



Original Research Article

Thrombolysis with novel tenecteplase in acute ischemic stroke: A prospective observational study from a rural tertiary care center in South India

Ahamed Subir¹, Krishnadas N.C.^{1,*}, P.A. Fazal Ghafoor¹, Mohammed Rafeeqe¹, Rajmohan V²

¹Dept. of Neurology, MES Medical College, Perinthalmanna, Kerala, India

²Dept. of Psychiatry, MES Medical College, Perinthalmanna, Kerala, India



ARTICLE INFO

Article history:

Received 25-05-2021

Accepted 12-06-2021

Available online 17-07-2021

Keywords:

Thrombolysis

Tenecteplase

Stroke

Rural

ABSTRACT

Introduction: Tenecteplase is an approved engineered recombinant tissue plasminogen activator for treatment of acute ischemic stroke with molecular and practical advantages. It could be quintessential in this era of endovascular care provided that more studies come out, especially from resource poor settings.

Aims: To observe the clinico-epidemiological profile and to assess the outcome of acute ischemic stroke patients treated with tenecteplase.

Materials and Methods: A prospective observational study of stroke patients treated with tenecteplase. On admission clinical characteristics, temporal, epidemiological, imaging parameters, outcome measures including baseline NIHSS, NIHSS at 1 hour, 24 hours, at discharge, and modified Rankin Scores (mRS) at 0, 1 and 3 months were recorded in a structured proforma.

Results: Out of the 19 patients thrombolysed with tenecteplase 68.4% were males. Mean age of the study population was 61.3 years. Hypertension (57.9%), diabetes mellitus (36.8%) and smoking (26.3%) were the most common risk factors. Time parameters like mean onset to door time, door to image and door to needle time were 126 minutes, 29 minutes and 66 minutes respectively, which were confirming with the international standards. Mean NIHSS was 11.1 and serial improvement was noted in the post treatment mean NIHSS scores at 1 hour, 24 hours and 7 days with values of 8.6, 8.0 and 7.7 respectively ($F=5.619, p=0.018$). The mean mRS score was 3.5 and the follow up mRS at 1 month (2.4) and 3 months (1.7) ($F=19.32, p<0.001$) revealed significant functional improvement. The spearman test showed a positive correlation of age with all the serial post treatment NIHSS and mRS scores even when it did not affect the baseline NIHSS and mRS scores suggesting a poor response to tenecteplase with increasing age. Major improvement in mRS scores described as either a score of 0 or 1 or else a three-point improvement from baseline was seen in 47% (9) of thrombolysed patients and a major improvement in NIHSS scores was seen in 26% (5) patients. Symptomatic intracranial hemorrhage (sICH) was seen in only 5% of the study population.

Conclusion: Thrombolysis with tenecteplase is faster, safer and effective but the treatment response decreases with increasing age.

© This is an open access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>) which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1. Introduction

About 85.5% of stroke deaths worldwide is 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 In most countries alteplase within 4.5 hours window period was the only approved thrombolytic therapy until 2016 after which tenecteplase, an engineered

* Corresponding author.

E-mail address: drnckd@gmail.com (Krishnadas N.C).

recombinant 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) came into use.³ 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 offers a great potential of improving current clinical practice to counter the stroke epidemics in the developing countries.

2. Materials and Methods

We conducted a prospective observational study on consecutive ischemic stroke patients above 18 years of age coming to MES Medical college in window period of 3 hours and treated with tenecteplase was included in the study. It was approved by the institutional ethics committee and written informed consent was obtained from all study participants. All baseline characteristics and NIHSS scores were noted, and CT or MRI brain was taken immediately. Patient was 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 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,⁴ and decrease in scores by values of 4 and 2 were considered as moderate and mild improvement respectively.^{5,6} A mRS of 0 or 1 or a three point improvement was considered as good functional outcome or a major improvement,⁴ two and single point improvement of mRS was used to indicate moderate and mild improvement respectively.^{7,8} Data analysis was done using SPSS software comparing the clinico-epidemiological and in hospital parameters with outcome measures, the serial NIHSS and mRS scores.

