Original Article

Tenecteplase and Alteplase for Thrombolysis of Acute Ischemic Stroke within 4.5 Hours: An Efficacy and Safety Study

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Abstract

Objective: To compare the efficacy and safety of thrombolysis using Tenecteplase (TNK) versus alteplase in acute ischaemic stroke (AIS) patients within 4.5-hour window period. **Methods:** This retrospective study involved the collection of data from consecutive AIS patients who underwent thrombolysis in the Department of Neurology at a tertiary care university hospital, between May 2018 to January 2021. Data including clinical history, neurological assessment using modified Rankin score (mRS), National Institutes of Health Stroke Scale (NIHSS), brain neuroimaging, treatment, and outcome details were collected. The primary efficacy outcome was the proportion of patients with good functional recovery (mRS of 0–2) at 90 days of follow-up. **Results:** Total of 42 patients with AIS underwent thrombolysis, of which 19 received alteplase and 23 got TNK. The median (range) onset to door time [120 (20-210) versus 120 (30-210) minutes; $P = 0.823$] and median (range) onset to needle time [150 (60-255) versus 160 (50-240) minutes; $P = 0.779$] were comparable in both alteplase and TNK groups, respectively. The primary outcome of good functional recovery (mRS ≤2) at 3 months was observed in more than half the patients in each group and was comparable ($P = 0.701$). Post-thrombolysis complications including cerebral haemorrhage (symptomatic or asymptomatic) were comparable between the two groups (31.6% vs 30.4%; $P = 0.936$), except a significantly higher proportion of patients on TNK required mechanical ventilation (10.5% v/s 43.5%; $P = 0.019$). **Conclusions:** This study showed a comparable efficacy and safety profile of alteplase and TNK in thrombolysis of AIS throughout the 4.5 hours window period. Moreover, the ease of administration and better pharmacodynamic properties favors tenecteplase.

Keywords: Acute ischaemic stroke, alteplase, efficacy, safety, tenecteplase, thrombolysis

Introduction

Stroke is the second leading cause of death after coronary artery disease, with a worldwide incidence rate of about 12.2 million per year.[1,2] The stroke diagnosis and management have witnessed considerable advancement over the past couple of decades, with intravenous thrombolysis using alteplase becoming the gold standard for managing acute ischaemic stroke (AIS) patients worldwide. Time is the brain, and the first critical step in stroke management is early identification of AIS patients and referral to centers capable of providing appropriate therapy as quickly as possible. Lack of health care facilities, as well as various transportation issues, have been the major hurdle in thrombolysis of AIS patients, which get several times magnified in the sub-Himalayan region of India.

Alteplase, a second generation rt-PA is the first FDA-approved thrombolytic agent for acute stroke. Its major limitations include a low recanalization rate, the possibility of intracerebral hemorrhage, susceptibility to plasminogen activation inhibitors, and short half-life necessitating it to be given as an infusion drug.[3] Tenecteplase (TNK), a variant of alteplase, overcomes these limitations.[4] It has recently been approved in India for treatment of AIS, albeit for those presenting within 3-hour window period.[5] TNK does not need to be given as an infusion agent. It can be administered in a single bolus dose. It's thrombolytic profile and potency appeared better than alteplase in animal studies.[4]

While the majority of western literature[6-9] focused on higher doses of TNK (0.25 mg/kg-0.4 mg/kg), a lower dose of 0.20 mg/kg has been approved in India for AIS.[10] However, there is limited data on the use of this dose in a real-world healthcare setting in India, with just two randomized open label trials demonstrating the efficacy and safety of 0.2 mg/kg TNK.[5,11] Recently, a single-center retrospective study (TENVALT) from southern India, compared the low dose of TNK to alteplase.[12] To date, the majority of Indian research published involved a population from the nation's southern region with a paucity of data from the northern part of India. Moreover, only a few of

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the comparative studies have reported the use of TNK within 3-4.5-hour window period,[13] with no such reports from India to date. Therefore, we conducted this study to compare the efficacy and safety of thrombolysis using TNK versus alteplase in AIS patients within the 4.5-hour window period.

