Original Article

Efficacy and safety of tenecteplase as bridging therapy in large vessel occlusions: A retrospective observational study

ABSTRACT

Background and Objectives: Clinical trials showed a higher recanalization rate of tenecteplase (TNK) over alteplase in large vessel occlusion (LVO) and better functional independence at the end of 3 months without increasing the risk of systematic intracranial haemorrhage (SICH). Indian data on the efficacy of tenecteplase as bridging therapy in LVOs are scarce. We aimed to review the outcomes and safety of tenecteplase up to 4.5 h in LVO patients who were taken for mechanical thrombectomy (MT).

Methods: This is a single-center retrospective study. Patients with acute ischemic stroke who had LVO and were taken to an angiographic suit for MT were included in the study. Other inclusion criteria were an age of more than 18 years, National Institute of Health Stroke Scale >4, modified Rank in score (mRS) of 2 or less before stroke, and no evidence of hemorrhage on noncontrast computed tomography of brain. The primary efficacy outcome was mRS score of 0–2 at the end of 3 months. Development of symptomatic intracerebral hemorrhage was considered the primary safety outcome.

Results: A total of 27 patients were included in this study. The mean age of presentation was 61 years. Most of the study subjects were males 59.25%. Hypertension was the most common risk factor seen in 19 (70.37%) of subjects. About 11 patients (40.74%) had M1 occlusion, 6 (22.22%) subjects had M2 occlusion, 8 (29.62%) patients had internal carotid artery occlusion, and 2 (7.4%) subjects had basilar occlusion. Early recanalization with IV thrombolysis (IVT) was noted in 5 (18.51%) of patients after IVT with tenecteplase. Functional independence (mRS: 0–2) was achieved in 15% (55.55%) of patients. Symptomatic intracranial hemorrhage was seen in 1 (3.7%) subjects and death within 90 days is noted in 3/27 (11.11%) subjects.

Conclusion: Tenecteplase is appearing to be an effective bridging agent before MT in LVOs considering its ease of administration, low cost, effective recanalization rates, and good functional recovery.

Keywords: Alteplase, mechanical thrombectomy, tenecteplase

INTRODUCTION

Worldwide, stroke ranks as the second leading cause of death and the third leading cause of composite death and disability.[1] Acute ischemic stroke (AIS) constitutes 85% of stroke cases. Novel treatments such as IV thrombolysis (IVT), and more recently, mechanical thrombectomy (MT) for large vessel occlusion (LVO) have reduced mortality by 10% compared with the older treatments and improved long-term disability prevention rates after AIS.[2,3] AIS management guidelines recommend intravenous thrombolysis with the tissue plasminogen activator alteplase within 4.5 h after the onset of stroke and MT within 24 h after onset.[4,5] Accumulating evidence from clinical trials suggests that

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tenecteplase may represent an effective treatment agent compared with alteplase for AIS.[6,7] In a recently published Randomized controlled trial (RCT), tenecteplase administration was associated with a 2-fold increase in the odds of successful recanalization of AIS patients with LVO before the initiation of endovascular treatment compared with patients receiving pretreatment with intravenous alteplase. Patients randomized to intravenous tenecteplase before endovascular treatment also had better functional outcomes at 3 months compared with patients receiving intravenous alteplase.[8] TNK has several advantages that make it an appealing and effective agent, it is generally cost-effective, has a high fibrin specificity and longer plasma half-life, enhanced plasminogen activator inhibitor-1 resistance, and can be dispensed as a single bolus, making it applicable in the prehospital settings.[9] Indian data on the usage of tenecteplase in LVOs before MT are sparse. In this study, we aimed to review the efficacy and safety of tenecteplase in LVOs as bridging therapy before MT in our center.

METHODS

This was a single-center, retrospective, observational study. We have studied a cohort of patients who received tenecteplase as a bolus dose for AIS secondary to LVO before taking to angiographic suit for MT. Patients were enrolled between April 1, 2021, and March 30, 2023.

