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ORIGINAL ARTICLES

Tenecteplase versus alteplase (TENVALT): A study comparing two thrombolytic agents in acute ischemic stroke

[1]Kaushik Sundar, [1]Lomesh Bhirud, [1]Ajay Panwar, [2]Jerin Jose Cherian, [3]Eldho Mathew Paul, [1]Gigy Varkey Kuruttukulam

[1]Department of Interventional Neurology, Rajagiri Hospital, Kochi, Kerala; [2]Indian Council of Medical Research, Delhi; [3]Department of Pharmacology, Rajagiri Hospital, Kochi, Kerala, India

Abstract

Background & Objective: The Indian data comparing the efficacy and safety outcomes of tenecteplase and alteplase in acute ischemic stroke is scarce. We aimed to compare the outcomes of two agents in an Indian population. *Methods:* TENVALT study was a single centre, retrospective study. Patients aged 18 years or older with acute ischemic stroke were included in this study if they presented within 3 hours of symptom onset and had a deficit with National Institute of Health Stroke Scale (NIHSS) score > 4, had a modified Rankin score (mRS) of 2 or less before the stroke onset and had no evidence of hemorrhage on non-contrast computed tomography of brain. A good functional recovery (mRS score of 0-2) at the end of three months was defined as the primary efficacy outcome. The development of symptomatic intracerebral hemorrhage was considered as the primary safety outcome. *Results:* A total of 120 patients (alteplase, n=65; tenecteplase, n=55) underwent stroke thrombolysis during this study. The mean age of the presentation in tenecteplase group was 66.6 years and in alteplase group was 62.5 years. Most of the study subjects were males in both the groups (tenecteplase, 78.2%; alteplase, 61.5%). Hypertension was the most common comorbidity in both the groups (tenecteplase, 67.3%; alteplase, 76.9%). Median mRS score at 3 months of follow up was 2 in tenecteplase and 1 in alteplase group; however, the difference between the total number of patients having good functional recovery (mRS 0-2) in the two groups was not statistically significant (tenecteplase 74.5 vs alteplase 87.7%, *P*=0.09). The total number of patients who had symptomatic intracranial hemorrhage was comparable between the two groups (tenecteplase, 5.5%; alteplase, 6.2%).
Conclusion: Tenecteplase appears to be an efficacious alternative to alteplase for stroke thrombolysis and may be better suited to developing countries considering its low cost and ease of administration.

Keywords: Alteplase, tenecteplase, stroke, thrombolysis, efficacy, safety

INTRODUCTION

The concept of 'Time is Brain' – has evolved as the mantra for treatment of acute ischemic stroke over the recent years. Stroke thrombolysis with recombinant tissue plasminogen activator (rt-PA), within 4.5 hours of symptom onset is the cornerstone of AIS management.[1,2] Currently, alteplase is the only internationally approved thrombolytic agent for acute stroke treatment.[3] Alteplase is a second generation rt-PA, which facilitates the conversion of plasminogen to plasmin, which in turn, converts fibrin (clots) to fibrin degeneration products. Although alteplase improves the likelihood of recovery in AIS, it has its own limitations as low recanalization rates, risk of intracranial hemorrhage, susceptibility to plasminogen activation inhibitors (PAI) and relatively short half-life resulting in its required administration as an infusion drug.[4] Tenecteplase which is a three point mutated variant of alteplase, has recently been approved in India for the treatment of ischemic stroke. Unlike alteplase, tenecteplase is available as a single bolus dose. Tenecteplase has shown a better thrombolytic profile and potency as compared to alteplase in animal models as well as *in vitro* studies.[5] There

Address correspondence to: Dr. Ajay Panwar, Department of Interventional Neurology, Rajagiri Hospital, Kochi, India. Tel: -8948800337, E-mail: ajay19panwar@gmail.com

is no Indian published data on the comparative analysis of the safety and efficacy of these two drugs in stroke. We therefore conducted this study to compare the efficacy and safety of tenecteplase versus alteplase among patients presenting to our centre with acute ischaemic stroke.