Materials and Methods

This is a single center, retrospective study involving patients with the diagnosis of AIS, admitted at a tertiary care university hospital in the Northern part of India, between May 2018 till January 2021, who underwent thrombolysis. We aimed to compare the efficacy and safety of alteplase versus TNK. The study protocol was approved by the Institute Ethics Committee (AIIMS/IEC/21/278/Date: 15/05/2021).

Inclusion and exclusion criteria

All AIS patients aged ≥18 years or older presenting within 4.5 hours of the onset of stroke symptoms were included if they had a pre-morbid modified Rankin score (mRS) of ≤2 and lacked evidence of intracerebral hemorrhage in non-contrast CT brain. All patients eligible for mechanical thrombectomy (MT) also underwent thrombolysis. However, MT could not be done due to its unavailability at our centre. Those AIS patients in whom thrombolysis was contraindicated, were excluded from the study. After recording a written informed consent from the patient or a close relative/caregiver, the included patients underwent thrombolysis using either alteplase or TNK as per the local availability of the thrombolytic agents and affordability of the patients.

Data collection

The admission and follow-up charts of AIS patients who underwent thrombolysis were reviewed for a thrombolytic agent used (alteplase vs TNK) along with demographic, clinical, and neuroimaging including magnetic resonance imaging (MRI)/Computed tomography (CT) of brain, treatment and outcome details. The stroke time periods including onset to door and onset to needle time were recorded. Findings on baseline CT/MRI Brain and a follow-up brain imaging 24 hours after receiving thrombolytic therapy were recorded. The type of stroke was classified according to the trial of ORG 10172 in acute stroke treatment (TOAST) criteria.[14] Complications developed during hospital stay including post-thrombolysis cerebral hemorrhage, sepsis, need for mechanical ventilation, ICU care, need for surgical intervention, hospital/ventilator acquired pneumonia, seizures, headache, acute kidney injury, or transaminitis were recorded. Hemorrhagic transformation in acute ischemic stroke following thrombolysis was classified into four groups: hemorrhagic infarction type 1 (HI1; small petechiae at the border of the infarcted area), hemorrhagic infarction type 2 (HI2; confluent petechiae in the infarcted area, but lacking mass effect), parenchymal hematoma type 1 (PH 1; hemorrhage ≤30% of the infarcted area with minimal mass effect), parenchymal hematoma type 2 (PH 2; dense hemorrhagic areas >30% of the infarcted area with significant mass effect).[15,16]

Drug administration

During the 4.5-hour window period, patients with AIS fulfilling inclusion criteria were given either TNK (0.2 mg/kg to a maximum of 20 mg as a single intravenous bolus)[10] or alteplase (0.9 mg/kg to a maximum of 90 mg, with 10% dose given as initial bolus and remainder as an intravenous infusion over 1 hour).[17]

Outcome measures

Primary outcome

The primary efficacy outcome was the proportion of patients with good functional recovery, defined as mRS score of 0 – 2, at 90 days.[18] An attending neurologist evaluated the patient in follow-up visits.

Secondary outcome

Asymptomatic or symptomatic intracerebral hemorrhage, defined as a new intracranial hemorrhage leading to worsening of NIHSS ≥4 points or death, within the first 24 hours after administration of thrombolytic agent[19] was a secondary outcome. A follow-up CT brain was done 24-hour following the thrombolytic therapy in all patients. In addition, a need for mechanical ventilation and decompression craniotomy, in-hospital mortality, and mortality at three months were analyzed.

Statistical analysis

Assessment of the normality of data was done using the Shapiro-Wilk method. Continuous and normally distributed variables were represented as mean ± SD (standard deviation) and compared by using an independent *t* -test between the "alteplase" and "TNK" group, while continuous but nonparametric variables were represented as median (range) and compared using Mann–Whitney U test. Fischer's exact test was used for comparing categorical variables. Multivariate binary logistic regression was used to find independent predictors of in-hospital mortality which included variables with $P < 0{\cdot}1$ on univariate analysis. All analyses were done using Statistical Package for Social Sciences 21 version (SPSS, IBM, Chicago, Illinois, United States) software. A variable with a two-tailed $P < 0{\cdot}05$ was considered statistically significant.

