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Evaluating the Safety of Tenecteplase Versus Alteplase for Acute Ischemic Stroke

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Abstract

Background/Objectives: This study aims to compare the safety of tenecteplase versus alteplase for acute ischemic stroke. Methods: This was a multicenter, retrospective cohort study including 11 Memorial Hermann Health System hospitals in Houston from 7 December 2022 to 7 June 2023. Adults presenting with an acute ischemic stroke who received alteplase or tenecteplase were included in this study. The primary outcome was the incidence of hemorrhagic conversion after 24 h of thrombolytic administration. Secondary outcomes included door-to-needle time, incidence of a major or minor bleed, length of hospital stay, incidence of any adverse effect, modified Rankin score at discharge, patient discharge disposition, medication cost, and mortality. Results: A total of 173 patients were reviewed, with 87 patients in the tenecteplase group and 86 patients in the alteplase group. Gender, actual body weight, and use of aspirin or dual antiplatelet therapy within 24 h of thrombolytic administration were statistically disproportionate between both groups. Hemorrhagic conversion occurred in seven patients in the tenecteplase group and eight patients in the alteplase group (p = 0.79). Medication cost was statistically significant between both groups. All other secondary outcomes were similar between tenecteplase and alteplase. Conclusions: In this underpowered study, we did not observe a statistically significant difference in the rate of 24 h hemorrhagic conversion between the tenecteplase and alteplase groups. Further studies with a large sample size are warranted to assess safety outcomes.

Keywords: tenecteplase; alteplase; acute ischemic stroke; thrombolytics

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1. Introduction

An acute ischemic stroke is a blockage of blood flow to the brain and a medical emergency that claims more than 795,000 lives in the United States every year [1,2]. Long-term medical complications include cognitive impairment, seizures, urinary or bowel incontinence, and depression [3]. Upon evaluation, the level of stroke severity can be determined by utilizing the widely used National Institute of Health Stroke Scale (NIHSS). Diagnosis of a stroke consists of clinical presentation and confirmation of an occlusion using non-contrast computed tomography (CT) or magnetic resonance imaging (MRI) [4]. Reperfusion therapy with an intravenous thrombolytic agent is the standard of care for patients presenting with an acute ischemic stroke. Alteplase has been the drug of choice for these patients presenting within 4.5 h of stroke symptom onset. In the American Heart Association/American Stroke Association 2019 Update to the 2018 Guidelines for the Early

Management of Patients with Acute Ischemic Stroke, tenecteplase is recommended as a reasonable alternative therapy to alteplase [4].

These medications bind to fibrin and convert plasminogen into plasmin, leading to thrombolysis. The alteplase treatment dose is 0.9 mg/kg (not to exceed 90 mg), given as an initial intravenous bolus (10% of the total dose) over one minute, followed by the remaining dose as an intravenous infusion over 60 min [5,6]. Tenecteplase has a three-point mutation that allows for higher fibrin specificity and a longer serum half-life of 90–130 min compared to the 5 min serum half-life of alteplase [5,7]. It was approved by the Food and Drug Administration for treatment of acute ischemic stroke in March 2025. The tenecteplase treatment dose is 0.25 mg/kg (not to exceed 25 mg), given as an intravenous bolus over 5 s [7]. The additional advantage of tenecteplase over alteplase is that it is easier to prepare and administer in emergent situations, as the reconstitution of tenecteplase occurs much faster and requires a smaller volume of diluent [7,8]. Although beneficial, these medications carry the risk of bleeding, including symptomatic intracerebral hemorrhage, and angioedema. Current evidence comparing tenecteplase and alteplase suggests comparable or possibly greater efficacy with tenecteplase and similar safety profiles [9]. A review by Alhadid and colleagues discussed similar or improved efficacy outcomes of tenecteplase compared to alteplase across several studies, including functional outcome at 90 days, time to treatment, and reperfusion rates [9]. Safety outcomes such as hemorrhagic events and angioedema have been found to be similar between tenecteplase and alteplase [9]. Due to these reasons, the switch from alteplase to tenecteplase as the primary thrombolytic for acute ischemic stroke was made within the Memorial Hermann Health System in March 2023. This study sought to evaluate the safety outcomes and cost implications of clinical practice in a "real-world" pre- and post-implementation of tenecteplase as the primary thrombolytic for acute ischemic stroke in a robust health system.