METHODS

TENVALT study was a single centre, retrospective, comparative study of a cohort of patients who received alteplase versus those receiving tenecteplase for acute ischemic stroke. Patients were enrolled between July 1, 2016 and June 30, 2018.

Inclusion and exclusion criteria

All the patients who was 18 years or older in age with acute stroke clinically were included in this study if they presented within 3 hours of symptom onset, had a deficit with National Institute of Health Stroke Scale (NIHSS) score > 4, had a modified Rankin score (mRS) of 2 or less before the stroke onset, had no evidence of hemorrhage on non-contrast computed tomography (CT) imaging of brain. Patients with contraindications for thrombolysis were excluded. A written informed consent for thrombolysis was obtained from the patient wherever feasible, or else by the close relative. The consent included a detailed explanation of the benefits and risks associated with stroke thrombolysis, with a special mention of the risk of hemorrhage. The study was reviewed and approved by the ethics committee of the Rajagiri Hospital.

Data entry and retrieval

The demographic, clinical and imaging details of all the patients for whom emergency stroke code is activated are prospectively entered into our hospital based central data repository. This encompass the stroke time frames including onset to door, door to CT and door to needle times are also entered by the attending stroke physician. We performed a retrospective data sorting and retrieval of the stroke code patients according to the defined inclusion and exclusion criteria.

Drug administration

Patients were then administered either tenecteplase or alteplase as per the treating stroke physician's discretion. Patients meeting inclusion criteria received either tenecteplase (0·2 mg/kg to a maximum of 20 mg as a single bolus intravenously) or alteplase (0·9 mg/kg to a maximum of 90 mg, with 10% of the dose as initial bolus, followed by 90% as intravenous infusion over 1 hour).

Angiographic evaluation and mechanical thrombectomy protocol

All the ischemic stroke patients in our study underwent an urgent baseline CT angiogram (CTA) of brain and neck vessels. The patients who were observed to have an intracranial large vessel occlusion on CTA were immediately shifted to catheter laboratory for digital subtraction angiography (DSA). The patients receiving tenecteplase were shifted after getting the bolus dose according to the aforementioned protocol; while in those receiving alteplase, we used a drip-and- ship treatment liaison system in which patient was transferred after starting alteplase infusion.[6] Mechanical thrombectomy was performed in patients confirmed to have a large vessel occlusion on DSA. Informed consents were obtained before performing DSA and mechanical thrombectomy.

Outcome measures

A good functional recovery (mRS score of 0-2) at the end of three months was defined as the primary efficacy outcome.The functional recovery in follow-up visits including the one at 3 months was assessed by the rehabilitation specialist who was blinded to the thrombolytic agent received by the patient. The primary safety outcome was assessed by analyzing patients with symptomatic intracerebral hemorrhage (defined as any fresh intracranial bleeding resulting in a decline of NIHSS >4 points or death) within the first 24 hours after administration of thrombolytic agent.[7] All patients underwent a follow-up brain imaging after 24 hour of receiving thrombolytic therapy. Further, the patients with a neurological deterioration causing any measurable worsening on NIHSS score underwent an immediate CT brain imaging to rule out hemorrhage.

Statistical analysis

Statistical analysis was conducted using IBM. SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were computed as percentages, while continuous variables as mean±S.D. mRS being an ordinal scale variable, its values were analysed as median. Chi-Square test was used for comparing categorical variables. All *P* values less than 0.01 were considered as significant.

RESULTS

A total of 120 patients underwent stroke thrombolysis during the study; of whom 65 received alteplase, while 55 were thrombolysed with tenecteplase. The baseline characteristics of the patients are as shown in Table 1. Most of the baseline characteristics were comparable in both the groups.

