

**THROMBOLYSIS WITH TENECTEPLASE IN PATIENTS WITH ACUTE ISCHEMIC STROKE – A PROSPECTIVE OBSERVATIONAL STUDY**

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**Introduction:** Tenecteplase is an approved engineered recombinant tissue plasminogen activator for treatment of acute ischemic stroke with molecular and practical advantages. It could be quite essential in this era of endovascular care provided that more studies come out.

**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. 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.

**Keywords:** Thrombolysis, Tenecteplase, Ischemic stroke.

### **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.<sup>1</sup> 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.<sup>2</sup> In most countries alteplase within 4.5 hours window period was the only approved thrombolytic therapy until 2016 after which tenecteplase, an engineered 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.<sup>3</sup> 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.

### **Materials and Methods**

A prospective observational study done in the Department of Emergency Medicine in

Basaveshwara medical college and Hospital, Chitradurga, Karnataka. The 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.<sup>4</sup> and decrease in scores by values of 4 and 2 were considered as moderate and mild improvement respectively.<sup>5,6</sup> A mRS of 0 or 1 or a three point improvement was considered as good functional outcome or a major improvement,<sup>4</sup> two and single point improvement of mRS was used to indicate moderate and mild improvement respectively.<sup>7,8</sup> 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**

Tenecteplase was used to thrombolyse 19 patients of which 13 were males. 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 parameter 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%<sup>6</sup> each followed by MCA complete occlusion strokes which accounted for 15.8%<sup>3</sup> in the study population. In the TOAST classification, 42.1%<sup>8</sup> 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). 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. 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. There was only one symptomatic intracranial hemorrhage (sICH) among the thrombolysed patients taking the bleeding risk to 5%.

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. 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: In hospital characteristics of 19 patients treated with tenecteplase**

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

**Table 2: 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 3: 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	

## DISCUSSION

Every five seconds, someone somewhere in the world suffers a stroke.<sup>4</sup> Differences in stroke risk and functional outcomes vary by age, sex, race, and ethnicity, but unfortunately also depend heavily on geography and urban-rural disparities.<sup>9</sup> In India, other factors influencing

urban-rural disparities include recognition of stroke symptoms, pre-hospital delays, adequacy of emergency services, and, most importantly, the cost of thrombolytic therapy. Tenecteplase is cheaper than conventional drugs and overcomes one of the major obstacles in acute stroke management in rural areas. Estimating the burden in rural India is very difficult as most of the literature focuses on urban areas.<sup>2</sup> This study investigated the efficacy and safety of tenecteplase in treating patients with acute stroke by investigating the local population and its characteristics. The mean age of the study population was 61 years, which was lower than in other stroke studies, but this may be due to the increased prevalence of risk factors (diabetes, smoking, and hypertension) in this region.<sup>10</sup> Approximately three-quarters of patients were admitted between 12:00 and 18:00, indicating a lack of awareness among the public and primary care physicians about early thrombolysis, as well as a lack of adequate access to stroke treatment and a delay in referral to a physician.<sup>5</sup> The mean times from treatment to hospital admission, admission to image acquisition, and hospital admission to needle acquisition were 126 minutes, 29 minutes, and 66 minutes, respectively, which were in line with international standards, enabling better care in the hospital setting. a well-functioning stroke protocol and stroke code. Most strokes were anterior circulation and were of moderate severity. Improvements in primary and secondary outcomes after treatment were comparable to other studies.<sup>11</sup> Our study showed a positive correlation between age and posttreatment scores in predicting outcome, which is consistent with the results of a young adult stroke study by Owais et al.<sup>12</sup> This suggests that the results also apply to the adult population and that the response to tenecteplase decreases with age. Another interesting observation was the greater improvement in mean mRS scores in moderate stroke compared with high-grade stroke, which actually showed a slight worsening, indicating a highly significant delay in improvement from treatment with moderate stroke in the d group. Only one patient

experienced sICH, representing a 5% risk of bleeding in this study population, which is similar to results from other studies.<sup>11</sup>

### **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.

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