Results

A total of 42 patients with AIS underwent thrombolysis between May 2018 and January 2021, with 19 receiving alteplase and the remainder getting TNK [Supplementary Figure 1]. Baseline demographic, clinical, and stroke characteristics were comparable between both treatment groups [Table 1]. Large vessel stroke was present in 52.6% and 61.9% of patients in alteplase and TNK groups respectively. Although these patients were eligible for MT, none of them underwent the procedure due to its unavailability at our centre. Infarction in the middle cerebral artery (MCA) territory was comparable in both groups, while anterior and posterior cerebral arteries (ACA and PCA) infarctions were commoner in the TNK group. The median onset to door time (time from onset of stroke

Table 1: Baseline demographic, clinical, and stroke characteristics

Characteristics	Alteplase (*n*=19)	Tenecteplase (*n*=23)	*P*
Demographic profile			
Age in years: Median (Range)	60 (40-81)	60 (26-84)	0.519
Gender- Male: *n* (%)	11 (57.9)	17 (73.9)	0.273
Risk factors			
Previous stroke or TIA	5 (26.3)	2 (8.7)	0.127
Hypertension	15 (78.9)	15 (65.2)	0.327
Diabetes mellitus	3 (15.8)	8 (34.8)	0.163
Coronary artery disease	5 (26.3)	2 (8.7)	0.127
Atrial fibrillation	5 (26.3)	4 (17.4)	0.483
Dyslipidaemia (LDL ≥100 mg/dl)	4 (21.1)	1 (4.3)	0.096
Smoker	11 (57.9)	9 (39.1)	0.226
Alcoholic	6 (31.6)	3 (13.0)	0.145
Transportation Time (in minutes)			
Onset to door time: Median (Range)	120 (20-210)	120 (30-210)	0.823
Onset to Needle time: Median (Range)	150 (60-255)	160 (50-240)	0.779
Clinical characteristics			
Baseline NIHSS: median (range)	9 (2-22)	12 (3-33)	0.612
ASPECT score: median (Range)	7 (1-10)	8 (2-10)	0.947
TOAST classification			
Large Vessel stroke	10 (52.6)	16 (61.9)	0.506
Cardioembolic stroke	3 (15.8)	3 (13)	1.000
Small vessel stroke	5 (26.3)	2 (8.7)	0.214
Other determined etiology	0 (0.0)	1 (4.3)	NA
Other undetermined etiology	1 (5.3)	1 (4.3)	1.000

ACA: anterior cerebral artery; ASPECT: Alberta Stroke Program Early CT Score; ICA: internal cerebral artery; MCA: middle cerebral artery; NA: not applicable NIHSS: National Institute of Health Stroke Scale; PCA: posterior cerebral artery; TIA: transient ischemic attack; TOAST: trial of ORG 10172 in acute stroke treatment

symptoms to reaching the hospital) was comparable in both alteplase and TNK groups [median (range) = 120 (20-210) versus 120 (30-210) minutes; $P = 0.823$]. The median onset to needle time was also comparable in both alteplase and TNK groups [median (range) = 150 (60-255) and 160 (50-240) minutes; $P = 0.779$].

Comparison of primary and secondary outcomes in the two groups is shown in Table 2. In the alteplase and TNK groups, the median NIHSS at admission [9 (range 2-22) vs 12 (range 3-33); $P = 0.612$] and the change in NIHSS from admission to discharge [3 (0 to 8) versus 4 (-2 to 15); $P = 0.074$] were comparable. Median mRS of Alteplase group at admission, discharge and 90 days was 5 (range 0-5), 4 (0-6), and 2 (0-6), while the same in TNK group was 4 (1-5), 2 (0-6) and 1 (0-6), respectively. The primary outcome of good functional recovery at 3 months with mRS scores ≤2 was observed in more than half the patients in each group and was comparable. Thus, both thrombolytic agents showed comparable efficacy in improving functional outcomes. In the patient with large vessel stroke, good functional recovery at 3 months was seen in 50% and 43.8% patients in Alteplase and TNK arms, respectively ($P = 0.76$).