Efficacy and safety

Table 2 shows outcome analysis of the two groups. Median mRS score at 3 months of follow up was 2 in the tenecteplase and 1 in the alteplase group. The good functional recovery at 3 months with mRS scores of 0-2 was observed among 74.5% of the patients in the tenecteplase group and among 87.7% in the alteplase group. This difference in the primary efficacy outcome did not achieve statistical significance (*P*=0.09). Thus, both the agents proved to be efficacious in improving functional outcomes. The total number of patients who had symptomatic intracranial hemorrhage was comparable between the two groups (tenecteplase, 5.5%; alteplase, 6.2%). Figure 1 shows a graphical representation of the primary efficacy and safety outcomes among the two groups.

Table 1: Basic characteristics of the patients in alteplase and tenecteplase groups

Characteristics		Tenecteplase (n=55)	Alteplase (n=65)	*P* Value
Age (years, mean±SD)		66.6±8.72	62.5±9.22	0.16
Gender (male)		43 (78.2%)	40 (61.5%)	0.07
Risk factors	DM	24 (43.6%)	28 (43.1%)	0.95
	HTN	37 (67.3%)	50 (76.9%)	0.23
	CAD	12 (21.8%)	14 (21.5%)	0.97
	AF	8 (14.5%)	6 (9.2%)	0.38
	CKD	2 (0.4%)	1 (0.2%)	0.59
	DLP	8 (14.5%)	14 (21.5%)	0.32
Onset To ER Arrival	<1 hour	11 (20.0%)	15 (23.1%)	0.43
	1-2 hour	22 (40.0%)	18 (27.7%)	
	2-3 hour	22 (40.0%)	32 (49.2%)	
NIHSS On arrival	<5	20 (36.4%)	23 (35.4%)	0.07
	5-10	14 (25.5%)	28 (43.1%)	
	11-20	16 (29.1%)	13 (20.0%)	
	>20	5 (9.1%)	1 (1.5%)	
ASPECTS	<6	4 (7.3%)	0 (0%)	0.03
	6-8	8 (14.5%)	5 (7.7%)	
	>8	43 (78.2%)	60 (92.3%)	
Presence of large vessel occlusion		18 (32.7%)	12 (18.5%)	0.09
Mechanical thrombectomy done		8 (14.5%)	5 (7.7%)	0.25

SD-Standard deviation, ER- emergency room, NIHSS- National institute of health stroke scale, ASPECTS-Alberta stroke program early CT score, DM- Diabetes mellitus, HTN- Hypertension, CAD-Coronary artery disease, AF- Atrial fibrillation, CKD-Chronic kidney disease, DLP- Dyslipidemia

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

Outome parameter	Tenecteplase (n=55)	Alteplase (n=65)	*P* Value
Recanalization of large vessel after IVT (without MT)	3 (16.7%)	1 (8.3%)	0.58
Any intracranial bleed during hospital stay	4 (7.3%)	8 (12.3%)	0.54
Symptomatic ICH	3 (5.5%)	4 (6.2%)	1.00
Good functional recovery at 3 months (mRS 0-2)	41 (74.5%)	57 (87.7%)	0.09

IVT- intravenous thrombolysis, MT- Mechanical thrombectomy, ICH- intracerebral hemorrhage

Large vessel recanalization rates

In some cases presumed to be large vessel occlusion on the basis of CT angiogram, large vessel recanalization was observed on DSA without the consequent need of mechanical thrombectomy. This vessel recanalization rate with thrombolysis alone was 16.7% with tenecteplase while 8.3% with alteplase, the difference was not statistically significant.

