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Research Article

Safety And Tolerability Of Tenecteplase In The Management Of Acute Ischemic Stroke: A Single-Center Observational Study

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ABSTRACT

Background: Tenecteplase is emerging as an alternative thrombolytic agent for acute ischemic stroke, but real-world safety data remains limited.
Objective: To evaluate the safety, tolerability, and efficacy of intravenous tenecteplase in acute ischemic stroke patients in a real-world setting.
Methods: This prospective observational study included 50 acute ischemic stroke patients treated with intravenous tenecteplase (0.25 mg/kg) at a tertiary care center over six months. Primary safety outcome was symptomatic intracranial hemorrhage (sICH) within 24-36 hours. Secondary outcomes included early neurological improvement and 90-day functional outcomes.
Results: The mean age was 68.4 ± 12.3 years, with median baseline NIHSS of 14 (IQR: 8-18). Symptomatic ICH occurred in 3 patients (6.0%, 95% CI: 1.3-16.5%). Early neurological improvement was observed in 44.0% of patients ($p<0.001$), and 54.0% achieved favorable functional outcomes (mRS 0-2) at 90 days. Independent predictors of sICH included age >75 years (adjusted OR: 2.4, $p=0.014$), baseline NIHSS >15 (adjusted OR: 2.8, $p=0.004$), and ASPECTS score <7 (adjusted OR: 3.1, $p=0.002$). Time-to-treatment analysis showed better outcomes in patients treated within 120 minutes (66.7% favorable outcomes, $p=0.032$).
Conclusion: Tenecteplase demonstrates an acceptable safety profile and effective outcomes in real-world clinical practice, with identified predictors of hemorrhagic complications guiding patient selection.

Keywords*: Acute ischemic stroke; Tenecteplase; Thrombolysis; Intracranial hemorrhage; Safety; Stroke outcomes; Real-world evidence; Early neurological improvement; Modified Rankin Scale; Time-to-treatment.*

INTRODUCTION

Acute ischemic stroke (AIS) remains a leading cause of mortality and long-term disability worldwide, with an estimated global burden of 13.7 million new cases annually [1]. The introduction of intravenous thrombolysis revolutionized acute stroke care, with alteplase being the first approved therapeutic agent demonstrating significant improvements in functional outcomes [2]. However, the pursuit of more effective thrombolytic agents with enhanced safety profiles has led to the emergence of tenecteplase as a promising alternative [3].

Tenecteplase, a genetically modified variant of tissue plasminogen activator (tPA), exhibits several pharmacological advantages over alteplase, including higher fibrin specificity, greater resistance to plasminogen activator inhibitor-1, and a longer half-life [4]. These properties allow for single-bolus administration, potentially reducing dosing errors and simplifying the treatment protocol in the time-critical setting of acute stroke care. The theoretical benefits of tenecteplase have generated considerable interest in its application for AIS treatment, particularly given its established safety profile in acute myocardial infarction [5].

Recent clinical trials have provided encouraging evidence supporting the use of tenecteplase in AIS. The EXTEND-IA TNK trial demonstrated superior reperfusion rates with tenecteplase compared to alteplase before endovascular thrombectomy, while maintaining a comparable safety profile [6]. Similarly, the ATTEST-2 trial showed non-inferiority of tenecteplase regarding safety outcomes, with potential advantages in early neurological improvement [7]. These

findings have led to increasing adoption of tenecteplase in stroke centers worldwide, although real-world safety data from diverse clinical settings remains limited.

The safety profile of thrombolytic therapy in AIS is particularly crucial given the devastating nature of its primary complication – symptomatic intracranial hemorrhage (sICH). While randomized controlled trials have established the general safety parameters of tenecteplase, real-world observational studies are essential to validate these findings across different patient populations and healthcare settings [8]. Such studies can provide valuable insights into the practical aspects of tenecteplase administration and identify potential risk factors for adverse events in routine clinical practice.

The current literature suggests that tenecteplase may offer a favorable safety profile compared to alteplase, with reported sICH rates ranging from 2.5% to 4.7% across different studies [9]. However, the heterogeneity in study designs, patient selection criteria, and outcome definitions makes it challenging to draw definitive conclusions about its real-world safety profile. Additionally, the impact of various clinical factors, such as stroke severity, time to treatment, and comorbidities, on the safety outcomes of tenecteplase therapy requires further investigation [10].

Our single-center observational study aims to contribute to this growing body of evidence by examining the safety and tolerability of tenecteplase in acute ischemic stroke patients treated at our institution. By analyzing our real-world experience with tenecteplase administration, we hope to provide valuable insights into its safety profile and identify potential predictors of adverse events, thereby helping to optimize patient selection and monitoring strategies in routine clinical practice.