Number of patients developing cerebral hemorrhage (symptomatic or asymptomatic) post-thrombolysis was comparable between the two groups (alteplase: 31.6%, TNK: 30.4%; $P = 0.936$). In patients with large vessel stroke, proportion of patients with cerebral haemorrhage (symptomatic or asymptomatic) were comparable (alteplase: 20% vs TNK: 31.3%; $P = 0.67$). In patients with post-thrombolysis intracerebral hemorrhage, the proportion of patients with HI1, HI2, and PH 1 were 15.8%, 10.5%, and 5.3% vs 17.4%, 4.3%, and 8.7% in alteplase vs TNK groups respectively. None of our patients developed PH 2. There were no other serious adverse effects. Need of decompressive craniotomy and mortality during hospital admission as well as that within 3 months were comparable in both groups including those with large vessel stroke. However, compared to alteplase, a significantly higher proportion of patients on TNK required mechanical ventilation (alteplase: 2 (10.5%) v/s TNK: 10 (43.5%); $P = 0.019$). A single patient in the TNK group developed angioedema.

Table 3 shows the subgroup analysis of primary efficacy and safety outcomes among TNK and alteplase groups in the two window period subgroups (<3 hours and 3-4.5 hours). For both subgroups of the window period (<3 hours and 3-4.5 hours), the thrombolytic agents were comparable for good functional recovery i.e., mRS ≤2 at 90 days as well as primary safety outcomes including any intracranial hemorrhage or symptomatic intracranial hemorrhage.

Discussion

This study showed comparable efficacy and safety of thrombolysis with either alteplase or TNK in AIS patients throughout the 4.5 hours' window period. A good functional recovery at 3 months with mRS scores ≤2 was comparable in both groups. Development of post-thrombolysis intracerebral hemorrhage following either drug was comparable. Patients in both groups had similar in-hospital mortality that at 90 days. Although there was a significantly higher requirement for mechanical ventilation in the TNK group, both groups had a comparable need for decompressive craniotomy.

The results of our study are concordant with those reported in multiple previous studies.[6,7,12,13] The largest phase 3 trial failed to show superiority of TNK over alteplase in terms of good functional recovery (mRS 0 and 1) at 3 months.[6] Our research varies from that of Parson *et al*.[8] and Campbell *et al*.[9] where the primary outcome was reperfusion after 24 hours. While TNK was found superior to alteplase in achieving the primary endpoint of reperfusion and clinical improvement at 24 hours by Parson *et al*.,[8] Campbell *et al*.[9] 2018 reported a comparably higher rate of occluded vascular area reperfusion with TNK as compared to alteplase (22% vs 10%; $P = 0.002$ for noninferiority; $P = 0.03$ for

Table 2: Efficacy and safety outcomes among tenecteplase and alteplase groups

Parameters Median (range)	Alteplase (*n*=19)	Tenecteplase (*n*=23)	*P*
Efficacy outcome			
NIHSS at admission	9 (2-22)	12 (3-33)	0.612
Change in NIHSS at discharge	3 (0-8)	4 (-2 to 15)	0.074
mRS at admission	5 (0-5)	4 (1-5)	0.511
mRS at 90 days	2 (0-6)	1 (0-6)	0.815
mRS ≤2 at 90 days	9 (52.9)	13 (59.1)	0.701
Change in mRS at 90 days	1 (-1 to 3)	2 (-2 to 4)	0.402
In Hospital mortality	3 (15.8)	6 (26.1)	0.418
Mortality at 90 days: *n* (%)	5 (26.3)	6 (26.1)	0.883
Need of Decompressive craniectomy	3 (15.8)	5 (21.7)	0.625
Need of Mechanical ventilation	2 (10.5)	10 (43.5)	0.019
Safety outcome			
Any ICH	6 (31.6)	7 (30.4)	0.936
Symptomatic ICH	1 (5.3)	2 (8.7)	0.667
Other serious side effects	0 (0)	1* (4.3)	NA

ICH: intracerebral hemorrhage; mRS: modified Rankin score; NA: not applicable; NIHSS: National Institute of Health Stroke Scale.
*Angioedema