2. Materials and Methods

2.1. Study Design

This was a multicenter, retrospective cohort study including 11 community and academic hospitals within the Memorial Hermann Health System located in the greater Houston area. Based on Joint Commission certifications and the Texas Department of State Health Services stroke designations accrediting the level of stroke care capabilities of each institution, 4 of these hospitals are Comprehensive (Level I) Stroke Centers and 7 are Primary (Level III) Stroke Centers. This study was approved by the institutional review board at the University of Texas Health Science Center.

Selection of Participants

Patients 18 years of age and older who presented with an acute ischemic stroke and received alteplase or tenecteplase were included. Patients who received alteplase were selected from the 3-month time period prior to the transition to tenecteplase as the primary thrombolytic for acute ischemic stroke in the health system. Patients who received tenecteplase were selected from the 3-month time period immediately following the change. Diagnosis of acute ischemic stroke at the time of presentation was determined based on confirmation of occlusion via CT or MRI. The level of stroke severity was assessed using the preferred NIHSS. Patients were excluded from this study if they presented with stroke mimics (e.g., seizures, migraines, or psychiatric disorders) or if they received either thrombolytic for other indications such as ST-elevated myocardial infarction or pulmonary embolism.

2.2. Outcomes

The primary outcome was the incidence of hemorrhagic conversion 24 h after intravenous administration of alteplase or tenecteplase. Hemorrhagic conversion was confirmed by CT or MRI. Secondary outcomes included incidence of a major or minor bleed, as defined by the International Society on Thrombosis and Hemostasis bleeding scale; incidence of any adverse effect; mortality; modified Rankin score at discharge; patient discharge disposition; length of hospital stay; door-to-needle time; and medication cost. Outcomes were evaluated based on diagnostic imaging and clinical documentation in the electronic medical record, as well as a purchasing report to determine medication cost.

2.3. Statistical Analysis

Baseline demographic data was analyzed using Fisher's exact test and the Mann–Whitney U test. Outcomes were analyzed using Fisher's exact test, the Mann–Whitney U test, or descriptive analysis, as appropriate. A power analysis was performed, which revealed that a total sample size of 1176 patients was needed to meet a power of 0.80. Statistical significance was defined as $\alpha = 0.05$. All statistical analyses were conducted using Minitab version 22.1 (Minitab, LLC, State College, PA, USA).

3. Results

3.1. Baseline Characteristics

A total of 191 patients were evaluated for inclusion, and 18 were excluded (Figure 1).

