male:Female)	33:17
NIHSS score at presentation	8 (6-10) #
NIHSS score at discharge	7 (5-9) #
Symptom onset to rTPA (in minutes)	120 (90-160) #
Door to needle time (in minutes)	50.1 21.32 *
Symptomatic ICH n= (%)	1 (2)
Risk factors n= (%)	
Diabetes mellitus	27 (54)
Hypertension	30 (60)
Dyslipidemia	10 (20)
Coronary Artery Disease	9 (18)
Atrial Fibrillation	13 (26)
Hypothyroidism	4 (8)
Prior history of stroke	7 (14)
Smoking	20 (40)
Alcohol intake	20 (40)
Ischemic stroke subtype n= (%)	
Large artery atherosclerosis	29 (58)
Small vessel occlusive stroke	12 (24)
Cardioembolism	8 (16)
Undetermined	1 (2)

*Value expressed as mean±SD; #Value expressed as median (interquartile range)

3.1. Outcome at 3 months

Favourable outcome in the form of functional independence (mRS score ≤2) was observed in 38 patients (76%) at three months' follow-up. Poor outcome (mRS score >2) was seen in the remaining 12 patients (24%).

3.2. Outcome on the basis of stroke subtype

The outcome at 3 months of various ischemic stroke subtypes following IV rt-PA administration is shown in Table 2. Large artery atherosclerosis had the most favourable outcome followed by small vessel occlusive stroke. However one patient (2%) with large artery atherosclerosis was the one to have symptomatic intracranial haemorrhage. None of our patients succumbed to the illness in the three-month follow-up.

Table 2: Outcome at 3 months of various ischemic stroke subtypes

Stroke subtype	Favourable outcome, n= (%)	Poor outcome, n= (%)	p value
Large artery atherosclerosis	23 (60.53)	6 (50)	0.042
Small vessel occlusive stroke	10 (26.32)	2 (16.67)	0.71
Cardioembolism	4 (10.53)	4 (33.33)	0.08

3.3. Predictive factors of outcome

Factors predicting favourable outcome in our study were age <60 years ($p = 0.03$), female gender ($p < 0.001$) and large vessel occlusion ($p < 0.001$). Factors predicting poor outcome were hypertension ($p < 0.001$), dyslipidemia ($p = 0.01$), prior stroke ($p < 0.001$) and symptomatic haemorrhage ($p = 0.02$).

4. Discussion

India is a developing economy where the burden of non-communicable diseases is steadily increasing. The changing lifestyle patterns is contributing heavily in this regard. Stroke is one of the leading causes of morbidity and mortality in India. The estimated adjusted prevalence rate of stroke range, 84-262/100,000 in rural and 334-424/100,000 in urban areas.[3] There are still several hurdles in implementing a proper stroke protocol initiative in India including poor patient awareness, transport delays and the high cost of IV rt-PA. It is in this background we have developed a modified stroke protocol for our institution which is in place since the early part of this millennium. We have this dedicated stroke unit located in a rural area where this study was conducted. To our knowledge all the prior stroke thrombolysis studies were conducted in urban population and hence the importance of this study.

The present study comprised the data of 50 patients who underwent IV thrombolysis with rt-PA. The data was collected over a 3-year period. The study included 33 males and 17 females whose mean age was 64.82 (12.21 standard deviation) years. Hypertension (60%) and diabetes mellitus (54%) were the most prominent risk factors involved.

We could achieve mean door to needle time period of 50.1 (SD 21.32) minutes. The recommended target of American Heart Association/American Stroke Association is ≤60 min.

Three months follow-up revealed favourable outcome in the form of functional independence (mRS score ≤2) in 38 patients (76%) and poor outcome (mRS

score >2) in the remaining 12 patients (24%). In a study by Litwin et al., 61% patients had favourable outcomes whereas in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), 54% patients had a good outcome.[4,5] In the NINDS trial favourable outcome was observed in only 39% patients.[2]

In our study large vessel atherosclerotic stroke carried a more favourable outcome. This is seen contradicting to the prior studies. Studies by the Helsinki Stroke Thrombolysis Registry Group and Pan et al. reported that patients with small-vessel disease strokes were likely to have a good outcome.[6,7] Molina et al., observed that the rate of complete recanalization at 6 h was higher in patients with cardioaortic embolic (CE) stroke.[8] This contradiction may be due to the fact that early recognition of the symptoms and the severity of these symptoms at onset in large artery stroke may alert the relatives to bring in the patient at the earliest.

The rate of symptomatic haemorrhage in our study was 2% as compared to 3.3% in the Standard Treatment with Alteplase to Reverse.

Stroke study and 6.4% in the NINDS study.[9]

A review by Meseguer et al. showed no evidence of gender differences in outcomes.[10] However, in our study, female gender showed favourable outcome at the end of three months.

Dyslipidemia was a factor predicting poor outcome in our study. This is due to the formation of non-dissolvable lipid-rich thrombus, which could in turn cause larger infarction and haemorrhagic transformation.[11] The other factors predicting poor outcome in our study were hypertension, prior stroke and symptomatic haemorrhage.

Our study has certain limitations. First, we observed the results in a small number of patients. The findings need to be confirmed with a larger sample size study which is underway at our hospital. Secondly it is a single-centre experience, and we assumed that this sample was representative of the rural population in India as a whole.

5. Conclusion

In conclusion, ischemic stroke patients can be thrombolysed in a safe and effective manner at par with accepted

international standards even in rural settings, if proper institutional protocol is formulated and its implementation is ensured. A larger prospective study is required to further delineate areas where further interventions can be made to improve stroke outcome.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

7. Source of Funding

None.

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