Case Report

Tenecteplase-induced Nonaneurysmal Subarachnoid Hemorrhage in a Patient with Acute Ischemic Stroke: A Case Report and Literature Review

Abstract

Recently, tenecteplase (TNK) has been used for intravenous thrombolysis in acute ischemic stroke (AIS). Although spontaneous subarachnoid hemorrhage (SAH) following thrombolysis with tissue plasminogen activator has been reported, there is a lack of literature regarding TNK-induced nonaneurysmal spontaneous SAH. Our index case received intravenous TNK within an hour of symptom onset of AIS. Following deterioration of sensorium, repeat noncontrast computed tomography was performed, which showed diffuse SAH. Cerebral angiography did not reveal any aneurysm. Nonaneurysmal SAH can be a complication of TNK thrombolysis, which is not reported in literature. Knowledge of this possible adverse reaction is critical for appropriate counseling and management.

Keywords: *Stroke, subarachnoid hemorrhage, tenecteplase, thrombolysis*

Biplab Das[1,2], Anshu Mahajan[1], Gaurav Goel[1], Arun Garg[3]

Departments of [1]Neurointervention and [3]Neurology, Institute of Neuroscience, Medanta the Medicity, [2]Department of Neurology and Interventional Neuroradiology, Fortis Memorial Research Institute, Gurgaon, Haryana, India

Introduction

Hemorrhagic stroke accounts up to 20% of cerebrovascular accident. About half of these caused by subarachnoid hemorrhage (SAH).[1] Most SAHs are commonly caused by trauma or rupture of saccular aneurysm. Drug causing nonaneurysmal SAH is unusual. Recombinant tissue plasminogen activator (rtPA) is recommended for the treatment of acute ischemic stroke (AIS).[2] Recently, tenecteplase (TNK) has been used for thrombolysis in AIS patients.[3,4]

Case Report

A 77-year-old gentleman had sudden-onset right-sided weakness for 38 min duration with dysarthria. At presentation, National Institutes of Health Stroke Scale (NIHSS) was 11. His blood pressure was 146 / 84 mm of Hg, pulse 88 per minute, regular and normal volume. He was conscious and obeying commands. A diagnosis of acute stroke was made in emergency triage and brain rescue code was activated. Urgent noncontrast computed tomography (CT) of the head and computed tomography angiography (CTA) was performed. CT head revealed no intracranial hemorrhage, and the Alberta Stroke Program Early CT score was 9 [Figure 1a]. Perfusion map showed small area of mismatch deficit (penumbra) in the left middle cerebral artery territory involving anterior temporal lobe and internal capsule [Figure 1b-g]. CTA did not reveal any major vessel occlusion, no aneurysm, or any feature of vasculitis. Basic investigation revealed normal coagulogram (international normalized ratio: 0.8), euglycemic (blood sugar: 134 mg%), and platelet count of 280 × 10^3/ml. After informed consent, he was thrombolyzed with TNK (body weight: 68 kg, TNK dose 17 mg, given intravenously over 1 min) in the CT suite. The patient was shifted to the stroke care unit for close monitoring of vitals and NIHSS. After approximately 10 min, the patient complained of severe headache and vomiting, followed by deep in sensorium. His NIHSS score increased to 20. Urgent portable CT head was performed, which showed diffuse SAH [Figure 2a and b]. He was intubated for poor respiratory effort and reduced Glasgow Coma Scale. Activated prothrombin complex concentrates and cryoprecipitate was given without delay. Digital subtraction angiography of the cerebral vessel was done, but did not reveal any underlying aneurysm or other abnormality [Figure 2c and d]. He was

How to cite this article: Das B, Mahajan A, Goel G, Garg A. Tenecteplase-induced nonaneurysmal subarachnoid hemorrhage in a patient with acute ischemic stroke: A case report and literature review. Asian J Neurosurg 2020;15:706-8.

Submitted: 01-Apr-2020 **Revised:** 07-Apr-2020
Accepted: 28-May-2020 **Published:** 28-Aug-2020

Address for correspondence:
Dr. Gaurav Goel, Department of Neurointervention, Institute of Neuroscience, Medanta the Medicity, Gurgaon, Haryana, India.
E-mail: drgauravgoel1@gmail.com

Access this article online

Website: www.asianjns.org

DOI: 10.4103/ajns.AJNS_131_20

Quick Response Code:

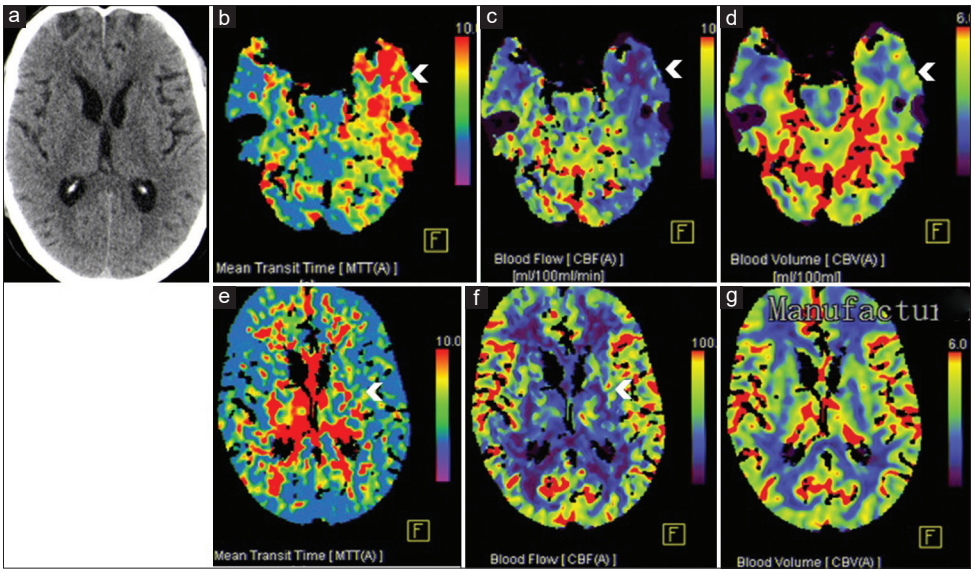

Figure 1: (a) Noncontrast computed tomography head showed no established acute infarct or hemorrhage. (b-g) Computed tomography perfusion images showed mismatch deficit (penumbra, white arrow head) in the left middle cerebral artery territory involving left anterior temporal lobe and internal capsule. Penumbra is defined as brain tissue with reduced cerebral blood flow, increased mean transit time and preserved cerebral blood volume

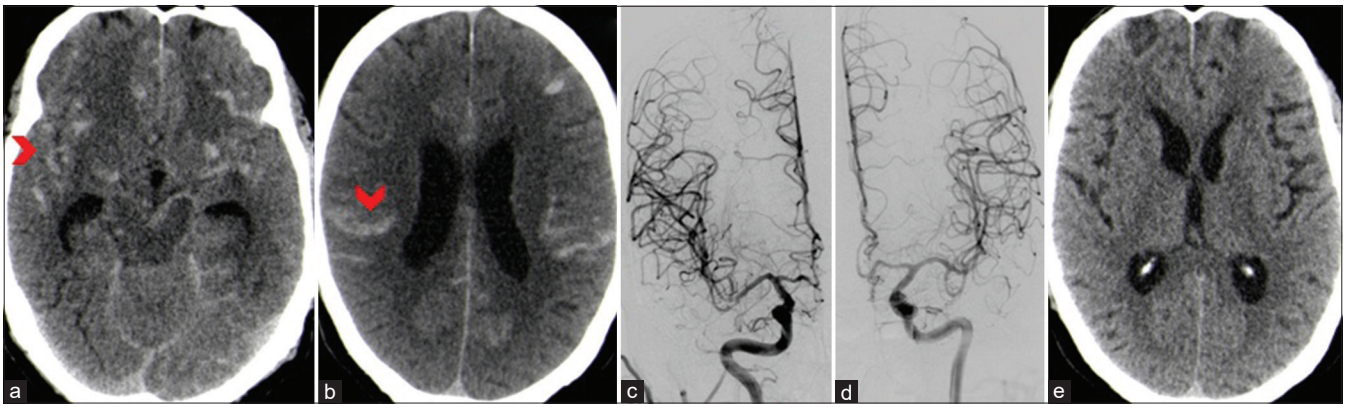

Figure 2: (a and b) Noncontrast computed tomography head showed acute subarachnoid hemorrhage (red arrow head) in bilateral Sylvian fissure, anterior interhemispheric fissure and in bilateral frontal sulci. (c and d) Cerebral digital subtraction angiography of bilateral internal carotid artery showed no evidence of aneurysm and vascular malformation. (e) Noncontrast computed tomography head was done after 2 weeks showed interval complete resolution of subarachnoid hemorrhage

managed conservatively for SAH with close monitoring for vasospasm. Repeat CT head showed improving SAH, no hydrocephalus [Figure 2e]. The patient was discharged after 2 weeks with Modified Rankin Scale (mRS) 4 and continued on medical therapy (aspirin 75 mg started after SAH resolved) and intensive physiotherapy. Six-week follow-up showed improvement of the right-sided deficit with mRS 3.