DISCUSSION

In this TENVALT study, patients with acute ischemic stroke treated with alteplase and tenecteplase had no significant difference in long

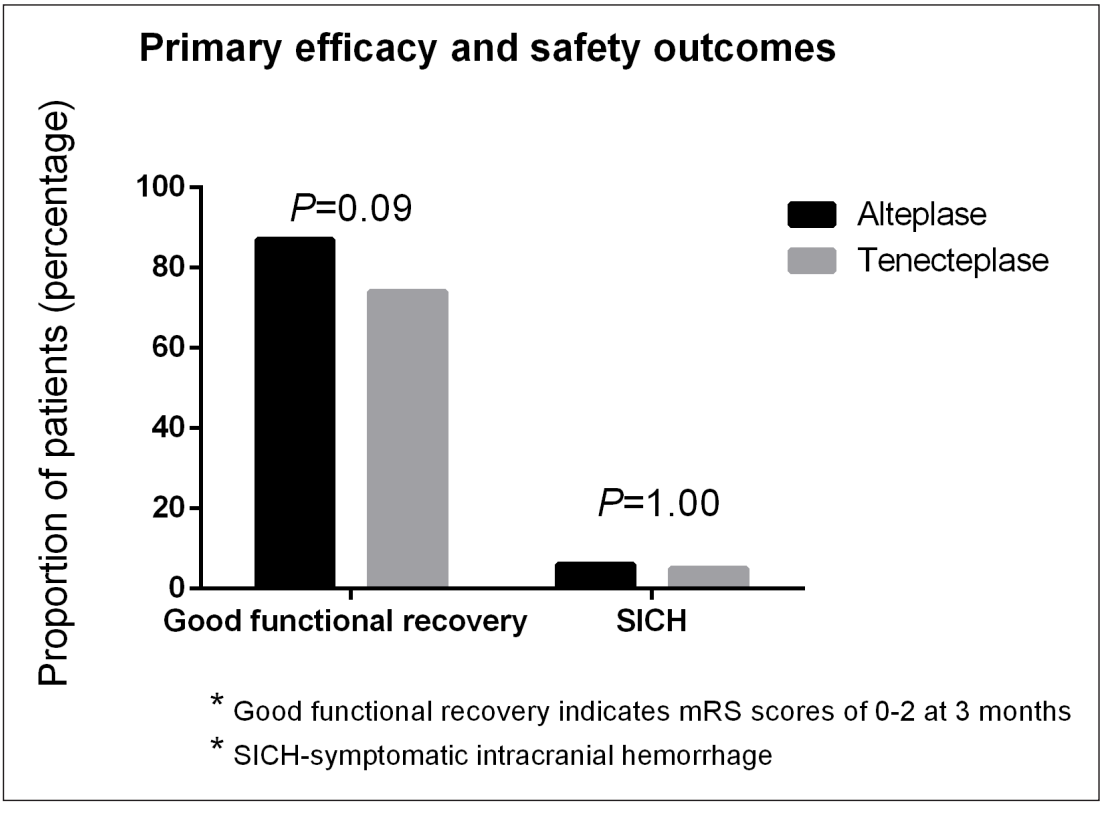

Figure 1. A graphical representation of the primary efficacy and safety outcomes among the alteplase and tenecteplase groups

term functional recovery. The safety profile among the two groups was also comparable.

The patients in the alteplase group were observed to have a lower median mRS score at 3 months; however, the primary efficacy outcome was comparable between both the groups. This observation is in contradiction with the results of some Western studies which reported the mRS score at 3 months in tenecteplase arm to be lower as compared to alteplase arm.[8,9] Besides, recent reviews have shown similar efficacy and safety profiles in both the groups.[10-12] Apart from the different ethnicity, other factor which may be responsible for this discordance in results is that we enrolled the patients only within 3 hour of the onset. Table 3 shows a comparative summary of the various studies which analysed the outcomes of tenecteplase versus alteplase in acute ischemic stroke.