3. Results

Tenecteplase was used to thrombolysed 19 patients of which 13 were males. The clinical findings have been summarized in the Table 1. Majority of the patients (73.7%) presented to the casualty between the time frame of 12 noon to 6 pm. Decreased awareness among patients and primary care physicians and difficult access to advanced stroke care could be the two factors resulting in acute stroke patients not getting care within window period outside the prime working hours in a rural setting. The time parameters

critical in stroke care were at par with the international standards. [Table 2]. Mean NIHSS at arrival was 11.1 and correspondingly in the stroke severity classification 73.7% (14) were moderate strokes. Out of the 19 strokes, 17 had anterior circulation infarcts and 2 had posterior circulation infarcts. The MRI findings based on specific arterial location revealed that the most common location was in MCA superior division and MCA subcortical region which is 31.6%⁶ each followed by MCA complete occlusion strokes which accounted for 15.8%³ in the study population [Figure 1]. In the TOAST classification, 42.1%⁸ each were in large artery occlusion and strokes of undetermined groups and rest belonged to the cardioembolic group(15.8%).

Post treatment serial improvement in the mean NIHSS scores were observed at 1 hour, 24 hours and 7days at 8.7,8.0,7.7 respectively (F=5.619, p=0.018) [Figure 2]. Even more significant was the improvement in the mRS scores which on admission was 3.5 and the serial improvements noted in the follow up mRS scores at 1 month and 3 months were 2.4 and 1.7 respectively (F=19.32, p<0.001) [Figure 2]. Major improvement in NIHSS was seen in 5 patients [26%] measured as a drop in NIHSS of 8 points or a score of 0 or 1 at 7 days. Moderate improvement (4-point change) and mild improvement in NIHSS (2-point change) was found in 15.8% and 36.8% respectively [Figure 3]. The major improvement in mRS characterized by a three-point improvement from the baseline or a final score of 0 or 1 was achieved in 47% (9) of thrombolysed patients. Moderate improvement (mRS less than 2) and mild improvement in mRS (one point change) was found in 26.3% and 10.5% respectively [Table 4]. There was only one symptomatic intracranial hemorrhage (sICH) among the thrombolysed patients taking the bleeding risk to 5%.

The non-parametric spearman correlation showed a positive correlation of age with all the serial post treatment NIHSS and mRS scores even when it did not affect the baseline scores as shown in the correlation plot [Figure 4]. This suggests a poorer response of stroke patients to tenecteplase with higher age. Other factor comparisons with age were found to have no significant correlations. There was also no significant difference in the serial NIHSS or mRS scores while comparing the anterior or posterior circulation strokes as both were equally beneficial.

One way Anova test used for studying correlation of stroke severity with serial NIHSS and mRS scores showed that except for the first month mRS scores (F=2.402, p=.122), all other scores like NIHSS during discharge (F=5.895, p=0.012) or mRS at 3 months (F=5.709, p=0.013) showed significant difference. On analysing further about this ambiguity, it was found that the mean mRS scores had worsened from 3.75 to 4 in the moderate to severe stroke category at 3 months while in the moderate stroke group the mRS scores improved from 2.14 to 1.28 thus making the improvement in mRS scores insignificant in the first

month between the groups. Thus, revealing an important finding that moderate to severe stroke group had mild worsening while the moderate stroke group had significant improvement with tenecteplase therapy.

Table 1: Clinico epidemiological details of patients

Variable	Subset	Valid Percent
Gender	Male	68.4
	Female	31.6
DM	Absent	63.2
	Present	36.8
HTN	Absent	42.1
	Present	57.9
CAD	Absent	63.2
	Present	36.8
Smoking	Absent	73.7
	Present	26.3
Alcohol	Absent	94.7
	Present	5.3
CHD	Absent	94.7
	Present	5.3
Previous CVA	Absent	84.2
	Present	15.8

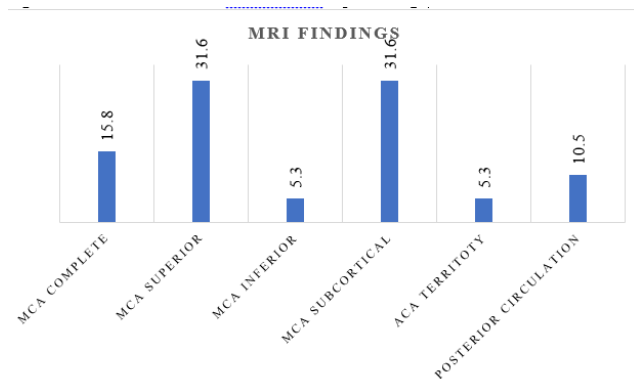


Fig. 1: MRI based stroke localization (in percentage)