Inclusion and exclusion criteria

All the patients of AIS who presented within 4.5 h of onset of symptoms, had LVO (defined as middle cerebral artery [M1, M2], internal carotid artery [ICA], CCA, and basilar occlusions), underwent thrombolysis with tenecteplase, and taken to angiographic suit for MT. Other inclusion criteria were an age of more than 18 years, a deficit with National Institute of Health Stroke Scale (NIHSS) score >4, a modified Rank in score (mRS) of 2 or less before the stroke onset, and no evidence of hemorrhage on noncontrast computed tomography (CT) imaging of brain. Patients with contraindications for thrombolysis were excluded from the study. A written informed consent for thrombolysis and thrombectomy 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 and MT are obtained.

Data entry and retrieval

The demographic, clinical, and imaging details of all the patients for whom the emergency stroke code is activated are prospectively entered into our hospital-based central stroke data register. The stroke timeframes including onset to door, door to CT and door to needle times, and door to groin puncture were entered by the attending ER physician and neuro interventionist. We performed a retrospective data sorting and retrieval of the stroke patients who underwent recanalization therapies according to the defined inclusion and exclusion criteria.

Drug administration

Patients were administered 0.25 mg/kg of tenecteplase as single bolus intravenously over 5 s.

Angiographic evaluation and mechanical thrombectomy protocol

All the ischemic stroke patients in our study underwent an urgent baseline magnetic resonance imaging (MRI) brain and TOF MR angiography of intracranial vessels. Patients in whom MRI could not be done, CT brain and CT angiogram of intracranial and extracranial vessels were done. The patients who had intracranial LVOs were immediately shifted to the catheter laboratory for digital subtraction angiography (DSA). The patients receiving tenecteplase were shifted after getting the bolus dose according to the aforementioned protocol. MT was performed in patients confirmed to have an LVO on DSA. Informed consents were obtained before performing DSA and MT.

Outcome measures

Early recanalization noted in the angiography suit and good functional recovery (mRS score of 0–2) at the end of 3 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 neurologist. 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 h after administration of thrombolytic agent. All patients underwent a follow-up brain imaging after 24 h 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 ± standard deviation mRS being an ordinal scale variable, its values were analyzed as median. One-way ANOVA test was used for comparing categorical variables. All $P < 0.01$ were considered significant.

RESULTS

A total of 27 patients underwent intravenous thrombolysis with tenecteplase and were taken to angiographic suit for DSA, followed by MT during the study period. The baseline characteristics of the patients are shown in Table 1.

Efficacy and safety outcome parameters

The recanalization after IVT with good distal flow (TICI2B/3) was seen in 5 (18.51%) patients. Median mRS score at 3 months of follow-up was 2. The good functional recovery at 3 months with mRS 0–2 was observed in 55.5% of patients. The total number of patients who had symptomatic intracranial hemorrhage was 1 (3.7%) [Figure 1]. Total number of deaths related to stroke in 3 months was 3 (11.11%). Total of 3 (11.11%) patients underwent decompressive hemicraniectomy. None of the patients had access site complications [Table 2].

Characteristics of patients who had recanalization with IV thrombolysis

A total of five patients with LVO had recanalization after IVT, out of which two patients had M2 occlusion, two patients had M1 occlusion, and one patient had ICA occlusion. Three of these five patients underwent thrombolysis within 3 h of onset of symptoms [Table 3].

DISCUSSION

In this single-center retrospective study of patients with AIS with LVO, intravenous thrombolysis with tenecteplase before endovascular thrombectomy is observed to be effective and safe. The recanalization rates in the present study are 18.51% when compared to recanalization rates with alteplase in LVO in other studies such as ESCAPE trial 5.1% (7/118) and[10] MR CLEAN-NO IV 3.7% (9/245).[11] Symptomatic intracranial hemorrhage in the ESCAPE trial was 6/165 (3.6%), in MR CLEAN-NO IV 14/266 (5.3%), in alteplase, followed by EVT group, in the present study, SICH is 1/27 (3.7%) which is comparable with above two RCTS. In the MR CLEAN-NO IV trial, death within 90 days in 42/266 (15.8%, in alteplase, followed by EVT group), in the ESCAPE trial, death within 30 days 44/233 (18.9%) in the intervention group, in the present study, death within 90 days is 3/27 (11.11%) which is comparable with the above two RCT. The higher recanalization rates of patients in the present study could be attributed to the higher fibrin specificity and more potent clot dissolution with tenecteplase[12] leading to faster vessel recanalization. The tenecteplase can be administered as a single bolus injection compared with alteplase which requires 1 h infusion after initial bolus.[12,13] The ease of tenecteplase administration constitutes an indisputable advantage in the acute stroke setting, enabling prompt AIS treatment in the emergency department or even in an ambulance. The clinical benefit of tenecteplase compared with alteplase has been reported to be more pronounced for patients with

