Original Article

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The Primary Experience with Tenecteplase Thrombolysis for Acute Ischemic Stroke: A Report from Iran

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ABSTRACT

Background & Objective: Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) has been considered as primary therapy in ischemic stroke patients. Alteplase is prescripted as the thrombolytic therapy for more than two decades. Tenecteplase is a new type of tPA that is reported to have beneficial effects in recent years. The present research focused on the effectiveness and the side effects of tenecteplase in the ischemic stroke.

Materials & Methods: Here we administrated 0.25 mg/kg tenecteplase in 36 individuals with acute ischemic stroke in the first 4.5 hours of stroke occurrence. The NIHSS in baseline, 24 hours, 7 days after and the modified Rankin scale (mRS) at 90 days were assessed. The primary efficacy outcome was reduction of at least 4 points in the NIHSS during 7 days and the secondary efficacy outcome was defined as mRS 0 and 1 at 90 days. The safety outcome was evaluated based on the symptomatic intracranial hemorrhage (ICH) and death occurance during 90 days.

Results: The mean NIHSS at baseline was 12.7±4.6, and the mean NIHSS corresponding to 24 hours after admission was 9.6±4.8. The mean 7-day NIHSS was 7.6±4.4. The primary and secondary efficacy outcomes were met in 18 (50%) and 22 (61.1 %) of the patients respectively. Symptomatic ICH was observed in one patient with lung cancer who died of respiratory failure.

Conclusion: This study confirmed the efficacy and safety of tenecteplase in thrombolysis for acute ischemic stroke treatment. Tenecteplase appears to be an appropriate therapy as thrombolytic agent against ischemic stroke.

Keywords: Tenecteplase, Ischemic Stroke, Thrombolysis, Alteplase, Tissue Plasminogen Activator

Introduction

Stroke is defined as an acute focal neurological damage caused by vascular accident (infarction or hemorrhage) of the central nervous system(1). Stroke is one of major reasons of mortality and inability worldwide (2). This neurological damage is not a solitary disease, but numerous genetic and acquired risk factors can cause this complication(1). In Iran, studies indicate that the average age of the highest frequency of stroke is approximately a decade lower than the world average age (3, 4). More stroke cases (85%) are ischemic, which is mainly caused by large artery thrombosis, cardiac embolism, and small vessel occlusion (1, 5). The overall incidence of ischemic and hemorrhagic stroke has greatly increased in the last ten years in elderly individuals over 75 years of age, reaching 1151-1216 per 100,000 people(6). The process of stroke rehabilitation, the consequences of reduced productivity and costs of care, lead to a large social and economic burden. Moreover, cerebrovascular problems are the basis for secondary disorders of the nervous system. For instance, the cerebrovascular damage is the main cause of late-onset epilepsy and the second underlying reason of dementia in the elderly population(1).

Up to now, the first-line thrombolytic drug against acute ischemic stroke accepted by Food and Drug Administration (FDA) is intravenous administration of recombinant tissue plasminogen activator (alteplase,

rtPA) which is more effective in 4.5 hours after symptoms onset(7). Despite numerous studies and researches, the use of this treatment has many limitations. Most of these limitations are due to the limited potential in recanalization, fast plasma clearance requiring 1- to 3-hour infusions and increased possibility of serious hemorrhage complications, especially intracranial hemorrhage outcomes. These limitations caused efforts to develop easier and safer treatment for thrombolysis which could present greater outcomes and reliable prescribing in the health system for the thrombolytic therapy for ischemic stroke (8, 9).

Tenecteplase is a subtype of alteplase with certain genetic modifications to make advantages, demonstrating14 times more specificity for binding to fibrin, 10 times more protection of fibrinogen, 80 times more preservation to plasminogen activator inhibitor-1 (PAI-1) function, faster thrombolysis and lower elimination rate. These pharmacokinetic characteristics made tenecteplase to stay longer in circulation, which can be prescribed in the single intravenous bolus for thrombolysis (10, 11).

