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Original article

Clinical Characteristics of Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis

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Abstract

Background and Aim: Stroke is one of the most common causes of morbidity, mortality, in developed as well as in developing countries. 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. Aim of this study was to clinical profile of patients with acute ischemic stroke receiving intravenous thrombolysis (rtPA-alteplase).

Material and Methods: Prospective Observational study of 30 cases of acute ischemic stroke receiving IV thrombolysis using rtPAalteplase at Tertiary care Institute of Gujarat, India. NIHSS score was assessed 24 hours after thrombolysis for all the subjects.

Results: 25 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. 5 cases received 20 mg of IV rtPA, of which 2 cases was already on dual antiplatelets, 2 cases was on anti-platelet plus oral anticoagulant, 1 case was more than 80 years of age. Primary outcome is defined as NIHSS reduction by at least 4 points, 24 hours of after thrombolysis. 18 subjects had achieved primary outcome in this study. 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 23 subjects (76.66 %) had favorable outcome at the end of 3 months.

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.

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Key Words: Morbidity, rtPA-alteplase, Stroke, Thrombolysis

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". About 85.5% of stroke deaths worldwide are accounted from the low and middle income countries in the Asia-Pacific region, and the number of disability-adjusted life-years in these countries is reported to be seven times higher than in the high-income countries.[1] In India, absolute number of stroke deaths have increased in the past two decades with a 100% increase in stroke incidence from 1970- 1979 to 2000-2008.[2]

Stroke has defied the considerable efforts of medical science to find an effective treatment and remains the third most common cause of death in the developed world, preceded only by ischemic heart disease and all cancers combined.[3] However, unlike ischemic heart disease and cancer, stroke leaves many more people disabled and dependent on family and social or health services. Despite a decline in stroke mortality in some but not all countries,1 there is rather little evidence of a decline in incidence.[4] Therefore, anticipated demographic changes, and thus increasing stroke numbers, make it even more important to find an effective treatment.[5]

Therapeutic approaches should reflect logical application of our present understanding of the sequence of events in the ischemic brain leading to cerebral infarction. After interruption of the blood supply, some tissue probably suffers irreperable damage within minutes, but a variable amount remains in a "shut-down" but viable state for several hours.[6] Neutralization of toxic metabolites released from infarcted cells or restoration of the blood supply might save the ischemic tissue and improve outcome. Thus two basic approaches have evolved: 1) to protect ischemic but still viable neurons from further damage by toxic metabolites and 2) to improve the blood supply to ischemic brain.

Using the first approach, nimodipine has not been shown to be of any benefit in moderately large groups of patients.6 Newer excitatory amino acid antagonists are being evaluated but may have unacceptable toxicity, and it remains to be seen whether the benefit in animals can be translated into benefit in elderly stroke patients.[7] Using the second approach, hemodilution is ineffective in the generality of ischemic stroke patients.[8] Antithrombotic therapy (with heparin, warfarin, or aspirin) has not been properly tested in large randomized clinical trials. Although variably used in acute stroke we do not know if these drugs improve outcome.[9] A randomized trial of aspirin and heparin in acute ischemic stroke has begun in Europe. That leaves thrombolysis, a theoretically attractive treatment with proven ability to dissolve arterial thrombus elsewhere in the body but with the potentially unattractive adverse effect of converting a simple (pale) infarct into a hematoma. Thrombolytic drugs were first used in the late 1950s for acute stroke.[10,11] Since then over 2,800 patients have been reported in the world literature. Despite this we do not know if thrombolysis works, nor what the risks of treatment are. Most of the literature consists of case

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reports or small series, with only six small randomized trials.[12- 17] Given the heterogeneity of the pathogenesis and outcome of acute ischemic stroke and that the magnitude of any treatment effect may be modest, both a proper control group and adequate numbers of patients are essential to ensure an unbiased and precise trial result.[18]

Material and Methods

Prospective Observational study of 30 cases of acute ischemic stroke receiving IV thrombolysis using rtPAalteplase at Tertiary care Institute of Gujarat, India, over a period of 2 years. It was approved by the institutional ethics committee and written informed consent was obtained from all study participants.

Inclusion criteria

• All cases with acute ischemic stroke receiving IV thrombolysis with rtPA-alteplase.

• Age ≥18 years.

Patients were excluded from the study if they had intracranial hemorrhage or subarachnoid hemorrhage, more than 6.5 hours after onset of stroke, rapidly improving symptoms, history of arterial puncture at a noncompressible site or lumbar puncture within 7 days, blood pressure > 200 mmHg systolic or > 120 mmHg diastolic, NIHSS score below 4 or more than 25, age more than 80 years, fibrinogen < 120 mg, below 100,000 platelet count, serum glucose levels < 50 mg/dl or > 400 mg/dl, use of anticoagulant in spite of international normalized ratio (INR), current taking oral anticoagulants with prothrombin time (PT) > 15 sec or INR > 1.7, gastrointestinal hemorrhage within 21 days, pericarditis, vasculitis, renal failure peritoneal or hemodialysis, or dementia, history of recent seizures, history of trauma or cardiopulmonary resuscitation or surgery within two weeks, active internal bleeding, pregnancy or delivery within two weeks, and genitourinary or gastrointestinal hemorrhage below 21 days.