Table 3: Efficacy and safety outcomes among tenecteplase and alteplase groups in the two subgroups of window period (<3 hours and 3-4.5 hours)

	Parameters	Alteplase	Tenecteplase	*P*
A	Window period <3 hours	(*n*=11)	(*n*=15)	
1	Efficacy outcome			
	mRS ≤2 at 90 days: *n* (%)	5 (45.5%)	8 (53.3%)	0.69
2	Safety outcome			
	Any ICH: *n* (%)	5 (45.5%)	4 (26.7%)	0.42
	Symptomatic ICH: *n* (%)	1 (9.1%)	1 (6.7%)	1.00
B	Window period 3-4.5 hours	(*n*=8)	(*n*=8)	
1	Efficacy outcome			
	mRS ≤2 at 90 days: *n* (%)	5 (62.5%)	5 (62.5%)	1.00
2	Safety outcome			
	Any ICH: *n* (%)	1 (12.5%)	3 (37.5%)	0.57
	Symptomatic ICH: *n* (%)	0 (0)	1 (12.5)	

ICH: intracerebral hemorrhage; mRS: modified Rankin score

superiority), before endovascular thrombectomy. The latter trial was powered for noninferiority and assessed reperfusion at 24 hours as the primary endpoint. Despite substantial reperfusion at initial angiographic assessment, the proportion of patients with functional independence at 90 days (64% vs 51%; $P = 0.06$) and early neurological improvement (reduction of at least 8 points or a score of 0 or 1 on the NIHSS at 72 hours) of their stroke deficit ($P = 0.053$) were comparable between TNK and alteplase groups.[9] The fact that reperfusion must transform into a better functional outcome, is still being questioned. Two recent metanalysis of five randomized controlled trials reported TNK and alteplase to be comparable with regard to functional independence (mRS 0–2) or risk of symptomatic or any intracerebral hemorrhage despite significantly better recanalization.[20,21]

It is worth analyzing subtle differences in the baseline characteristics of previous studies including ours. The baseline NIHSS score of studies showing better functional outcomes[8] or relatively better functional recovery at 3 months[9] with TNK compared to alteplase was 14 and 17, respectively, while the baseline NIHSS in studies showing similar functional outcomes at 3 months[6,7,12,13] including our study, is 12 or less. Higher NIHSS suggests proximal occlusion with a large clot burden. It can be construed that both TNK and alteplase show similar efficacy for small clot burden. However, when faced with an occlusion due to larger clot, TNK fares better compared to alteplase, probably owing to its higher fibrin specificity. TNK was developed as a plasminogen activator with greater fibrin specificity and reduced clearance compared with alteplase.[4] Besides above, advantages of TNK include ease of administration as a single-bolus and shorter time to initiate interfacility transfer following intravenous lytic administration. In our study, the patients in the TNK group showed greater early clinical improvement (a larger change in NIHSS), although statistically insignificant. However, the primary efficacy outcome was similar in both groups. This observation is consistent with the findings of several Indian and Western studies depicting comparable efficacy as well as safety outcomes in both TNK and alteplase groups.[8,9,20,22,23] However, our study differed from previous Indian studies with respect to the time to thrombolysis. While previous Indian studies included patients within 3 hours of stroke onset, we extended the time to thrombolysis to 4.5 hours.[5,11] Subgroup analysis comparing the safety and efficacy end points of TNK and alteplase within 3 hours and 3 – 4.5 hours showed comparable results.

The secondary outcome with respect to safety i.e., intracranial hemorrhage (symptomatic and asymptomatic) was comparable between both TNK and alteplase groups in this study but was higher than that reported in the previous trials.[6,9] While NOR-TEST trial reported any intracerebral hemorrhage and symptomatic intracerebral hemorrhage in 10% and 3% vs 10% and 2% in TNK and alteplase groups respectively,[6] the EXTEND-IA TNK trial reported symptomatic intracerebral hemorrhage in 1% patients each in TNK and alteplase groups.[9] Increased intracerebral hemorrhage in our study might have resulted because of a higher proportion of our patients suffering large vessel stroke in both TNK and alteplase groups (61.9% vs 52.6%) as compared to NOR-TEST (20% vs 20%)[6] and EXTEND-IA TNK (21% vs 18%)[9] trials. Although our study did not compare various doses of TNK during thrombolysis, it has been suggested by previous studies that a higher dose of TNK is associated with greater risk of symptomatic intracranial hemorrhage.[24] We observed a comparable need of decompressive hemicraniectomy in both groups, however, the need of mechanical ventilation was greater in the TNK group, which could have resulted due to greater large vessel stroke with higher NIHSS at admission in the tenecteplase group. Only a single patient in the TNK