In 2019, the number of prevalent individuals, occurrence patients, and mortality due to stroke in Iran were 963,512; 102,778; and 40,912, respectively. The age-standardized occurrence ratio and the age-standardized mortality ratio reduced from 1990 to 2019. Among all Iranian stroke cases within 2019, 44.7% were associate with hypertension and 28.8% with elevated fasting plasma glucose(12). The prevalence of the stroke accrue and death ratio reduced in all provinces of Iran from 2019. Stroke was cause of 4.48% of all disabilities in 2019 (3.38% related to ischemic stroke, 0.87% related to intracerebral hemorrhage, and 0.22% related to subarachnoid hemorrhage). Alteplase thrombolysis prescripts in stroke patients with adequate criteria. This is the first descriptive study of the experience of administering tenecteplase in Iran (12).

Tenecteplase is approved treatment for ST-segment elevation myocardial infarction at 0.5 mg/kg with less systemic bleeding risk during treatment (10, 13). Tenecteplase administration before thrombectomy resulted to greater reperfusion rate and elevated functional outcomes in compared to alteplase administration among the ischemic stroke patients administrated during 4.5 hours following stroke occurrence(14). Tenecteplase has been reported to have superior safety profile to alteplase (15, 16). A multi central meta-analysis of the randomized clinical trials for administration of tenecteplase in ischemic stroke thrombolysis reported greater impact on physiological and imaging outcomes at 0.25 mg/kg dose of tenecteplase in comparison with 0.4 and 0.1 mg/kg of tenecteplase (17, 18). The purpose of the current report was to investigate the effectiveness and the side effects of treatment with tenecteplase 0.25 mg/kg in the acute ischemic stroke patients.

Materials and Methods

Individuals with acute ischemic stroke have been admitted in the research. The cases aged more than 18 years, affected with ischemic stroke, presenting during 4.5 hours following the occurrence of symptoms, absence of contraindications for receiving thrombolytic treatment, informed consent to administration in the research have been included in the study. Exclusion parameters were significant cerebral trauma or intracranial hemorrhage, previous stroke in the past three months, arterial perforation in a non-compressible location in the past 7 days, aneurysm, cranial or spinal operation, high blood pressure (systolic above 185 mmHg or diastolic above 110 mmHg), acute hemorrhage of internal organs, platelet count lower than 100,000/mm^3, recent administration of anticoagulants. Moreover, fibrinogen levels below 150 mg/dL, CT scan showing infarction in several lobes that causes hypodensity greater than one-third of the cerebral hemisphere, seizures at onset with residual postictal neurological disturbances, recent acute myocardial infarction (3 months prior) were other exclusion criteria.

The ethics committee of Jundishapur University and Golestan Hospital of Ahvaz at each site approved the present trial, and the informed consent form was read and signed by the patient or legal representative before enrollment. Immediately after the patient's arrival, computed tomography (CT) was performed. After brain CT, the physicians based in stroke care unit, evaluated the eligibility for thrombolytic therapy and study entry. Thrombolysis was prescribed for the patients if there was no intracranial hemorrhage. A specialist doctor and trained intern examined all patients. The presence of the patient during the treatment time window, the contraindications for the treatment of thrombolysis, blood pressure, the oxygen saturation level and capillary sugar estimation were checked. The blood samples were taken for other standard laboratory tests. Tenecteplase were administrated (0.25 mg/kg to a maximum of 25 mg) as an intravenous bolus. The patients were in the stroke care unit after administration of tenectaplase, and their blood pressure, oxygen saturation, and cardiac rate were closely monitored. The fibrinogen levels were checked two and four hours after injection. If the fibrinogen level was less than 150 mg/dL or in case of decreased level of consciousness or if the functional deficiency did not improve after 24 hours, the CT and MRI were performed to check the possibility of re-infraction and ICH.