4. Discussion

One person develops stroke somewhere in the world every 5 seconds.⁴ 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.⁹ 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. 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 literature are from urban cities.²

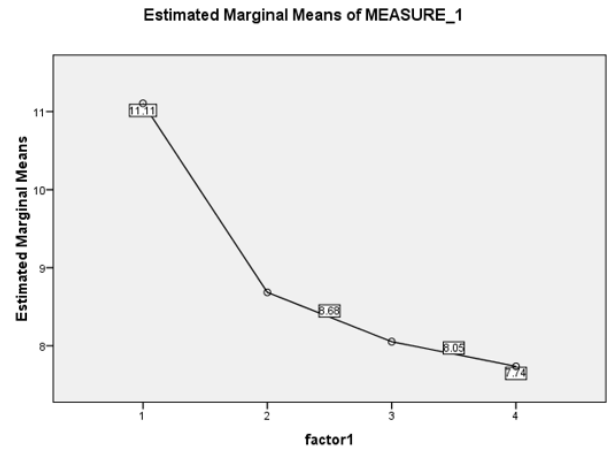


Fig. 2: Serial changes in NIHSS scores with treatment with tenecteplase

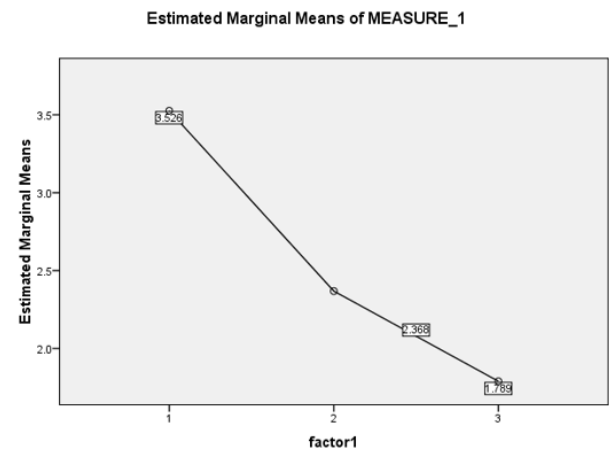


Fig. 3: Serial changes in mRS scores with treatment with tenecteplase

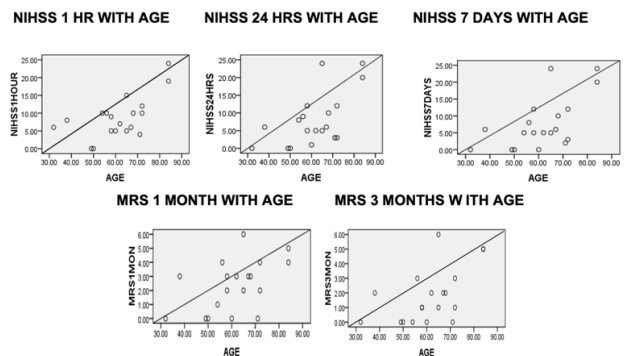


Fig. 4: Correlation plots for post treatment NIHSS & mRS scores and age shows positive correlation of age with all the post treatment scores.

Table 2: In hospital characteristics of 19 patients treated with tenecteplase

	N	Minimum	Maximum	Mean	Std. Deviation
Age	19	32.0	84.0	61.3	13.42
Onset to door time	19	30.0	180.0	126.0	44.30
Door to imaging time	19	5.0	110.0	29.10	27.61
Door to perfusion time	19	15.0	160.0	65.78	33.70
NIHSS on Admission	19	4.0	19.0	11.10	5.20
NIHSS at 1 hour	19	.0	24.0	8.6842	5.91
NIHSS at 24 hours	19	.0	24.0	8.0526	7.52
NIHSS at 7 days	19	.0	24.0	7.7368	7.64
mRS on admission	19	2.0	5.00	3.5263	1.12
mRS at 1 month	19	.0	6.00	2.3684	1.83
mRS at 3 months	19	.0	6.00	1.7895	1.87