Table 1: Baseline characteristics of patients

Characteristics of the patient	*n*=27, *n* (%)
Age (years), mean±SD	61±15.04
Gender (male)	16 (59.25)
Risk factors	
Type 2 DM	14 (51.85)
HTN	19 (70.37)
CAD	7 (25.29)
Dyslipidemia	12 (44.44)
CKD	4 (14.81)
Rheumatic heart disease	3 (11.11)
NIHSS score on arrival	
<5	0
5–10	2 (7.4)
11–20	19 (70.37)
>20	6 (20.68)
Onset to IVT time	
IVT in 0–3 h	11 (37.93)
IVT in 3–4.5 h	14 (51.85)
Unknown time of onset	2 (7.4)
Drip and ship (received IVT outside our hospital)	4 (14.81)
Onset to groin puncture time	
Onset to groin time up to 6 h	16 (59.25)
Onset to groin time beyond 6 h	9 (33.33)
Diffusion/CT aspect	
<6	3
6–8	22
>8	0
LVO	
M1	11 (40.74)
M2	6 (22.22)
ICA	8 (29.62)
Basilar artery	2 (7.4)

SD: Standard deviation, NIHSS: National Institute of Health Stroke Scale, DM: Diabetes mellitus, HTN: Hypertension, CAD: Coronary artery disease, AF: Atrial fibrillation, CKD: Chronic kidney disease, DLP: Dyslipidaemia, LVO: Large vessel occlusion, MCA: Middle cerebral artery, ICA: Internal carotid artery, CT: Computed tomography, IVT: Intravenous thrombolysis

Table 2: Efficacy and safety outcomes table

Efficacy outcomes	*n*=27, *n* (%)
Recanalization after IVT (0–4.5 h)	5 (18.51)
Received IVT in 3 h	5 (18.51)
Received IVT in 3–4.5 h	2 (7.4)
Recanalization after MT	18 (66.66)
Functional independence MRS (2≤) at 3 months	15 (55.55)
Any hemorrhage	4 (14.81)
Symptomatic hemorrhage	1 (3.7)
DECRA	3 (11.11)
Death	3 (11.11)
Access site complications	0

IVT: Intravenous thrombolysis, MT: Mechanical thrombectomy, MRS: Modified Rank in score

viable penumbra and considerable mismatch in baseline neuroimaging,[13] providing further support to the hypothesis that earlier and more complete tenecteplase-induced reperfusion in patients. In an Indian study, TENVALT[14] which compared two thrombolytic agents TNK and alteplase, a total of 45 patients received TNK of which 18 patients had LVO of which 3 patients (16.6%) had early recanalization during the digital subtraction angiogram. In EXTEND 1A TNK part 2,[15] a randomized controlled study comparing 0.25 mg versus 0.4 mg dosage of TNK in LVOs, a total of 150 patients received 0.25 mg TNK. In EXTEND 1A TNK part 2 trial, 19.3% (29/150) of subjects had early recanalization, 56% (84/150) of patients had functional independence at the end of 3 months, and 1.3% (3/150) had symptomatic hemorrhage. In the present study, we observed early recanalization rates with IVT were 18.51% (5/27), functional independence at the end of 3 months to 55.55% (15/27) which is comparable to EXTEND 1A TNK part 2 trial. In our study, symptomatic hemorrhage rates are 3.7% (1/27) which is similar to 1.3% (2/150) SICH rates of EXTEND 1A TNK part 2. Death within 90 days in the EXTEND 1A part 2 trial is 22/150 (15%, TNK 0.25 mg group), in the present study, death within 90 days is 11.11% (3/27) which is comparable with the above RCT. Comparision of safety and efficacy outcomes of present study with extend 1a tnk part 2 trial is shown in Table 4.