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.

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, 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

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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

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

Results

In this study the mean and median time period from onset of symptoms to needle are 185 and 181 minutes respectively. The mean door to needle time is 53.60 minutes. 5 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.

25 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. 5 cases received 20 mg of IV rtPA, of which 2 cases was already on dual antiplatelets, 2 cases was on anti-platelet plus oral anticoagulant, 1 case was more than 80 years of age. 23 cases had NIHSS score of range 10 to 22.

Primary outcome is defined as NIHSS reduction by at least 4 points, 24 hours of after thrombolysis. 18 subjects had achieved primary outcome in this study. After thrombolysis, the

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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.

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. 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 23 subjects (76.66 %) had favorable outcome at the end of 3 months.

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

Window period	Number of subject	Percentage (%)
<=4.5 hours	28	93.3
>4.5 hours	2	6.6

Table 2: Door to needle time

Door to needle time	Number of subject	Percentage (%)
<= 30 minutes	2	6.66
31 to 45 minutes	11	36.6
46 to 60 minutes	12	40
>60 minutes	5	16.6

Table 3: National institute of health stroke scale Score (NIHSS) at admission

Score N	Number of subject	Percentage (%)
5-9	5	16.6
10-22	23	76.6
23-42	2	6.66

Table 4: Time interval between thrombolysis and first dose of ecosprin

Time interval	Number of subject	Percentage (%)
At 12 hours	12	40
12 to 24 hours	26	85.6
More than 24 hours	2	6.66

Discussion

One person develops stroke somewhere in the world every 5 seconds.[19] The differences in stroke risk and functional outcome depends on age, gender, race, ethnicity and unfortunately largely on the geographical terrain as well as the urban- rural divide.[20] In India, additional factors affecting the rural urban divide include includes awareness of stroke symptoms, prehospital delays, adequacy of ambulance services, and most importantly the cost of thrombolytic therapy.

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Tanne D et al noted that the risk of intra-cerebral hemorrhage was more common in the elderly as compared to the young population.[21]They concluded that rtPA treatment was useful in elderly. 25 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, 5 cases received 20 mg of IV rtPA, of which 2 case was already on dual antiplatelets, 2 case was on anti-platelet plus oral anticoagulant, 1 case was more than 80 years of age. 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.[22] 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. 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.[23] 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.[23] 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.[24] They concluded that alteplase improved the reperfusion rates significantly.

In the present study, we found significant improvement after IA thrombolysis in our patients. The NIHSS score decreased significantly after treatment with IA thrombolysis as advocated by other studies.[25] Huded et al.[26] showed that 47.1% of patients after IA thrombolysis had mRS score of less than or equal to 2 at 90 days follow up. Lisboa et al.[27] noted that good outcome was significantly higher (41.5%) in IA thrombolysis group compared to control group (23%). Mattle et al.[28] showed in their study that good outcome was significantly increased in IA thrombolysis group (53%) compared to IV thrombolysis group (23%) (P = 0.0200). Nam et al.[29] demonstrated an increase in good outcome by 20% after IA thrombolysis compared to IV thrombolysis. Some studies established IA thrombolysis as more advantageous and independently associated with good outcome, however some studies found poor functional outcomes.[30]

The disadvantages of IA thrombolysis include additional delay because an angiography has to be performed and a microcatheter needs to be placed before commencement of therapy and additional risks associated with the endovascular procedure. With the advent of stent retrievers, studies suggest that IA rt-PA may be less effective compared to the second generation mechanical thrombectomy devices.[31]

In our study limitations include the small sample size as it was based on a small, single center involvement, non-randomized design and non-blinded nature of the study without a control group.

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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. Our study has demonstrated that IA thrombolytic therapy has significant benefit even up to 6.5 hours onset of stroke and might be beneficial in this selected population who are not fit for IV rtPA.

References

1. Marfatia S, Monz B, Suvarna V, Bhure S, Sangole N. Treatment Costs of Stroke Related to Nonvalvular Atrial Fibrillation Patients in India—A Multicenter Observational Study. Value Health Reg Issues. 2014;3:205–10. doi:10.1016/j.vhri.2014.02.002.

2. Kamalakannan S, Gudlavalleti A, Gudlavalleti V, Goenka S, Kuper H. Incidence & prevalence of stroke in India: A systematic review. Indian J Med Res. 2017;146(2):175–85. doi:10.4103/ijmr.ijmr_516_15.

3. Bonita R: Epidemiology of stroke: Lancet 1992;339:342-344.

4. Broderick JP, Phillips SJ, Whisnant JP, O'Fallon WM, Bergstralh EJ: Incidence rates of stroke in the eighties: The end of the decline in stroke? Stroke 1989;20:577-582.

5. Malmgren R, Bamford J, Warlow CP, Sandercock PAG, Slattery J: Projecting the number of patients with first ever strokes and patients newly handicapped by stroke in England and Wales. Br Med J 1989;298:656-660.