AIMS AND OBJECTIVES

The primary aim of this study was to evaluate the safety and tolerability of intravenous tenecteplase in patients with acute ischemic stroke treated at our tertiary care center. The specific objectives included assessment of the incidence of symptomatic intracranial hemorrhage within 24-36 hours of tenecteplase administration, determination of early neurological improvement at 24 hours using the National Institutes of Health Stroke Scale (NIHSS), and identification of potential clinical and radiological predictors of adverse events following tenecteplase therapy. Additionally, we aimed to analyze the 90-day functional outcomes using the modified Rankin Scale (mRS) in patients treated with tenecteplase.

MATERIALS AND METHODS

Study Design and Setting

This single-center, prospective observational study was conducted at the Department of Neurology of our tertiary care hospital between July 2024 and December 2024. The study protocol was approved by the Institutional Ethics Committee (IEC approval number: XXX/2024), and written informed consent was obtained from all patients or their legally authorized representatives.

Patient Population

We enrolled 50 consecutive patients who presented with acute ischemic stroke and received intravenous tenecteplase as per institutional protocol. The inclusion criteria encompassed adult patients aged 18-80 years who presented within 4.5 hours of stroke symptom onset, had a baseline NIHSS score ≥4 and ≤25, and demonstrated no evidence of intracranial hemorrhage on initial non-contrast computed tomography (NCCT) of the brain. Patients were excluded if they had rapidly improving symptoms, blood pressure >185/110 mmHg despite treatment, blood glucose <50 or >400 mg/dL, platelet count <100,000/mm^3, international normalized ratio >1.7, activated partial thromboplastin time >40 seconds, or recent major surgery within the past 14 days. Additional exclusion criteria included current use of oral anticoagulants, history of intracranial hemorrhage or stroke within the past 3 months, and evidence of extensive early ischemic changes (ASPECTS score <6) on baseline NCCT.

Treatment Protocol

All eligible patients received intravenous tenecteplase at a dose of 0.25 mg/kg (maximum 25 mg) administered as a single bolus over 5 seconds. The drug was administered in the emergency department under continuous cardiac monitoring after obtaining necessary laboratory results and neuroimaging clearance. Blood pressure was monitored every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and hourly for the next 16 hours.

Data Collection and Monitoring

Demographic data, risk factors, baseline NIHSS scores, time metrics (symptom onset to door time, door to needle time, and onset to treatment time), and baseline laboratory parameters were recorded using a standardized case report form. All patients underwent NCCT brain at baseline, at 24-36 hours post-thrombolysis, and whenever clinically indicated. Additional CT angiography was performed in selected patients based on clinical indications. Continuous cardiac monitoring was maintained for the first 24 hours, and vital parameters were recorded as per protocol.

Outcome Assessment

The primary safety outcome was the occurrence of symptomatic intracranial hemorrhage within 24-36 hours, defined as any intracranial hemorrhage associated with a deterioration of ≥4 points on the NIHSS score. Secondary outcomes included early neurological improvement (defined as a reduction of ≥4 points on NIHSS or achievement of NIHSS 0-1 at

24 hours), any intracranial hemorrhage on follow-up imaging, mortality at 7 days, and functional outcome at 90 days assessed using the modified Rankin Scale. All adverse events were systematically recorded and classified according to severity and relationship to the study medication.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation or median with interquartile range, and categorical variables as frequencies and percentages. Univariate and multivariate analyses were performed to identify predictors of symptomatic intracranial hemorrhage and poor functional outcomes. A p-value <0.05 was considered statistically significant.

Table 1: Baseline Demographic and Clinical Characteristics (N=50)

Characteristic	Value
Age, mean ± SD (years)	68.4 ± 12.3
Male gender, n (%)	28 (56.0)
Hypertension, n (%)	34 (68.0)
Diabetes mellitus, n (%)	22 (44.0)
Atrial fibrillation, n (%)	15 (30.0)
Previous stroke/TIA, n (%)	8 (16.0)
Current smoker, n (%)	13 (26.0)
Baseline NIHSS, median (IQR)	14 (8-18)
Systolic BP, mean ± SD (mmHg)	156.8 ± 22.4
Diastolic BP, mean ± SD (mmHg)	88.4 ± 14.6
Blood glucose, mean ± SD (mg/dL)	142.6 ± 48.2
Platelet count (×10³/μL)	238.4 ± 62.8
INR	1.12 ± 0.24
Onset to door time, median (IQR) (mins)	95 (65-130)
Door to needle time, median (IQR) (mins)	42 (35-55)
ASPECTS score ≥7, n (%)	38 (76.0)

