e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(11); 85-89

Original Research Article

A Hospital Based Study to Assess the Outcome of Acute Ischemic Stroke Patients Treated with Tenecteplase: An Observational Study

Prashant Kumar Thakur

Senior Resident, Department of Neurology, AIIMS Patna, Bihar, India

Received: 22-06-2023 Revised: 12-07-2023 / Accepted: 26-08-2023
Corresponding author: Dr. Prashant Kumar Thakur
Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to assess the outcome of acute ischemic stroke patients treated with tenecteplase.

Material & Methods: A prospective observational study of acute ischemic stroke patients treated with tenecteplase. On admission, clinical characteristics, temporal, epidemiological, imaging parameters, outcome measures including baseline National Institutes of Health Stroke Scale(NIHSS) score, NIHSS at 1 hour, 24 hours, at discharge, and modified Rankin Scale Scores (mRS) at 0, 1 and 3 months were recorded in a structured proforma. Twenty patients were included in the study.

Results: During the study, a total of 20 patients underwent intravenous(IV) thrombolysis with tenecteplase. Mean age was 60.32 years with 70% of the study subjects being males. Hypertension was the commonest risk factor present in 60% of the cases, followed by dyslipidemia in 50%. Most of the patients had large artery stroke subtype, with the infarct region belonging to the territory of middle cerebral artery in all the 20 cases. The mean time from onset of symptoms to arrival at the medical emergency was 115 (±12.48) minutes (min) while mean "door to needle" time was 56 (±18.22) min. The study subjects had a mean NIHSS score of 12 (±3.14) and a median mRS score of 5 (range: 3–5) at the baseline. The primary clinical efficacy outcome was an improvement in NIHSS score of 4 or more points at 24 h. Mean NIHSS scores at 2 h and 24 h were 11.49 (±5.15) and 9.31 (±5.25), respectively. We used "one-way repeated measures analysis of variance" test and observed a significant difference between the NIHSS scores at baseline and 24 h (P = 0.012).

Conclusion: Tenecteplase was found to be the safer, faster and cost- effective thrombolytic agent in acute ischemic stroke and is as much suited for the rural setting, as for the urban ones. More studies on this novel thrombolytic agent will throw light on its superiority even in the rural settings thus preventing the stroke epidemics, enhanced by its customized usage especially in this era of endovascular care.

Keywords: Acute Ischemic Stroke, Tenecteplase, Thrombolysis, Dyslipidemia.

Introduction

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. [1] In most countries alteplase within 4.5 hours window period was the only approved thrombolytic therapy until 2016 after which tenecteplase, an engineered recombinant tissue Plasminogen Activator(t-PA) with higher fibrin specificity, longer half-life, faster onset of action and convenience of single bolus administration was approved by drug controller general of India (DCGI) and came into use. [2] Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (rt-PA) has assumed vital importance in the successful treatment of acute ischemic stroke.

Conventionally, alteplase infusion has proved to be efficacious in improving the functional outcomes when given within 4.5 hours (h) of the stroke onset, and it is the only worldwide approved rt-PA agent for stroke thrombolysis. [3,4] Endogenous tPA is a serine protease in endothelial cells that catalyzes the cleavage of plasminogen to plasmin and subsequent degradation of fibrin in thrombi as part of coagulation homeostasis. [5] Synthesis of this wild-type tPA by recombinant DNA technology, [6] enabled therapeutic fibrinolysis targeting arterial thrombi for the reversal of acute ischemic disease. [2]

Alteplase infusion requires a second, dedicated intravenous catheter insertion that may delay treatment initiation if intravenous access is difficult to obtain. Because of the very short plasma half-life of alteplase, a gap between the end of bolus and start of infusion, a common occurrence perhaps

exacerbated by the pressure to minimize door to needle times, will result in an under dosing. [7,8,9]

Besides, tenecteplase has some pharmacological advantages in comparison to alteplase. It has a longer duration of action and higher fibrin specificity. Further, it can be given as a single bolus injection, unlike alteplase which is given as a continuous infusion after the bolus dose, thus offering the advantage of a convenient administration. This study compares the clinico-epidemiological as well as in-hospital parameters with the immediate as well as the serial outcome measures until 3 months of treatment with this novel, affordable and cheaper drug in a 24 hours stroke care facility from a rural tertiary centre in a developing country like India. More studies on tenecteplase from rural settings offer a great potential of improving current clinical practice to counter the stroke epidemics in developing countries.