Primary safety outcome defined as symptomatic intracerebral bleed with worsening of NIHSS >4 in the first 24 hours after admission was similar in both tenecteplase and alteplase arm. Previous studies on tenecteplase had conflicting reports

Table 3: A comparison of various studies which analysed the outcomes of tenecteplase versus alteplase in ischemic stroke

Study	Study design	Methods			Results	
		Time window (hr)	Tenecteplase dose	rtPA (Alteplase) dose	Efficacy	Safety
Campbell *et al*.[8] (2018)	Randomized trial	4.5	0.25 mg/kg	0.9 mg/kg	Tenecteplase resulted in a better 90-day functional outcome than alteplase (mRS 2 vs 3; P=0.04).	SICH occurred in 1% in both groups
Parsons *et al*.[9] (2012)	Randomized trial- Triple arm	6	0.25 mg/kg and 0.1 mg/kg	0.9 mg/kg	0.25 mg/kg tenecteplase was superior to the lower dose and alteplase for all efficacy outcomes, including functional outcome at 90 days (P=0.02).	Intracranial bleed was comparable among the three groups.
Huang *et al*.[13] (2015)	Randomized trial	4.5	0.25 mg/kg	0.9 mg/kg	Efficacy outcomes were comparable between the two groups.	Safety outcomes were comparable between the two groups.
Logallo *et al*.[17] (2017)	Randomized trial	4.5	0.4 mg/kg	0.9 mg/kg	Excellent functional outcome (mRS 0-1) at 3 months was comparable in both the groups (P=0.52)	Adverse events were also comparable (P=0.74)
Kaushik *at al*. *(present study)* (2019)	Retrospective study	3	0.2 mg/kg	0.9 mg/kg	Good functional outcome (mRS 0-2) at 3 months was not significantly different among the two groups (P=0.09)	SICH was comparable between the two groups (tenecteplase-5.5%, alteplase-6.2%)

rtPA- recombinant tissue plasminogen activator, SICH- Symptomatic intracranial hemorrhage, mRS- modified rankin scale

on safety outcome. Parsons *et al*. in their study had tested two tenecteplace doses (0.1 and 0.25 mg/kg) while Huang *et al*. examined only 0.25 mg/kg.[9,13] In both these studies the safety profile was comparable with alteplase; whereas in a trial by Haley *et al*. tenecteplace dose of 0.4mg/kg was compared with 0.9mg/kg alteplase and was observed to significantly increase the risk of symptomatic intracranial hemorrhage (3/19 [16%] patients). In this study, we used tenecteplase 0.2mg/kg (max dose 20 mg) and the safety outcome was comparable between the two groups. Considering the results of the previous studies, the tenecteplase dose of 0.2 mg/kg appears optimal for safety and efficacy.[14]

In the treatment of acute ischemic stroke, recanalization of the vessel is important for efficacy to achieve functional outcome. In EXTEND-IA trial, among patients with acute ischemic stroke from major cerebral vessel occlusion within 4.5 hours after the onset of symptoms, intravenous tenecteplase resulted in a significantly higher incidence of reperfusion of the occluded vascular territory before endovascular thrombectomy than did intravenous alteplase (22% vs 10%; *P*=0.02).[8] In our study, there was no significant difference between the two agents. The reason could be fewer number of cases with large vessel occlusion in our study. Notwithstanding, the low frequency of recanalization with thrombolytic agent alone clearly highlights the importance of mechanical thrombectomy for intra-arterial clot retrieval.

There are a few limitations in our study. Firstly, it was a single centre retrospective study. Secondly, the study design was a non-randomized one and the number of patients enrolled in the two arms were small to adequately empower the study. A large scale multi-centric prospective randomized study in our clinical settings would be ideal to further test the hypothesis of this study.

In view of the lower cost (tenecteplase costs almost half of the alteplase for a 60 Kg patient) and ease of administration, tenecteplase may have a great potential as a stroke thrombolytic agent especially in the resource limited settings of developing countries.[15] It may be enormously helpful in overcoming the emerging stroke epidemic.[16]

DISCLOSURE

Conflict of interest: None

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