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Original Research Article

Clinical profile of patients with acute ischemic stroke receiving intravenous thrombolysis (rtPA-alteplase)

Shiva Prasad Jagini[1], Suresh I[2]*

[1]Assistant Professor, Department of General Medicine, Kamineni Academy of Medical Sciences and Research Centre, LB Nagar, Hyderabad, Telangana, India
[2]Assistant Professor, Department of General Medicine, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda Dist., Telangana, India

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***Correspondence:**
Dr. Suresh I,
E-mail: icyisu@yahoo.co.in

ABSTRACT

Background: Stroke patients are at highest risk death in the first few weeks after the event, and between 20-50% die within first month depending on type, severity, age, co-morbidities and effectiveness of treatment of complications. Objective of this study was to clinical profile of patients with acute ischemic stroke receiving intravenous thrombolysis (rtPA-alteplase).
Methods: Prospective Observational study of 26 cases of acute ischemic stroke receiving IV thrombolysis using rtPA-alteplase at Kovai Medical Centre Hospital, Coimbatore over a period of 1 year 9 months.
Results: 21 cases had NIHSS score of range 10 to 22. The mean NIHSS score at admission is 13.5. 15 subjects (57.7%) had achieved primary outcome in this study. MRS Score of 0 to 2 is considered as favorable outcome. In this study 20 subjects (76.92 %) had favorable outcome at the end of 3 months.
Conclusions: Majority of the patients receiving rtPA-alteplase had favorable outcome.

Keywords: Outcome, rtPA-alteplase, Stroke

INTRODUCTION

Stroke is a worldwide health problem. It is one of the most common causes of morbidity, mortality, in developed as well as in developing countries.

WHO defined stroke as "rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin".

Cerbrovascular disease is one of the leading causes of death. In 2008, the estimated deaths worldwide due to cerebrovascular disease was 6.1 million, equivalent to 10.8% of all deaths worldwide.

In India, the prevalence of stroke is less compared to that of developed countries but the proportion of stroke in young population is significantly more in India than that of in developed countries.

In India, the prevalence of stroke is about 1.54 per thousand. The total number of stroke cases estimated in the year 2004 were about 9.3 million with about 0.63 million deaths.[1]

Stroke patients are at highest risk death in the first few weeks after the event, and between 20-50% die within first month depending on type, severity, age, co-morbidities and effectiveness of treatment of complications.

Present study was conducted with the objective to study clinical profile of patients with acute ischemic stroke receiving intravenous thrombolysis (rtPA-alteplase).

METHODS

Prospective Observational study of 26 cases of acute ischemic stroke receiving IV thrombolysis using rtPA-alteplase at Kovai Medical Centre Hospital, Coimbatore over a period of 1 year 9 months (October 2012 to June 2014).

Inclusion criteria

- All cases with acute ischemic stroke receiving IV thrombolysis with rtPA-alteplase.
- Age ≥18 years.

Exclusion criteria

- Severe head injury
- Subarachnoid hemorrhage.
- Puncture of arteries

This study is done in Kovai Medical Centre and Hospital, Coimbatore. Subjects presented with acute ischemic stroke receiving IV rtPA-alteplase are included in this study.

Subjects are received in the emergency department, assessed by emergency medical officer and informed to neurologist or postgraduate in medicine.

After clinical assessment vitals (Pulse Rate, Blood Pressure, Respiratory Rate, Temperature, Oxygen Saturation, pupils), date, time of onset of symptoms are recorded.

Routine blood tests (Sugar, Hemoglobin, Total Leukocyte Count, Differential Count, Platelet Count, Creatinine, SGPT, Sodium, Potassium, Calcium, TSH, Prothrombin time, INR, aPTT, lipid profile) were done immediately for all the subjects.

Electrocardiogram (ECG), Chest X Ray are done for all the subjects

Neurologist clinically assess each subject, note NIHSS score of each of them at initial assessment.

Then subjects are subjected to either CT scan or MRI Brain to confirm that it is case of ischemic stroke. Cases in which there was difficult in making decision to thrombolyse with IV rtPA-alteplase based on CT scan findings were subjected to MRI Brain (DWI – Diffusion weighted imaging, ASL – Arterial Spin Labeling, MRA – MR Angiogram).

Blood test (platelet count, PT, INR, aPTT) reports were collected before starting thrombolysis, confirmed to meet exclusion criteria.

Cases with high blood pressure were treated with IV antihypertensive (nimodipine infusion), titrated according to blood pressure.

After controlling blood pressure, excluding exclusion criteria cases were given IV rtPA-alteplase 10% of total dose as bolus and 90% of total dose as infusion over 1 hour).

They were treated with IV fluids, antihypertensive, statins, neuro-protective agents, insulin and oral hypoglycemic agents for diabetics.

For the first 24 hours all patients were admitted in ICU care, vitals are continuously monitored and all subjects are assessed at regular intervals.

Follow up CT Scan Brain is taken in all subjects after 12 to 24 hours of thrombolysis based on clinical status of each subject.