Residents and emergency nurses were aware of the treatment assignment. Neurological deficiency were evaluated by the NIH Stroke Scale/Score (NIHSS), which was recorded at the time of admission, at 24 hours following admission, and at 7 days later. Clinicians trained to the evaluation and monitoring of

ischemic stroke cases overviewed the NIHSS, and focal experts were responsible for training supervisors at each site. The Modified Rankin Scale (mRS) has been obtained in 90 day post stroke assessment by outpatient consultant nurse. Primary efficacy outcome was defined as at least 4 score improvements in NIHSS at 7 days after thrombolysis, and secondary efficacy outcome was defined as mRS 0 and 1 at 90 days after ischemic stroke. All medical evaluations during the patient's stay in the hospital were recorded in a provincial online database named STROK (STroke Registry of Khuzestan; http://www.STROK.ir/).

Results

In the current study, 36 patients were enrolled between July 21 and December 22 ,2022. The age of the cases was between 37- 85 years old and the mean age of the cases was 63.83 years. The gender distribution of the participants was 27.7% female (10 patients) and 72.2% male (16 patients). Of the 36 patients studied, 55.5% had history of high blood pressure (20 patients) and 33.5% had diabetes. In addition, 22% of patients (8 patients) were smoker. The history reports of patients showed that one patient had a previous history of atrial fibrillation, one case evidently reported hyperlipidemia, and 8 patients (22.2%) had coronary heart disease. Two cases reported the previous ischemic stroke before this admission. The cause of stroke was large artery occlusion in 27.7% of patients. Patient characteristics are shown in Table 1.

Table 1. Characteristics of Stroke Cases at Baseline

Age — Year	63.8±11.2*
Gender of patients— no. (%)	
Male	26(72.2)
Female	10(27.7)
Hypertension— no. (%)	20(55.5)
Diabetic patients — no. (%)	11(30.5)
Smoker patients — no. (%)	8(22)
History of atrial fibrillation— no. (%)	1(2.7)
Hyperlipidemia— no. (%)	1(2.7)
Coronary heart disease— no. (%)	8(22.2)
Previous history of ischemic stroke	2(5.5)
Cause of stoke— no. (%)	
Large artery atherosclerosis	10(27.7)
Small artery atherosclerosis	2(5.5)
Cardiac embolism	14(38.8)
Undetermined or other	10(27.7)

NIHSS corresponding to the admission time was recorded with the mean of 12.7±4.6 (from 6 to 22), The mean of NIHSS corresponding to 24 hours after admission was 9.6±4.8 (from 3 to 20) that was significantly different with baseline NIHSS ($P < 0.001$). The mean NIHSS score recorded on the seventh day after stroke was 7.6±4.4, which was significantly different from the 24-hour NIHSS score ($P < 0.001$). In 50% of patients, NIHSS changes during 7 days were equals or more than four score which indicated as primary efficacy outcome. During four days after treatment, symptomatic ICH was observed in one cases among the patients who suffered from lung cancer. This patient died five days after treatment because of pulmonary complications and respiratory failure. Two patients developed small asymptomatic ICH which did not affect the NIHSS. These two patients discharge 7 days after injection and the secondary efficacy outcomes were excellent in both of theme. Consequently, 22 cases (61.1%) met secondary efficacy outcomes with mRS 0 and 1. The data summarized in the Table 2.

Table 2. Functional assessment of stroke patients treated with tenecteplase

NIHSS* (baseline)	12.7±4.6#
NIHSS (24-hour)	9.6±4.8
NIHSS (7-day)	7.6±4.4
mRS+(90-day)	1.5±1.3
Primary efficacy outcome	18 patients (50%)
Secondary efficacy outcome	22 patients (61 %)

***Scores on the National Institutes of Health Stroke Scale (NIHSS), the standard neurologic assessment, range from 0 (normal function) to 42 (death), the lower scores indicated less functional deficits in stroke.**
+Scores on the modified Rankin scale range from 0 (no neurologic deficit) to 6 (death).
#Plus–minus values are means ± SD (standard deviation).