The aim of the present study was to assess the outcome of acute ischemic stroke patients treated with tenecteplase.

Material & Methods

A prospective observational study including consecutive acute ischemic stroke patients above 18 years of age coming to Department Of Neurology, AIIMS Patna, Bihar, India for 10 months and treated with tenecteplase. 20 patients were included in the study. All baseline characteristics and NIHSS scores were noted, and Computed Tomography(CT) or Magnetic Resonance Imaging (MRI) of brain was taken immediately.

Patients were thrombolysed with tenecteplase if there were no contraindications for thrombolysis. A check CT was done after 24 hours or earlier if there was clinical deterioration.

Clinical, epidemiological, imaging parameters, outcome measures including baseline NIHSS, NIHSS at 1 hour, 2 hours, discharge and mRS [modified Rankin Scale Score] at 0, 1 and 3 months were filled in a structured proforma. The primary outcome measured was NIHSS at discharge and secondary outcome was mRS at 3 months. An NIHSS of 0 or 1 or a drop in NIHSS by eight scores was considered as major improvement. [10] Decrease in scores by values of 4 and 2 were considered as moderate and mild improvement respectively. [11,12] A mRS of 0 or 1 or a three point improvement was considered as good functional outcome or a major improvement, 10 two and single point improvement of mRS was used to indicate moderate and mild improvement respectively. [13,14]

Data Analysis

Data analysis was done using SPSS software comparing the clinico-epidemiological and in hospital parameters with outcome measures, the serial NIHSS and mRS scores.

Results

Table 1: Baseline characteristics of patient's thrombolyzed with tenecteplase

Variables	Values(%)
Age (years, mean±SD)	60.32±12.48
Gender (Male)	14 (70)
Risk factors	
Hypertension	14 (70)
Dyslipidemia	10 (50)
Diabetes Mellitus	4 (20)
Smoking	4 (20)
Stroke subtype	
Large artery	14 (70)
Lacunar	6 (30)
Cereberal circulation	
Anterior cereberal artery	0
Middle cereberal artery	20 (100)
Posterior cereberal artery	0
Laterality	
Right hemisphere	12 (60)
Left hemisphere	8 (40)
Onset to door time (min., mean±SD)	115±12.48
Door to imaging time (min., mean±SD)	37±17.53
Door to needle time (min., mean±SD)	56±18.22
Baseline NIHSS score (mean±SD)	12±3.14
Baseline Mrs score (median)	5

During the study, a total of 20 patients underwent IV thrombolysis with tenecteplase. Mean age was 60.32 years with 70% of the study subjects being males. Hypertension was the commonest risk factor present in 60% of the cases, followed by dyslipidemia in 50%. Most of the patients had large artery stroke subtype, with the infarct region belonging to the territory of middle cerebral artery in all the 20 cases. The mean time from onset of symptoms to arrival at the medical emergency was 115 (±12.48) minutes (min) while mean "door to needle" time was 56 (±18.22) min. The study subjects had a mean NIHSS score of 12 (±3.14) and a median mRS score of 5 (range: 3–5) at the baseline.