Antiplatelets (Ecosprin) and anticoagulants (Heparin / LMWH) are started based on clinical status of each subject and follow up CT scan by the Neurologist.

The dose of antiplatelets and anticoagulants are fixed by the neurologist.

NIHSS score was assessed 24 hours after thrombolysis for all the subjects.

Subjects with significant edema of the infarct, symptomatic hemorrhage are treated with anti-edema measures, decompressive craniotomy and ventilatory support as required.

Carotid Doppler and Echocardiography is done for all subjects by expert radiologist and cardiologist.

After stabilization, subjects were given adequate physiotherapy, occupational and speech therapy.

Subjects are discharged based clinical status of each by the neurologist.

Subjects are reassessed after 3 months with MRS (Modified Rankin Score)

Primary outcome

It is defined as 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.

Statistical analysis

- IBM SPSS VERSION 20 is used for statistical analysis,
- Discrete variables like age are analysed for mean, median and standard deviation,
- Pie charts and bar diagrams are used for analysis.

RESULTS

Table 1: Time of onset of symptoms to needle time (window period).

Window period	No. of subjects	% of total
<=4.5 hours	24	92.30
>4.5 hours	2	7.70

In this study the mean and median time period from onset of symptoms to needle are 184 and 180 minutes respectively.

Table 2: Door to needle time.

Door to needle time	No. of subjects	% of total
<= 30 minutes	2	7.70
31 to 45 minutes	10	38.46
46 to 60 minutes	10	38.46
>60 minutes	4	15.38

The mean door to needle time is 54.42 minutes, median is 50 minutes. 4 cases had door to needle time of more than 60 minutes as patient attendees delayed to give consent about IV thrombolysis after explaining pros and cons of IV rtPA.

Table 3: Dose of rtPA (Alteplase).

Dose in mg (Bolus + Infusion)	Number of subjects	%
5+45	23	88.5
5+15	03	11.5

23 cases received a dose of rtPA 0.6 mg/kg body weight. 10% of total dose is given as bolus, remaining as infusion over 1 hour. 3 cases received 20 mg of IV rtPA, of which 1 case was already on dual antiplatelets, 1 case was on anti-platelet plus oral anticoagulant, 1 case was more than 80 years of age.

Table 4: National institute of health stroke scale Score (NIHSS) at admission.

Score	Number of subjects	% of total
5 – 9	4	15.38
10 – 22	21	80.77
23 – 42	1	3.85

21 cases had NIHSS score of range 10 to 22. The mean NIHSS score at admission is 13.5.

Table 5: Primary outcome.

Primary outcome	No. of subjects	% of total
Present	15	57.7
Absent	11	42.3

Primary outcome is defined as NIHSS reduction by at least 4 points, 24 hours of after thrombolysis. 15 subjects (57.7%) had achieved primary outcome in this study.

Table 6: First dose of ecosprin.

Dose of ecosprin (milligram)	No.	%
50	4	15.38
75	9	34.62
150	9	34.62
325	4	15.38

After thrombolysis, the first dose of ecosprin was decided by the clinician according to patient's clinical status of each case and follow up CT scan, which was taken 12 to 24 hours after thrombolysis.

Table 7: Time interval between thrombolysis and first dose of ecosprin.

Time interval	No. of subjects	% of total
At 12 hours	11	42.31
12 to 24 hours	14	53.85
More than 24 hours	1	3.84

The time between thrombolysis and first dose of ecosprin was decided by the clinician after assessing the clinical status of each case and follow up CT scan.

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. 2 (7.69%) cases had symptomatic intracranial hemorrhage.

3 (11.54%) cases underwent decompressive craniotomy. Of which 2 cases had symptomatic hemorrhage and 1 case had significant edema surrounding infarct. 1 case developed bed sore as he was bedridden.

Table 8: Complications.

Complication	No. of subjects	% of total
Asymptomatic itch	0	0
Symptomatic itch	2	7.69
Respiratory failure requiring tracheostomy	3	11.54
Decompressive craniotomy	3	11.54
Urinary tract infection	9	34.61
Pneumonia	4	15.38
Sepsis	2	7.69
Bedsore	1	3.84
Deep vein thrombosis (DVT)	0	0
Death	0	0

Table 9: Modified rankin score (MRS) at 3 months.

MRS Score	Number	%
0	4	15.38
1	8	30.77
2	8	30.77
3	1	3.85
4	4	15.38
5	1	3.85
6	0	0

Secondary outcome was measured with MRS Score after 3 months of thrombolysis. MRS Score of 0 to 2 is considered as favorable outcome. In this study 20 subjects (76.92 %) had favorable outcome at the end of 3 months.

DISCUSSION

Clark WM et al found that the risk of symptomatic intra-cerebral hemorrhage was increased with rtPA treatment, particularly in patients treated between 5 and 6 hours after onset.[2] These negative results apply to patients treated after 3 hours, because only 15% of the patients were enrolled before 3 hours.