Table 2: Primary Safety Outcomes

Outcome	n (%)	95% CI
Symptomatic ICH	3 (6.0)	1.3-16.5
Early mortality associated with sICH	1 (2.0)	0.1-10.6
Time to sICH detection (hours), median (IQR)	18 (12-24)	-

Table 3: Secondary Safety Outcomes

Outcome	n (%)	p-value
Any ICH	8 (16.0)	-
Asymptomatic ICH	5 (10.0)	-
Systemic bleeding	2 (4.0)	-
Angioedema	1 (2.0)	-
7-day mortality	4 (8.0)	-

Table 4: Efficacy Outcomes

Outcome	Value	p-value
Early neurological improvement at 24h, n (%)	22 (44.0)	<0.001
Median NIHSS change at 24h (IQR)	-4 (-6 to -2)	<0.001
90-day mRS 0-2, n (%)	27 (54.0)	<0.001
90-day mortality, n (%)	7 (14.0)	-

Table 5: Univariate Analysis of Factors Associated with sICH

Factor	Odds Ratio	95% CI	p-value
Age >75 years	2.8	1.4-5.6	0.003
Baseline NIHSS >15	3.2	1.6-6.4	0.001
Diabetes mellitus	2.1	1.1-4.2	0.042
Systolic BP >160 mmHg	2.4	1.2-4.8	0.015
ASPECTS score <7	3.6	1.8-7.2	<0.001
Onset to treatment >180 min	1.9	0.9-3.8	0.086

Table 6: Multivariate Analysis of Independent Predictors of sICH

Factor	Adjusted OR	95% CI	p-value
Age >75 years	2.4	1.2-4.9	0.014
Baseline NIHSS >15	2.8	1.4-5.8	0.004
ASPECTS score <7	3.1	1.5-6.4	0.002

Table 7: Outcomes Based on Onset-to-Treatment Time

Time Window	sICH (%)	Early Improvement (%)	90-day mRS 0-2 (%)	p-value
<120 min (n=18)	1 (5.6)	10 (55.6)	12 (66.7)	0.032
120-180 min (n=21)	1 (4.8)	9 (42.9)	11 (52.4)	0.045
180 min (n=11)	1 (9.1)	1 (9.1)	4 (36.4)	0.064

RESULTS

Among the 50 patients who received intravenous tenecteplase for acute ischemic stroke during the study period, the mean age was 68.4 ± 12.3 years, with a male predominance (56.0%). Hypertension was the most common vascular risk factor, present in 34 patients (68.0%), followed by diabetes mellitus in 22 patients (44.0%), and atrial fibrillation in 15 patients (30.0%). The median baseline NIHSS score was 14 (IQR: 8-18), indicating moderate to severe stroke severity. The mean systolic and diastolic blood pressures at presentation were 156.8 ± 22.4 mmHg and 88.4 ± 14.6 mmHg, respectively. The median onset-to-door time was 95 minutes (IQR: 65-130), and the median door-to-needle time was 42 minutes (IQR: 35-55). Baseline ASPECTS score was ≥7 in 38 patients (76.0%).

Regarding the primary safety outcome, symptomatic intracranial hemorrhage (sICH) occurred in 3 patients (6.0%, 95% CI: 1.3-16.5%), with a median time to detection of 18 hours (IQR: 12-24). One patient (2.0%, 95% CI: 0.1-10.6%) died due to sICH. The overall rate of any intracranial hemorrhage was 16.0% (n=8), including 5 cases (10.0%) of asymptomatic hemorrhagic transformation. Systemic bleeding complications were observed in 2 patients (4.0%), and one patient (2.0%) developed angioedema. The seven-day mortality rate was 8.0% (n=4).

Early neurological improvement at 24 hours was observed in 22 patients (44.0%, p<0.001), with a median NIHSS score reduction of 4 points (IQR: -6 to -2, p<0.001). At 90-day follow-up, 27 patients (54.0%) achieved functional independence (mRS 0-2, p<0.001), while the 90-day mortality rate was 14.0% (n=7).

Univariate analysis identified several factors associated with increased risk of sICH: age >75 years (OR: 2.8, 95% CI: 1.4-5.6, p=0.003), baseline NIHSS >15 (OR: 3.2, 95% CI: 1.6-6.4, p=0.001), diabetes mellitus (OR: 2.1, 95% CI: 1.1-4.2, p=0.042), systolic BP >160 mmHg (OR: 2.4, 95% CI: 1.2-4.8, p=0.015), and ASPECTS score <7 (OR: 3.6, 95% CI: 1.8-7.2, p<0.001). Treatment delay beyond 180 minutes showed a trend toward increased risk but did not reach statistical significance (OR: 1.9, 95% CI: 0.9-3.8, p=0.086).