group developed angioedema which was managed successfully using intravenous hydrocortisone and diphenhydramine. Angioedema is a rare complication, reported in nearly two percent of AIS patients who are thrombolysis with either TNK or alteplase.[7,25]

Retrospective design, single-centr study, and small sample size are the major limitations of our study. However, the outcome parameters were sufficiently robust and the results are in keeping with those reported in previous literature. A multicentre randomized study with a larger sample size, in clinical settings similar to ours, is desirable to confirm our findings.

Conclusion

The present study showed a comparable efficacy and safety profile of tenecteplase and alteplase in thrombolysis of AIS throughout the 4.5 hours' window period. Moreover, the ease of administration and better pharmacodynamic properties favors tenecteplase.

Authors' contributions to the manuscript

Dr. Dhar N: Writing the first draft; data collection; statistics.

Dr. Kumar M: Writing the first draft; statistics; review and critique.

Dr. Tiwari A: Writing the first draft; data collection; statistics; Review and critique.

Dr. Desai I: Writing the first draft; data collection; statistics.

Dr. Madhaw G: Writing the first draft; data collection; statistics.

Dr. Kumar N: Conception; design; review and critique.

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Conflicts of interest

There are no conflicts of interest.

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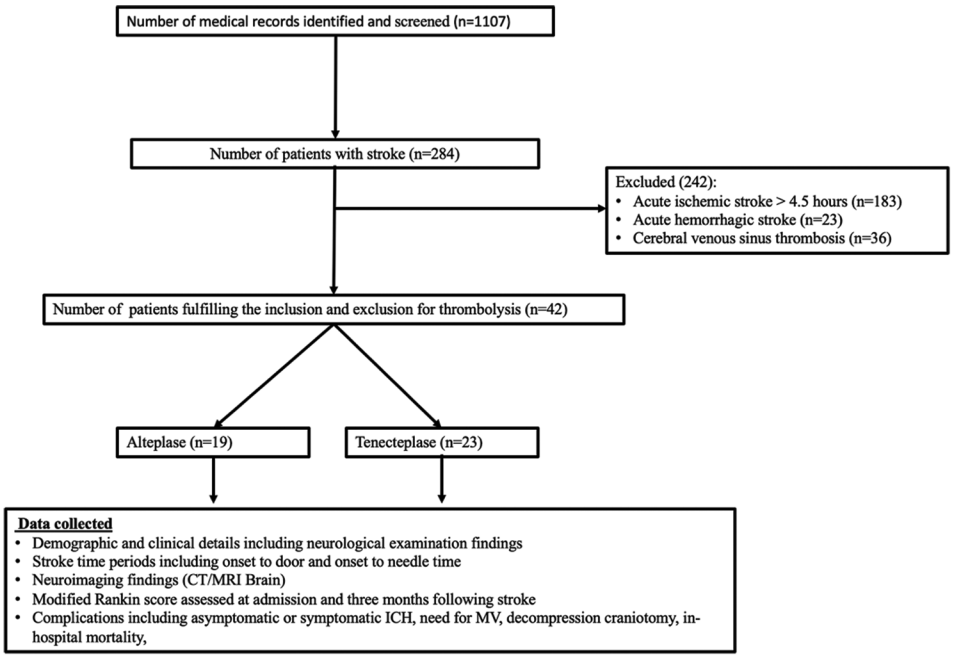

Supplementary Figure 1: CONSORT flowchart for screening, inclusion, and exclusion of cases. CT: Computed tomography; ICH: intracerebral hemorrhage; MRI: magnetic resonance imaging; MV: mechanical ventilation