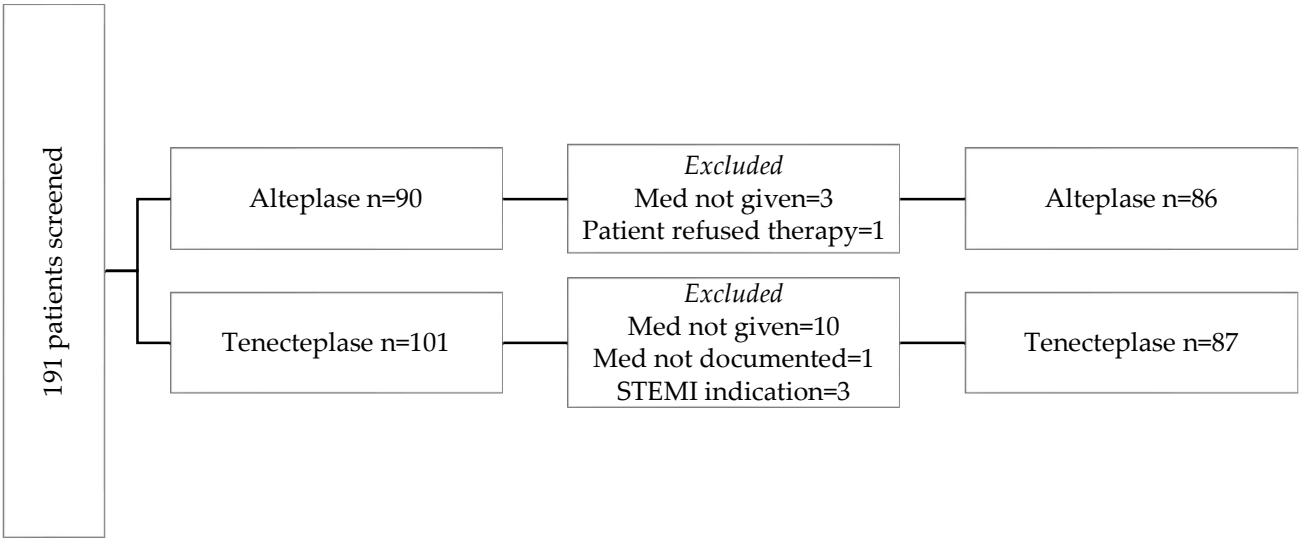


Figure 1. Screening and enrollment.

Upon evaluation, 87 patients were in the tenecteplase group, and 86 patients were in the alteplase group. In the alteplase group, 57% were females compared to the 40% in the tenecteplase group ($p = 0.03$). Actual body weight was disproportionate between both groups, with a median [interquartile range (IQR)] weight of 87.2 [75.6–103] kg in the tenecteplase group and 77.1 [65.1–90.1] kg in the alteplase group ($p < 0.01$). There were six patients (6.9%) that received aspirin or dual antiplatelet therapy within 24 h of thrombolytic administration compared to zero patients in the alteplase group ($p = 0.03$). All other baseline characteristics between the tenecteplase group and alteplase group were similar (Table 1). Similar characteristics included a median [IQR] age of 65 [53–75] and 64 [52–75] years, median [IQR] NIHSS of 7 [3–14] and 8 [4–13], and median [IQR] hemoglobin of 13.4 [12.1–14.5] and 13.3 [12.4–14.5] g/dL, respectively. The median stroke onset to thrombolytic administration time was 2 h in both groups.

Table 1. Baseline characteristics.

Characteristics	Tenecteplase (n = 87)	Alteplase (n = 86)	*p*-Value
Age (years), median (IQR)	65 (53–75)	64 (52–75)	0.69
Females n (%)	35 (40)	49 (57)	0.03
Actual body weight (kg), median (IQR)	87.2 (75.6–103)	77.05 (65.1–90.1)	<0.01
NIHSS before admission, median (IQR)	7 (3–14)	8 (4–13)	0.71
Stroke onset to thrombolytic administration (h), median (IQR)	2 (1–3)	2 (1–2.5)	0.79
Hemoglobin (g/dL), median (IQR)	13.4 (12.1–14.5)	13.3 (12.4–14.5)	0.90
Use of aspirin or DAPT within 24 h, n (%)	6 (6.9)	0 (0.0)	0.03

NIHSS: National Institute of Health Stroke Scale, DAPT: dual antiplatelet therapy.

3.2. Primary and Secondary Outcomes

Hemorrhagic conversion occurred in seven (8.1%) patients in the tenecteplase group and eight (9.3%) patients in the alteplase group ($p = 0.79$). In the tenecteplase group, five patients (5.8%) experienced major bleeding located in the cerebral (n = 4) and gastrointestinal (n = 1) sites, and three (3.4%) experienced minor bleeding that included hematuria, hemoptysis, and hematoma. In the alteplase group, four patients (4.7%) experienced major bleeding located in the cerebral site, and four (4.6%) experienced minor bleeding that included hematochezia, hematoma, and retinal hemorrhage. Adverse events (n = 2) in the tenecteplase group were tongue and right distal middle finger swelling and seizure. Adverse events (n = 2) in the alteplase group included significant angioedema of the tongue, posterior pharynx, and larynx requiring intubation and seizure. Mortality occurred in six patients (6.9%) in the alteplase group and one patient (1.1%) in the tenecteplase group ($p = 0.06$). The documentation of modified Rankin scores at discharge was inconsistently noted in the electronic medical record. Based on the limited entries, the median [IQR] modified Rankin score resulted in 3 [0–4] in the tenecteplase group and 4 [2–6] in the alteplase group ($p < 0.01$). Patient disposition at discharge included home, home with home health, skilled nursing facility, rehabilitation facility, long-term acute care facility, hospice, transfer to another facility, or leaving against medical advice (Figure 2).