Discussion

Stroke is the main cause of disability in the elderly population in worldwide. Considering the aging of the human population, there is a need to develop knowledge about stroke and its treatment methods over the next few decades (19, 20). Although great strides have been made to understand the pathophysiological mechanisms underlying stroke, several gaps remain unsolved regarding the early diagnosis of stroke and the development of therapies that can significantly improve the individual's health status and reduce complications of acute ischemic stroke(21).

Mechanical thrombectomy is a beneficial therapy in the large arterial obstructions (22). The basis of mechanical thrombectomy is the insertion of an endovascular catheter and other devices to remove or break up a thrombus that has barricaded an intracranial artery(23). This procedure is usually operated as a puncture of the femoral artery in the patient under general anesthesia or sedation. There are some problems with the use of mechanical thrombectomy included: restricted access to the trained neurosurgery specialist, equipment limitations with the navigation cable in the dedicated intracranial arteries, vessel injury, embolization in distal area, vessel disconnection, and vasospasm causing stroke exacerbation(24). These limitations lead the approaches towards use of more efficient pharmacological treatments to progress the intravenous thrombolysis.

The Intravenous thrombolysis using rtPA, is the unique accepted systemic therapy in the acute ischemic stroke which is most advantageous when prescript in the time limitation of the first 4.5 hours following stroke occurrence(25). The natural tPA is physiologically released from vascular endothelial cells and converts plasminogen to plasmin. Plasmin cleaves fibrin into the fibrinogen degradation products(9). This process breaks down the fibrin structure in the thrombus structure, which leads to thrombolysis and finally re-canalization of the vessel (Figure 1). Alteplase is a recombinant tPA that reported to be advantageous effects in ischemic stroke thrombolysis since1995 (9, 26). In the first report, the National Institute of Neurological Disorders and stroke rtPA Stroke Study, also known as the NINDS trial, validated the effectiveness and safety outcomes of this thrombolytic drug in ischemic stroke management(27). To date, the most common thrombolytic treatment against ischemic stroke is alteplase. The short half-life and low specificity for fibrin are the most important limitations of this thrombolytic medicine (9).

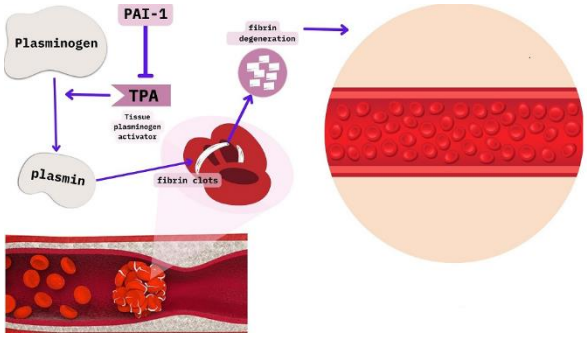

Figure 1. The clot blocks the blood flow pathway. The fibrin protein in the blood clot structure is broken and lysed by tPA. Then the clot skeleton is destroyed and blood flow is restored. The activity of PAI-1 causes the breakdown and inactivation of tPA. tPA: Tissue plasminogen activator; PAI-1: Plasminogen activator inhibitor 1.

Tenecteplase (TNK) is a mutated product of tissue plasminogen activator that has shown an increased beneficial effect on recanalization than alteplase in acute myocardial infarction and also has the less side effect of hemorrhagic incidence (9). Tenecteplase has 527 amino acids, with several distinct domains including domains of fibronectin, epidermal growth factor, Kriegel 1, Kriegel 2 and serine protease domains(28). As respects, in the amino acid sequence of tenecteplase there are substitution in three positions. The substitution of threonine 103 with asparagine and glutamine 117 with asparagine enhances the half-life of tenecteplase in the circulation. The amino acid substitution at positions 296-299 protects tenecteplase against PAI-1 function and enhanced the specify for fibrin(9, 29). The biochemical properties of tenecteplase promote pharmacological advantages in compare to alteplase. The greater stability of tenecteplase in the plasma makes it possible to be injected as an intravenous bolus rather than a contiguous infusion(30). A single bolus of tenecteplase for "drip and send" cases has made the treatment process more feasible. In addition, the poor selection of alteplase for fibrin leads to excessive systemic hemorrhage risk and fracture of the blood-brain barrier, which can lead to increased risk of cerebral and hemorrhagic edema after stroke. In addition, tenecteplase has an inhibitory effect on platelet accumulation and affects the coagulation procedure by decreasing the hemorrhagic adverse effects(31, 32).