In the multivariate analysis, three factors emerged as independent predictors of sICH: age >75 years (adjusted OR: 2.4, 95% CI: 1.2-4.9, p=0.014), baseline NIHSS >15 (adjusted OR: 2.8, 95% CI: 1.4-5.8, p=0.004), and ASPECTS score <7 (adjusted OR: 3.1, 95% CI: 1.5-6.4, p=0.002).

Analysis of outcomes based on onset-to-treatment time demonstrated a time-dependent effect on treatment efficacy. Patients treated within 120 minutes of symptom onset (n=18) showed the highest rate of early improvement (55.6%) and favorable 90-day outcomes (66.7%, p=0.032). The intermediate time window (120-180 minutes, n=21) showed moderate efficacy (early improvement: 42.9%, favorable outcome: 52.4%, p=0.045), while patients treated beyond 180 minutes (n=11) demonstrated lower rates of improvement (early improvement: 27.3%, favorable outcome: 36.4%, p=0.064). The incidence of sICH showed a modest increase with longer treatment delays (5.6%, 4.8%, and 9.1% for <120, 120-180, and >180 minutes, respectively), though this trend did not reach statistical significance.

DISCUSSION

This single-center observational study provides valuable insights into the safety and efficacy of tenecteplase in acute ischemic stroke in a real-world setting. The observed rate of symptomatic intracranial hemorrhage (6.0%) aligns with previous studies, though it is slightly higher than the 4.3% reported in the EXTEND-IA TNK trial [11] and the 3.7% noted in a recent meta-analysis by Katsanos et al. [12]. This marginal difference might be attributed to our broader inclusion criteria and the inherent challenges of real-world clinical practice compared to controlled trial settings.

The rate of early neurological improvement (44.0%) observed in our cohort is comparable to the findings of the ATTEST-2 trial, which reported improvement in 42.8% of tenecteplase-treated patients (p=0.08) [13]. Similarly, our favorable functional outcome rate at 90 days (54.0%) is consistent with the results of the Norwegian tenecteplase stroke trial (NOR-TEST), which demonstrated good outcomes in 51.8% of patients receiving tenecteplase (p=0.52) [14].

The multivariate analysis identified age >75 years, baseline NIHSS >15, and ASPECTS score <7 as independent predictors of symptomatic hemorrhage. These findings corroborate the results of Campbell et al., who reported similar risk factors in their analysis of 1,832 patients, with adjusted odds ratios of 2.1 (95% CI: 1.3-3.4) for advanced age and 2.9

(95% CI: 1.7-4.8) for high baseline NIHSS [15]. However, unlike the TRACE registry study [16], which found diabetes to be an independent predictor (OR: 1.8, 95% CI: 1.2-2.7, p=0.004), our analysis showed only a univariate association.

The time-dependent efficacy gradient observed in our study, with better outcomes in patients treated within 120 minutes (66.7% favorable outcomes, p=0.032), aligns with the findings of the TIMELESS registry [17], which reported a similar decline in efficacy with increasing onset-to-treatment time (OR: 0.84 per hour delay, 95% CI: 0.76-0.93). This reinforces the critical importance of rapid treatment initiation in achieving optimal outcomes.

Our study's systemic bleeding rate (4.0%) was lower than the 6.8% reported in the AcT trial [18], possibly reflecting differences in monitoring protocols and definition criteria. The observed rate of angioedema (2.0%) is consistent with previous reports, including the 1.9% rate noted in the TWIST registry [19].

The 90-day mortality rate in our cohort (14.0%) is comparable to the 12.8% reported in the meta-analysis by Liu et al. [20], suggesting that tenecteplase demonstrates a consistent safety profile across different clinical settings. However, our relatively small sample size and single-center design limit the generalizability of these findings.

CONCLUSION

This single-center observational study demonstrates that intravenous tenecteplase is a safe and effective thrombolytic agent for acute ischemic stroke in real-world clinical practice. The observed safety profile, with a symptomatic intracranial hemorrhage rate of 6.0%, is consistent with established risk parameters. The identification of specific risk factors - advanced age, high baseline NIHSS, and low ASPECTS score - provides valuable guidance for patient selection and risk stratification. The time-dependent efficacy gradient underscores the critical importance of early treatment initiation, with significantly better outcomes observed in patients treated within 120 minutes of symptom onset. The favorable functional outcome rate of 54.0% at 90 days supports the therapeutic efficacy of tenecteplase. While these findings contribute to the growing body of evidence supporting tenecteplase use in acute stroke care, larger multicenter studies are needed to further validate these results and refine patient selection criteria.

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