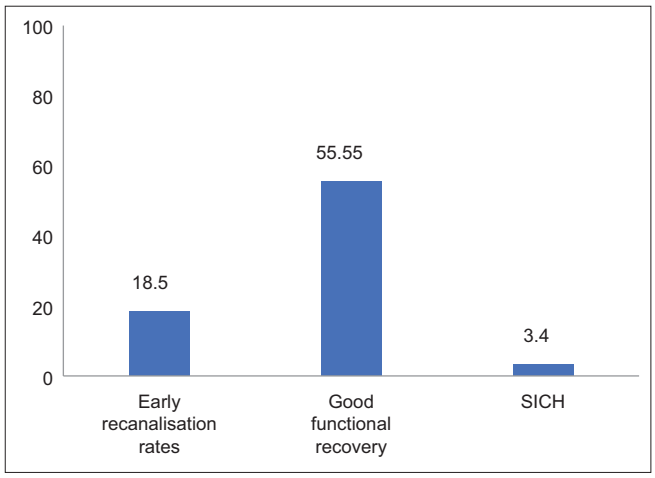

Figure 1: Chart representing primary efficacy and safety outcomes

Table 3: Characteristics of patients who had recanalization with IV thrombolysis

Age	Onset to IVT time	LVO	Onset to groin time
28	3 h 45 min	M2	5 h
40	2 h 15 min	M2	4 h
72	45 min	ICA	7 h 15 min
55	1 h 45 min	M1	2 h 30 min
55	2 h 50 min	M1	4 h 15 min

IVT: Intravenous thrombolysis, LVO: Large vessel occlusion, ICA: Internal carotid artery

In a systemic review and meta-analysis done by Katsanos *et al*.,[16] it was found that AIS patients with LVO receiving intravenous thrombolysis with tenecteplase have three-fold higher odds of achieving successful recanalization and two-fold higher odds of having favorable clinical outcomes at 3 months compared with patients receiving intravenous alteplase. The above meta-analysis is a review of the Australian TNK trial[17] and EXTEND 1A TNK trial.[8]

In the present study, four patients received TNK in the drip-and-ship model, of whom one patient had early recanalization noted in the angiographic suit. A recent French report highlights that tenecteplase and alteplase may yield similar complete recanalization rates (21% vs. 18%) in LVO patients pretreated with intravenous thrombolysis in the drip-and-ship setting.[18] There are few limitations in our study such as small sample size, single-center retrospective study, and no comparative data with alteplase. A large-scale multi-centric prospective randomized study with tenecteplase and alteplase as bridging agents in our clinical settings would be ideal to test the hypothesis of better bridging thrombolytic agents before MT in LVOs.

CONCLUSION

In view of the lower cost and ease of administration, higher early recanalization rates, and better functional outcomes, tenecteplase may have great potential as a bridging therapy in LVOs before MT. Because of the ease of administration, it is enormously helpful in the drip-and-ship model before being shifted for MT in LVO.

Table 4: Comparison of the present study with EXTEND 1 A TNK part 2 study

Study	Study design	Recanalization rates (%)	Functional independence at 3 months mRS of 0–2 (%)	Symptomatic hemorrhage (%)	Results
EXTEND 1A TNK part 2 (0.25 mg group)	RCT	29/150 (19.3)	84/150 (56)	2/150 (1.3)	0.25 mg/kg TNK is as efficacious as 0.4 mg/kg in LVO
Present study	Retrospective observational	5/25 (18.5)	15/27 (55.55)	1/27 (3.7)	Early recanalization rates of 18.5%, functional recovery of 55.55% are comparable with other TNK trials and better than alteplase, with a SICH rates of 3.4%

LVO: Large vessel occlusion, mRS: Modified Rank in score, TNK: Tenecteplase, SICH: Systematic intracranial haemorrhage

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Conflicts of interest

There are no conflicts of interest.

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