6. Astrup J, Siesjo BK, Symon L: Thresholds in cerebral ischemia — the ischemic penumbra. Stroke 1981;12:723-725.

7. Spedding M, Kilpatrick AT, Alps BJ: Activators and inactivators of calcium channels: Effects in the central nervous system. Fundam Clin Pharmacol 1989;3:3s-29s.

8. Asplund K: Hemodilution in acute stroke. Cerebrovasc Dis 1991; l(suppl 1):129-138.

9. Marsh EE, Adams HP, Biller J, Wasek P, Banwart K, Mitchell V, Woolson R: Use of antithrombotic drugs in the treatment of acute ischemic stroke: A survey of neurologists in practice in the United States. Neurology 1989;39:1631-1634.

10. Marder VJ, Sherry S: Thrombolytic therapy: Current status. N Engl J Med 1988;318:1512-1520.

11. Sussman BJ, Fitch TSP: Thrombolysis with fibrinotysin in cerebral arterial occlusion. JAMA 1958;167:1705-1709.

12. Meyer JS, Gilroy J, Barnhart MI, Johnson JF: Therapeutic thrombolysis in cerebral thromboembolism. Neurology 1963;13:927-937.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 03, 2023

13. Meyer JS, Gilroy J, Barnhart MI, Johnson JF: Anticoagulants plus streptokinase therapy in progressive stroke. JAMA 1964;189:373.
14. Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, Kitano K, Tsutsumi A, Yamadori A: Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. Neurology 1992;42:976-982
15. Ohtomo E, Araki G, Itoh E, Tougi H, Matuda T, Atarashi J: Clinical efficacy of urokinase in the treatment of cerebral thrombosis. Clin Eval 1985;13:711-751.
16. Abe T, Kazama M, Naito I, Ueda M, Tanaka T, Higuchi H, Saso S, Kariyone S, Yoshimura M: Clinical evaluation for efficacy of tissue cultured urokinase (TCUK) on cerebral thrombosis by means of multi-center double-blind study. Blood Vessels 1981;12: 321-341.
17. The Japanese Thrombolysis Study Group: Intravenous tissue plasminogen activator in acute thromboembolic stroke: A placebocontrolled, double blind trial, in del Zoppo GJ, Otis S, Mori E (eds): Proceedings of the Second International Conference on Thrombolysis in Acute Ischemic Stroke. New York, Springer-Verlag.
18. Barnett HJM: The contribution of multicenter trials to stroke prevention and treatment. Arch Neurol 1990;47:441-444.
19. Wouters A, Nysten C, Thijs V, Lemmens R. Prediction of Outcome in Patients With Acute Ischemic Stroke Based on Initial Severity and Improvement in the First 24h. Front Neurol. 2018;9:308. doi:10.3389/fneur.2018.00308.
20. Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. Continuum (Minneap Minn). 2017;23((1, Cerebrovascular Disease)):15–39. doi:10.1212/con.0000000000000416.
21. Tanne D, Gorman MJ, Bates VE. Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke in Patients Aged 80 Years and Older The tPA Stroke Survey Experience. Stroke. 2000;31:370-5.
22. Hacke W, Kaste M, Bluhmki E. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. N Engl J Med. 2008;359:1317-29.
23. Diedler J, Ahmed N, Sykora M. Safety of Intravenous Thrombolysis for Acute Ischemic Stroke in Patients Receiving Anti-platelet Therapy at Stroke Onset. Stroke. 2010;41:288-94.
24. Ogata T, Christensen S, Nagakane Y. The Effects of Alteplase 3 to 6 Hours After Stroke in the Epithet– defuse Combined Dataset Post Hoc Case–Control Study. Stroke. 2013;44:87-93.
25. Wang P, Guan HJ, Wang ZM. Clinical evaluation of intra-arterial thrombolysis treatment of wake-up stroke under ct perfusion imaging guidance. Biomed Res 2015; 26(1): 135-41.
26. Huded V, Dhomne S, Shrivastava M, Saraf R, Limaye U. Intra-arterial thrombolysis in acute ischemic stroke: a single center experience. Neurol India 2009; 57(6): 764-7.
27. Lisboa RC, Jovanovic BD, Alberts MJ. Analysis of the safety and efficacy of intra-arterial thrombolytic therapy in ischemic stroke. Stroke 2002; 33(12): 2866-71.
28. Mattle HP, Arnold M, Georgiadis D, Baumann C, Nedeltchev K, Benninger D, et al. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. Stroke 2008; 39(2): 379-83.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE 03, 2023

29. Nam J, Jing H, O'Reilly D. Intra-arterial thrombolysis vs. standard treatment or intravenous thrombolysis in adults with acute ischemic stroke: a systematic review and meta-analysis. Int J Stroke 2015; 10(1): 13-22.
30. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. Stroke 2006; 37(3): 922-8.
31. Goldstein JH, Denslow SA, Goldstein SJ, Marx WF, Short JG, Taylor RD, et al. IntraArterial Therapy for Acute Stroke and the Effect of Technological Advances on Recanalization: Findings in a Community Hospital. N C Med J 2016; 77(2): 79-86.