Discussion

TNK is a thrombolytic agent primarily used for acute coronary event. Recently, this has been evaluated for the management of AIS. The advantage of this drug is being more fibrin specific, single bolus dose, and a longer duration of action. Different trials have evaluated the safety and efficacy of this thrombolytic drug with dose ranging from 0.2 to 0.4 mg/kg bolus dose.[5,6] A recent analysis, "Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis," observed improved recanalization rate with TNK at 24 h and better outcome with good recanalization.[3] However, a significant limitation is its open-label design, heterogeneity in study design, and imaging evaluation. Another recently concluded Phase 3, randomized, open-label, blinded endpoint, superiority trial of TNK versus Alteplase for Thrombolysis in AIS (Norwegian tenecteplase stroke trial) was done in 1107 in Norway.[4] Patients were randomly assigned (1:1) into two groups, TNK, 0.4 mg/kg bolus, or alteplase, 0.9 mg/kg infusion within 4.5 h of symptom onset. The drugs were comparable on outcomes using modified Rankin score 0–1, suggesting no difference between two drugs. The rates of intracerebral hemorrhage were similar in two groups.

Intracerebral hemorrhage is a known complication of thrombolysis and the risk is always explained to the

patient or family members before treatment.[7] However, tissue plasminogen activator causing nonaneurysmal diffuse SAH is unusual with limited literature knowledge.[8,9] Alteplase causing aneurysmal SAH has been reported in literature.[8,9] TNK has recently been used in different trials for thrombolysis in AIS.[3,4] Several pathophysiological mechanisms have been proposed for SAH following thrombolysis after stroke. In a patient with incidental aneurysm, rtPA can rapidly dissolve the thrombus located with the unruptured aneurysm sac, which can increase the blood turbulence leading to rupture.[10] Within the neurovascular matrix following systemic rtPA a dysregulated extracellular proteolysis can cause hemorrhagic transformation in the infracted brain parenchyma. In addition, disruption of the integrity of the vascular basal lamina after rtPA infusion can induce variation of vascular permeability.[9,11] Nonaneurysmal SAH induced by intravenous TNK in acute stroke patient is not reported in literature. To the best of our knowledge, this is the first report of nonaneurysmal SAH in AIS patient following TNK thrombolysis; however, in a series of fifty patients who received empiric TNK in cardiac arrest, unresponsive to standard interventions, one patient had fatal complication with SAH.[7]

Conclusion

Intracranial hemorrhage including SAH is a known dreaded complication of intravenous thrombolysis. TNK-induced nonaneurysmal SAH is an unusual but possible rare complication of intravenous thrombolysis in acute stroke patient knowledge of which is crucial in both counseling of patient or family members and proper management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Goel G, Gupta V, Chinchure S, Gupta A, Kaur G, Jha AN. A decade after International Subarachnoid Aneurysm Trial: Coiling as a first choice treatment in the management of intracranial aneurysms – Technical feasibility and early management outcomes. Asian J Neurosurg 2014;9:137-43.
2. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, *et al*. 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:3020-35.
3. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, *et al*. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): A phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol 2015;14:368-76.
4. Logallo N, Kvistad CE, Nacu A, Naess H, Waje-Andreassen U, Asmuss J, *et al*. The Norwegian tenecteplase stroke trial (NOR-TEST): Randomised controlled trial of tenecteplase vs. alteplase in acute ischaemic stroke. BMC Neurol 2014;14:106.
5. Haley EC Jr., Lyden PD, Johnston KC, Hemmen TM; TNK in Stroke Investigators. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. Stroke 2005;36:607-12.
6. Haley EC Jr., Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, *et al*. Phase IIB/III trial of tenecteplase in acute ischemic stroke: Results of a prematurely terminated randomized clinical trial. Stroke 2010;41:707-11.
7. Bozeman WP, Kleiner DM, Ferguson KL. Empiric tenecteplase is associated with increased return of spontaneous circulation and short term survival in cardiac arrest patients unresponsive to standard interventions. Resuscitation 2006;69:399-406.
8. Chou CL, Lin YJ, Po HL, Chang CK. Subarachnoid hemorrhage – A rare complication after intravenous thrombolysis in an ischemic stroke patient. Am J Emerg Med 2010;28:984.e1-3.
9. Kim HJ, Kang DW, Kwon SU, Kim JS, Jeon SB. Aneurysmal subarachnoid hemorrhage following intravenous thrombolysis in acute ischemic stroke. J Neurocrit Care 2017;10:107-111.
10. Lagares A, Gómez PA, Lobato RD, Alén JF, Campollo J, Benito-León J. Cerebral aneurysm rupture after r-TPA thrombolysis for acute myocardial infarction. Surg Neurol 1999;52:623-6.
11. Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. Stroke 2013;44:3613-22.