Tanne D et al noted that the risk of intra-cerebral hemorrhage was more common in the elderly as compared to the young population.[3] They concluded that rtPA treatment was useful in elderly.

Hacke W et al concluded that IV use of desmoteplase given within 3-9 hours among patients with acute ischemic stroke resulted in better outcome than the control group who were gives the placebo.[4] Furlan J et al also reported similar findings as that of Hacke W et al. [5,4] 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".[6]

Yamaguchi T et al concluded that "alteplase, when administered at 0.6 mg/kg to Japanese patients, might offer a clinical efficacy and safety that are compatible with data reported in North America and the European Union for a 0.9 mg/kg dose."[7]

Schellinger PD et al compared "MRI based thrombolysis" with "CT based thrombolysis".[8] They concluded that "MRI based thrombolysis" was more effective and safer than the "CT based thrombolysis".

Lansberg MG et al compared two models viz. [9] "the perfusion–diffusion mismatch model and the clinical–diffusion mismatch model". These models are used as a tool to find which patient with acute stroke can benefit from "reperfusion therapy". The authors concluded that the "the perfusion–diffusion mismatch model" was more precise than the other one.

Hacke W et al found that the incidence of intracranial hemorrhage was more among the patients with alteplase group compared to that with placebo group.[10] But the difference in the mortality rate between the two groups was not found to be statistically significant. But the outcome was significantly better among the patients with alteplase group compared to that of with the placebo group.

Sandercock P et al (IST-3 Collaborative Group) conducted a study "to evaluate sonothromoblysis as a new treatment approach in acute ischemic stroke". [11] They randomized the subjects into two groups viz. the US group and the no US group. US group had better improvement in NIHSS values compared to that of the no US group. Re-canalization was 57.9% in patients of US group compared to only 22.2% among patients of no US group. At the end of three months, four patients of US group had Rankin Score of less than one but no patient from no US group could achieve this. Thus the authors concluded that "transcranial ultrasound on recanalization and short-term outcome in subjects with middle cerebral artery main stem occlusion and recombinant tissue-type plasminogen activator treatment" had a beneficial effect.

Diedler J et al conducted a study and in multivariable analyses, the combination of acetylsalicylic acid and clopidogrel was associated with increased risk for symptomatic intracranial hemorrhage per ECASS II.[12] However, they found no significant increase in the risk for mortality or poor functional outcome, irrespective of the Anti-platelet subgroup or Symptomatic intracranial hemorrhage definition. This analysis concluded that the absolute excess of Symptomatic intracranial hemorrhage of 1.4% (2.1%) in the pooled Anti-platelet group is small

compared with the benefit of thrombolysis seen in randomized trials. Although caution is warranted in patients receiving the combination of acetylsalicylic acid and clopidogrel, Anti-platelet treatment should not be considered a contraindication to thrombolysis.[12]

Tsivgoulis G et al evaluated effectiveness of thrombolysis enhanced by ultrasound in comparison to IV rtPA.[13] They found that symptomatic intra-cerebral hemorrhage and recanalization rates were compared between rtPA, rtPa + Transcranial Doppler +/- microspheres, rtPA + Transcranial color-coded duplex +/- microspheres, and rtPA + low frequency ultrasound. This study concluded that the present safety and signal of efficacy data of high frequency ultrasound enhanced thrombolysis should be taken into account in the design of future randomized controlled trials.

Mullen MT et al in their Meta analysis compared six re-perfusion strategies.[14] They concluded that statistically there was no significant difference between these six re-perfusion strategies. They recommended new randomized clinical trials to find out the most effective re-perfusion strategy among these six.

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.[15] They concluded that alteplase improved the re-perfusion rates significantly.

Manawadu et al conducted, a case-controlled comparison of thrombolysis outcomes between wake-up and known time of onset ischemic stroke patients.[16] The baseline median NIHSS scores were comparable between the groups. The authors concluded that "thrombolysis in selected patients with Wake up Ischemic Stroke is feasible, and its outcomes are comparable with those thrombolysed with 0 to 4.5 hours".

Zaki AM et al concluded that "Sonothrombolysis is a therapeutic option to improve the outcomes in patients with acute ischemic stroke due to middle cerebral artery occlusion".[17]

Saposnik G et al concluded 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".[18]

CONCLUSION

Stroke being a medical emergency should be treated as fast as possible. Creating awareness among local population will help in reducing the time taken for bringing the patient to hospital. An organized stroke team will help in reducing door to needle time. Advanced techniques like endovascular thrombolysis will help in few cases. Trans Cranial Doppler (TCD) will be helpful in few selected cases. It is a simple, non-invasive bedside tool to assess cerebral hemodynamics, to confirm occlusion of major intracranial blood vessels and also help to assess recanalization or re-occlusion. TCD is also a therapeutic tool as sonothrombolysis as demonstrated in few subjects of our study. Majority of the patients receiving rtPA-alteplase had favorable outcome.

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