Table 2: Outcome analysis after tenecteplase thrombolysis

Variables	Mean±SD	P Value
NIHSS score		
Baseline	12.88±3.77	
2 hours	11.49±5.15	0.060
24 hours	9.31±5.25	0.012
mRS Score		
Baseline	5	0.001
90 days	1	

The primary clinical efficacy outcome was an improvement in NIHSS score of 4 or more points at 24 h. Mean NIHSS scores at 2 h and 24 h were 11.49 (±5.15) and 9.31 (±5.25), respectively. We used "one-way repeated measures analysis of variance" test and observed a significant difference between the NIHSS scores at baseline and 24 h (P = 0.012).

Discussion

However, recent randomized controlled trials (RCTs) have compared the results of alteplase and tenecteplase in stroke thrombolysis and observed tenecteplase to have an efficacy and safety at least, similar or superior to alteplase. [14-16] Besides, tenecteplase has some pharmacological advantages in comparison to alteplase. It has a longer duration of action and higher fibrin specificity. Further, it can be given as a single bolus injection, unlike alteplase which is given as a continuous infusion after the bolus dose, thus offering the advantage of a convenient administration. Based on these advantages and the results of above-mentioned RCTs, tenecteplase has been recently approved for ischemic stroke thrombolysis in India within 3 h of the stroke onset. Moreover, it offers the additional benefit of reasonable pricing, being available at a cost which is nearly half of the alteplase. 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. [17] In India, additional factors affecting the rural urban divide include awareness of stroke symptoms, prehospital delays, adequacy of ambulance services, and most importantly the cost of thrombolytic therapy. Tenecteplase with its cheaper cost when compared to its predecessor helps jump one of the major hurdles in acute stroke care in rural settings. The burden from rural India is extremely difficult to estimate since most of the published literatures are from urban cities. [1]

During the study, a total of 20 patients underwent IV thrombolysis with tenecteplase. Mean age was 60.32 years with 70% of the study subjects being males. Hypertension was the commonest risk factor present in 60% of the cases, followed by dyslipidemia in 50%. Most of the patients had large artery stroke subtype, with the infarct region belonging to the territory of middle cerebral artery in all the 20 cases. The mean time from onset of symptoms to arrival at the medical emergency was 115 (±12.48) minutes (min) while mean "door to needle" time was 56 (±18.22) min. The study subjects had a mean NIHSS score of 12 (±3.14) and a median mRS score of 5 (range: 3–5) at the baseline. In another single arm study respecting tenecteplase in stroke, Belkouch et al [18] reported a 24 h improvement of NIHSS score by >4 points in 77% (10/13) cases. Among Indian patients, none of the studies have reported the results of tenecteplase in stroke thrombolysis so far. However, our observations regarding the efficacy of Tenecteplase are similar to the results of previous Indian data regarding alteplase. Durai Pandian et al. from All India Institute of Medical Sciences reported 65% patients to have an improvement of 4 or more points in NIHSS score at 48 h with alteplase. [19] We observed highly significant difference between NIHSS scores at baseline and 24 h which is in agreement with the previously published studies on tenecteplase. [15] The primary clinical efficacy outcome here means an improvement in NIHSS score of 4 or more points at 24 h. Mean NIHSS scores at 2 h and 24 h were 11.49 (±5.15) and 9.31 (±5.25), respectively. We used "one-way repeated measures analysis of variance" test and observed a significant difference between the NIHSS scores at baseline and 24 h (P = 0.012). Our study showed positive correlation of

age with post treatment scores which helped predict outcome and this agrees to study results of young stroke by Owais et al. [20] It suggested that the results hold true even for the adult population that there is poorer response to tenecteplase with advancing age. Another interesting observation was the significant improvement in mean mRS scores in the moderate strokes when compared to the higher degree strokes which as a matter of fact showed mild worsening which points to the fact that there is a very significant delayed treatment improvement in moderate stroke group with tenecteplase. Only one patient had symptomatic Intracranial Hemorrhage(sICH) accounting to 5% of bleeding risk in this study population which was similar to other studies. [18]

Conclusion

Tenecteplase was found to be the safer, faster and cost- effective thrombolytic agent in acute ischemic stroke and is as much suited for the rural setting, as for the urban ones. More studies on this novel thrombolytic agent will throw light on its superiority even in the rural settings thus preventing the stroke epidemics, enhanced by its customized usage especially in this era of endovascular care.