Symptomatic intracranial hemorrhage is a desperate outcome following thrombolysis against ischemic stroke, and multiple biomarkers were studied.

However, the alterations of biomarkers to symptomatic ICH is not clearly understood(20). A variety of biomarkers have been reported to importantly alter following thrombolysis. Some molecules including brain-derived neurotrophic factor (BDNF), C-C motif chemokine ligand (CCL)-24, interleukin (IL)-6, IL-10, IL-18, and vascular endothelial growth factor (VEGF) were increased and some molecules, such as CCL-11, intercellular adhesion molecule-1, and IL-7 were decreased following thrombolysis treatment(33).

Here we administrated tenecteplase 0.25 mg/kg for all patients and we observed an approvable safety during tenecteplase administration. Several clinical studies analyzed the safety of tenecteplase administration in reperfusion therapy for ischemic stroke (34, 35). Campbel et al. reported tenecteplase injection at the dose of 0.25 mg/kg in the time range of 4.5 hours following symptom onset, resulted to greater reperfusion occurrence and better functional consequences in compared with alteplase (14). Some studies reported that tenecteplase in the dose higher than 0.25 mg/kg (0.4 mg/kg) is not safe enough and increases the possibility of ICH and death (36, 37). Moreover, tenecteplase injection at the dose of 0·25 mg/kg resulted to greater reperfusion and higher clinical outcomes than alteplase in individuals with ischemic stroke (38). Additionally, 0.25 mg/kg tenecteplase was advised in the 2019 guidelines of American Heart Association/American Stroke Association for patients without contraindications to intravenous (IV) fibrinolysis who were also meet criteria for mechanical thrombectomy (39).

Due to the insufficient number of researches and reports on tenecteplase administration outcomes, the recommendation profiles and level of documents are not satisfiable (32). Tenecteplase 0.25 mg/kg during 4.5 hours following symptom presentation, has been recommended the 2021 European Stroke Organization guidelines, prior to mechanical thrombectomy (32). Nevertheless, in the medical and pharmacological approaches, tenecteplase is still used with cautious in ischemic stroke thrombolysis, and strong recommendation to prescribe tenecteplase requires more evidences obtained from clinical reports.

However, the primary and secondary outcomes of this study confirmed the efficacy and safety of tenecteplase for ischemic stroke treatment. Tenecteplase administration appears to be an appropriate option for stroke thrombolysis. An important limitation of our study was the restricted number of stroke patients treated with tenecteplase. Since the availability of tenecteplase in Iran is not feasible, it was not possible to perform the appropriate clinical trial in the larger patient population. This can affect the frequency of parameters and data analysis. Moreover, another limitation of our study is the lack of comparison between tenecteplase and alteplase, which should be considered in the future studies.

Conclusion

In this study, tenecteplase administration improved NIHSS index in ischemic stroke patients 24 hours after stroke and one week later. Moreover, 61.7% of patients had an excellent mRS outcomes three months after the stroke. Symptomatic ICH was seen in only one patient. The primary and secondary outcomes of this study confirmed the efficacy and safety of tenecteplase for ischemic stroke treatment. According to the current research, tenecteplase administration appears to be an appropriate option for stroke thrombolysis.

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Authors' Contribution

Conceptualization and resources, S.R.; methodology, E.B.; investigation, F.K and P.M.; validation, A.B.; data analysis, writing and interpretation, M.A. D.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval and consent to participate

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