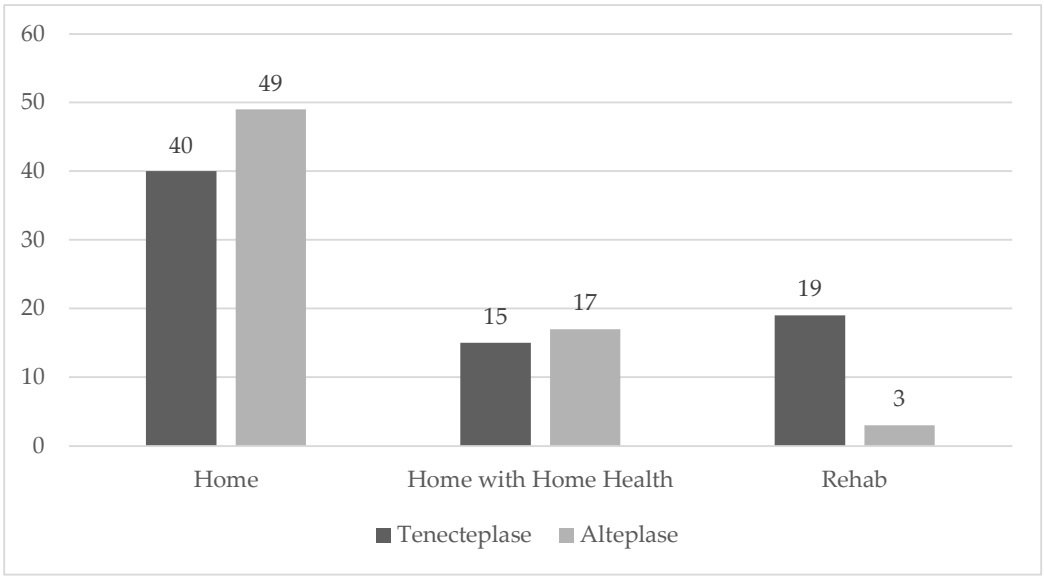


Figure 2. Most common patient discharge dispositions.

Length of stay was slightly longer in the tenecteplase group, with a median [IQR] of 4 [2–6] days when compared to a median of 3 [2–5] days in the alteplase group. Door-to-needle time was similar between the tenecteplase and alteplase groups, with medians [IQR] of 31 [23–37] minutes and 30 [21.5–38] minutes, respectively ($p = 0.77$). Tenecteplase was 16.3% less expensive than alteplase ($p < 0.01$). The outcomes are summarized in Table 2.

Table 2. Outcomes.

	Tenecteplase (n = 87)	**Alteplase (n = 86)**	***p*-Value**
Primary Outcome			
Hemorrhagic conversion, n (%)	7 (8.1)	8 (9.3)	0.79
Secondary Outcomes			
Bleeding, n (%)			
Major	5 (5.8)	4 (4.7)	1.00
Minor	3 (3.4)	4 (4.6)	0.72
Adverse drug events, n (%)	2 (2.3)	2 (2.3)	1.00
Mortality, n (%)	1 (1.1)	6 (6.9)	0.06
Modified Rankin score at discharge (n = 38), median (IQR)	3 (0–4)	4 (2–6)	<0.01
Length of hospital stay (days), median (IQR)	4 (2–6)	3 (2–5)	0.05
Door-to-needle time (minutes), median (IQR)	31 (23–37)	30 (22–38)	0.77
Medication cost (USD)	Tenecteplase is 16.3% less expensive than alteplase		<0.01