References

1. 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.
2. Warach SJ, Dula AN, Milling TJ. Tenecteplase Thrombolysis for Acute Ischemic Stroke. Stroke. 2020;51(11):3440–51.
3. Marier JR. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995 Dec 14;333(24):1581-7.
4. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. New England journal of medicine. 2008 Sep 25;359(13): 1317-29.
5. Llevadot J, Giugliano RP, Antman EM. Bolus fibrinolytic therapy in acute myocardial infarction. Jama. 2001 Jul 25;286(4):442-9.
6. Pennica D, Holmes WE, Kohr WJ, Harkins RN, Vehar GA, Ward CA, Bennett WF, Yelverton E, Seeburg PH, Heyneker HL, Goeddel DV. Cloning and expression of human tissue-type plasminogen activator cDNA in E. coli. Nature. 1983 Jan 20;301 (5897):214-21.
7. Acheampong P, May MT, Ford GA, Dixit AK. Bolus-infusion delays of alteplase during thrombolysis in acute ischaemic stroke and functional outcome at 3 months. Stroke research and treatment. 2014 Apr 30;2014.
8. Smith C, Al-Nuaimi Y, Wainwright J, Sherrington C, Singh A, Kallingal J, Douglass C, Parry-Jones A, Smith C, Dixit A, Majid A. The influence of bolus to infusion delays on plasma tissue plasminogen activator levels. International Journal of Stroke. 2014 Oct;9(7) :939-42.
9. Brodoehl S, Günther A, Witte OW, Klingner CM. How to manage thrombolysis interruptions in acute stroke?. Clinical Neuropharmacology. 2015 May 1;38(3):85-8.
10. 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 24 h. Frontiers in neurology. 2018 May 7;9:308.
11. Marsh EB, Lawrence E, Gottesman RF, Llinas RH. The NIH Stroke Scale has limited utility in accurate daily monitoring of neurologic status. The Neurohospitalist. 2016 Jul;6(3):97-101.
12. Bruno A, Saha C, Williams LS. Using change in the National Institutes of Health Stroke Scale to measure treatment effect in acute stroke trials. Stroke. 2006 Mar 1;37(3):920-1.
13. Lai SM, Duncan PW. Stroke recovery profile and the Modified Rankin assessment. Neuroepidemiology. 2001 Feb 9;20(1):26-30.
14. NOR-TEST: Tenecteplase Similar to Alteplase in Stroke – Medscape.
15. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, O'Brien B, Bladin C, McElduff P, Allen C, Bateman G. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. New England Journal of Medicine. 2012 Mar 22; 366(12):1099-107.
16. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, Ford I, Muir KW. Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST): phase 2 randomised clinical trial. Lancet Neurology. 2015;14(4):368-76.
17. Guzik A, Bushnell C. Stroke epidemiology and risk factor management. CONTINUUM: Lifelong Learning in Neurology. 2017 Feb 1; 23 z(1):15-39.
18. Belkouch A, Jidane S, Chouaib N, Elbouti A, Nebhani T, Sirbou R, Bakkali H, Belyamani L. Thrombolysis for acute ischemic stroke by tenecteplase in the emergency department of a Moroccan hospital. Pan African Medical Journal. 2015;21(1).

19. Pandian JD, Sudhan P. Stroke epidemiology and stroke care services in India. Journal of stroke. 2013 Sep;15(3):128.
20. Owais M, Panwar A, Valupadas C, Veeramalla M. Acute ischemic stroke thrombolysis with tenecteplase: An institutional experience from South India. Annals of African Medicine. 2018 Apr;17(2):90.