Table 3: Improvement based on NIHSS at discharge

NIHSS outcome	Frequency	Percent	Cumulative
No improvement	4	21.1	21.1
Mild improvement	7	36.8	57.9
Moderate improvement	3	15.8	73.7
Major improvement	5	26.3	100.0
Total	19	100.0	

Table 4: Improvement based on mRS at 3 months.

mRS outcome	Frequency	Percent	Cumulative
No improvement	3	15.8	15.8
Mild improvement	2	10.5	26.3
Moderate improvement	5	26.3	52.6
Major improvement	9	47.4	100.0
Total	19	100.0	

The present study looked into the efficacy and safety of tenecteplase for treatment of acute stroke patients looking into the rural population and their characteristics. The mean age of the study population was 61 years which was low when compared to other stroke studies which could be due to the increase in the prevalence of risk factors (diabetes mellitus, smoking and hypertension) in this region.¹⁰ About three fourth of the patients presented within the 12 noon to 6 pm time frame suggesting lack of awareness both among people and primary care physicians regarding early thrombolysis and lack of proper access to stroke care and delay in referral.⁵ Time parameters like mean onset to door time, door to image and door to needle time were 126 minutes, 29 minutes and 66 minutes respectively, were at par with the international standards confirming the better in-hospital care with a well-functioning stroke protocol and stroke code in place. Majority of strokes were anterior circulation strokes and also were of moderate severity. The effect of tenecteplase on severe strokes could not be observed from this study. Post therapy improvements in primary outcomes and secondary outcomes were comparable to other studies.¹¹ 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.¹² It suggests that the results holds 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 sICH accounting to 5% of bleeding risk in this study population which was similar to other studies.¹¹

5. 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.

6. Source of Funding

No financial support was received for the work within this manuscript.

7. Conflicts of Interest

There are no conflicts of interest.

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. Warach SJ, Dula AN, Milling TJ. Tenecteplase Thrombolysis for Acute Ischemic Stroke. *Stroke*. 2020;51(11):3440–51. doi:10.1161/strokeaha.120.029749.
4. 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.
5. Marsh EB, Lawrence E, Gottesman RF, Llinas RH. The NIH Stroke Scale Has Limited Utility in Accurate Daily Monitoring of Neurologic Status. *Neurohospitalist*. 2016;6(3):97–101. doi:10.1177/1941874415619964.
6. 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;37(3):920–1. doi:10.1161/01.str.0000202679.88377.e4.
7. Sue-Min L, Duncan PW. Stroke Recovery Profile and the Modified Rankin Assessment. *Neuroepidemiology*. 2001;20(1):26–30. doi:10.1159/000054754.
8. Broderick JP, Adeoye O, Elm J. The Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. *Stroke*. 2017;48(7):2007–12.
9. Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. *Continuum (Minneapolis)*. 2017;23(1, Cerebrovascular Disease):15–39. doi:10.1212/con.0000000000000416.
10. Béjot Y, Delpont B, Giroud M. Rising Stroke Incidence in Young Adults: More Epidemiological Evidence, More Questions to Be Answered. *J Am Heart Assoc Cardiovasc Cerebrovasc Dis*. 2016;5(5):e003661. doi:10.1161/jaha.116.003661.
11. Belkouch A, Jidane S, Chouaib N, Elbouti A, Nebhani T, Sirbou R, et al. Thrombolysis for acute ischemic stroke by tenecteplase in the emergency department of a Moroccan hospital. *Pan Afr Med J*. 2015;21. doi:10.11604/pamj.2015.21.37.6491.
12. Panwar A, Owais M, Valupadas C, Veeramalla M. Acute Ischemic Stroke Thrombolysis with Tenecteplase: An Institutional Experience from South India. *Ann Afr Med*. 2018;17(2):90–3. doi:10.4103/aam.aam_50_17.

Author biography

Ahamed Subir, Assistant Professor

Krishnadas N.C, Associate Professor

P.A. Fazal Ghafoor, Professor and HOD

Mohammed Rafeeqe, Associate Professor

Rajmohan V, Professor

Cite this article: Subir A, Krishnadas N.C, Ghafoor PAF, Rafeeqe M, Rajmohan V. Thrombolysis with novel tenecteplase in acute ischemic stroke: A prospective observational study from a rural tertiary care center in South India. *IP Indian J Neurosci* 2021;7(2):119-123.