4. Discussion

In this multicenter, retrospective cohort study, the incidence of hemorrhagic conversion 24 h after thrombolytic administration was demonstrated to be similar when comparing tenecteplase and alteplase. Previous trials have compared the safety outcomes of tenecteplase and alteplase after administration. Menon and colleagues reported similar rates of symptomatic intracerebral hemorrhage, angioedema, and mortality with tenecteplase and alteplase [10]. In the NOR-TEST 2 trial, tenecteplase dosed at 0.4 mg/kg was associated with higher incidence of symptomatic intracranial hemorrhages [11]. Due to worse outcomes, the study was terminated prematurely. The EXTEND-IA TNK trial reported a higher incidence of reperfusion and better functional outcome with tenecteplase dosed at 0.25 mg/kg than alteplase dosed at 0.9 mg/kg [12]. Our study dosed both thrombolytics as evaluated by the EXTEND-IA TNK trial. Tenecteplase was dosed at 0.25 mg/kg, administered as a single bolus over 5 s with a maximum dose of 25 mg. Alteplase was dosed at 0.9 mg/kg, administered as an initial bolus (10% of total treatment dose), followed by an intravenous infusion (90% of total treatment dose) over 60 min.

Upon evaluation of secondary outcomes, the incidence of major or minor bleeding between both groups was similar. Upon evaluation of patients experiencing any bleeding, only one patient received aspirin within 24 h of tenecteplase administration. Additionally, the incidence of adverse events between both groups occurred in one patient in each group as angioedema, and both patients received intravenous famotidine, diphenhydramine, and methylprednisolone. Significant angioedema persisted as swelling of the tongue, posterior pharynx, and larynx in the patient who received alteplase, despite the administration of this medication regimen, resulting in urgent intubation to maintain the patient's airway. Per treatment guidelines, angioedema reactions should be closely monitored following thrombolytic administration, and the recommended empiric treatment includes intravenous histamine-2 receptor antagonists, diphenhydramine, and methylprednisolone [4]. Regarding the seven patients that expired in our study, six patients presented with severe stroke

severity and one patient presented with moderate stroke severity. This correlation was expected when compared to previous research on mortality in acute ischemic stroke [13,14]. Moreover, assessment of modified Rankin scores revealed statistically significant differences between both groups based on available reporting at discharge. A secondary analysis of the ACT trial published by Bala and colleagues showed a trend toward increased benefit with tenecteplase over alteplase based on 90-day functional outcome (modified Rankin score 0–1) [15]. Subsequently, in our study, a majority of patients had the functionality to discharge home or home with home health compared to long-term health facilities. Interestingly, other studies have shown reduced door-to-needle time with tenecteplase when compared to alteplase due its quicker preparation and bolus administration [16,17]. This study reported similar door-to-needle median times of roughly 30 min when comparing both thrombolytics. This can be attributed to the lack of experience with tenecteplase preparation during the first few months of rollout at the study sites. Of note, Memorial Hermann Health System has created specific packaging for tenecteplase in acute ischemic stroke. This packaging includes the tenecteplase vial, sterile water diluent, dosing card for reference, tenecteplase warning label, and two syringes with needles for preparation. Repackaging of this product was implemented to increase preparation efficiency and reduce door-to-needle time. Another strategy to reduce door-to-needle time at Memorial Hermann Health System is the utilization of mobile stroke units. This introduces the ability to obtain CT imaging and administer tenecteplase prior to hospital arrival. The cost savings comparison between both thrombolytics was expected to favor of tenecteplase, as reported in previous studies. Gao and colleagues assessed the cost-effectiveness between tenecteplase and alteplase for patients with acute ischemic stroke before thrombectomy [18]. The study concluded in their long-term cost effectiveness analysis that treatment with tenecteplase was associated with nominally lower costs (AUD 96,357) compared to alteplase (AUD 106,304). The prices of both thrombolytics were evaluated based on a purchase report from each Memorial Hermann Health System hospital in our study.

Limitations

This study has notable limitations involving baseline characteristics and research outcomes. Power was not met in this study based on the number of patients, leading to question the clinical significance. The timing of the transition to tenecteplase limited the study to only 3 months of data post-implementation. Tenecteplase has now been utilized as the first-line thrombolytic for acute ischemic stroke across the Memorial Hermann Health System for over two years. A follow-up study can potentially meet the sample size needed to substantially evaluate the clinical significance.

More exclusions occurred in the tenecteplase group when tenecteplase was ordered but ultimately not given. The off-label use of tenecteplase at the time may have led to patient apprehension and ultimate refusal of receiving tenecteplase. Exclusions in both groups occurred due to patient reevaluation and the discovery of rapidly improved symptoms or relative contraindications to thrombolytic administration.

Regarding baseline characteristics, gender, actual body weight, and use of aspirin or dual antiplatelet therapy within 24 h of administration were disproportionate between both groups. Aspirin or dual antiplatelet use within 24 h of thrombolytic administration was noted to be potentially caused by automatic default timing of medications in the morning when inputting the order. To avoid increasing the risk of symptomatic intracranial hemorrhage caused by early administration of aspirin or dual antiplatelet therapy, post-thrombolytic order sets should be carefully reviewed in patients with acute ischemic stroke.

In addition, thrombolytic use for acute ischemic stroke at Memorial Hermann Health System aligns with national guideline thrombolytic eligibility recommendations and con-

traindications. Excluding patients with certain past medical histories and clinical presentation such as a history of recent bleeding or stroke, concomitant therapeutic anticoagulation, and high blood pressure from receiving thrombolytics subsequently reduces the risk of bleeding complications and hemorrhagic conversion [4,8]. However, patient-specific risk factors for bleeding were not evaluated in this study. The predisposition to bleeding of more patients receiving antitplatelets in the tenecteplase group was not reflected in the safety outcomes, possibly due to an imbalance in other confounding factors. Additionally, a safety benefit with tenecteplase may have been masked by the disproprotionate antiplatelet administration.

The use of the NIHSS to determine stroke severity is a critical predictor of functional outcomes, as severe strokes are associated with increased mortality and worse functional outcomes post discharge [19]. A majority of patients in our study presented with mild to moderate stroke symptoms in both groups based on the reported NIHSS. Further stratification by stroke severity could delineate the role of tenecteplase in acute ischemic stroke.

Inconsistencies in the documentation of the modified Rankin score in the electronic medical record created a gap in the efficacy assessment. Due to this, while the modified Rankin scores reported are statistically significant, they should be considered exploratory, subject to a high risk of bias due to the limited sample size. Standardization of modified Rankin score documentation in the physical/occupational therapy notes and as a required entry in the discharge summary note template should be considered to assess stroke disability in participants appropriately and consistently. With this, the evaluation of modified Rankin scores and the mortality rate at 90 days should be considered for a comprehensive functional outcome. In retrospect, lengthening the time frame of this study can increase the number of patients eligible for inclusion.

5. Conclusions

In summary, this study captured objective clinical practice evidence to add to the growing research on tenecteplase safety outcomes. This multicenter study creates a unique retrospective view of a hospital system transitioning to tenecteplase in its early stages. In this underpowered study, there was no observed statistically significant difference in safety outcomes between tenecteplase and alteplase in patients with mild to moderate acute ischemic stroke. However, the results suggest a cost reduction afforded by the system-wide transition to tenecteplase. Further study with a larger population is warranted to assess safety outcomes between tenecteplase and alteplase.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of University of Texas Health Science Center at Houston INSTITUTE (protocol code HSC-MH-23-0565, approved 23 June 2023).

Informed Consent Statement: Patient consent was waived due to the study evaluation posing no physical risk to patients as no interventions or procedures requiring consent will be performed. The only identified harm is a potential breach of privacy and protected health information in which steps were taken to ensure patient information is de-identified.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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