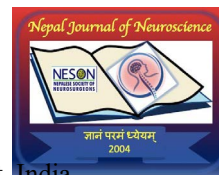


“Hemorrhagic Transformation Following Thrombolytic Therapy in Acute Ischemic Stroke: A Case Series of 5 Patients”



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Abstract

Stroke stands as a global health menace, causing substantial disability and mortality. Timely intervention, specifically within the critical "Golden Hour" following acute ischemic stroke, is imperative. Thrombolytic agents like tissue plasminogen activators (tPA) are pivotal for clot dissolution and blood flow restoration, yet their use introduces the risk of hemorrhagic transformation (HTF). In a recent case series involving five patients receiving thrombolytic therapy for acute ischemic stroke, we illuminate the occurrence of post-treatment HTF, its clinical ramifications, and the intricate challenges in its management. Early intervention in acute ischemic stroke aims to safeguard at-risk brain tissue, with thrombolytic therapy, notably tPA, serving as a primary treatment avenue. However, the associated risk of HTF hovers around 30%–35%, influenced by factors like age, comorbidities, and infarct size. The vulnerable ischemic penumbra, marked by a compromised blood-brain barrier and free radical generation, is particularly susceptible. Treatment decisions, guided by the National Institutes of Health Stroke Scale (NIHSS), pivot on stroke severity assessment, emphasizing the need for vigilant post-treatment monitoring. In conclusion, navigating the delicate balance between the benefits of early thrombolysis and the risks of HTF remains a persistent challenge in optimizing outcomes for acute ischemic stroke patients.

Keywords: Acute ischemic stroke, Hemorrhagic transformation, Tissue plasminogen activators.

Introduction

Stroke remains one of the leading causes of disability and mortality worldwide, posing substantial burden on healthcare systems and quality of life for affected individuals. Globally, stroke is the second leading cause of death.¹ A stroke, disrupting brain blood flow, can lead to severe damage if not promptly addressed. The "Golden Hour," the critical first 60 minutes after a stroke, emphasizes the urgent need for swift intervention. Intravenous thrombolytic therapy with drugs like

tissue plasminogen activator tPA effectively dissolves clots in ischemic strokes, with mechanical thrombectomy as an option for large clots. Timely treatment in crucial hour enhances recovery and reduces long-term disabilities.

Recombinant tPA is recommended for the treatment of acute ischemic stroke (AIS).² Tenecteplase and Alteplase have been used for thrombolysis in AIS patients.^{3,4} Treatment with thrombolytic agents also carries some risks, the most serious being the development of Hemorrhagic transformation (HTF).⁵ We reported five cases to the Indian Pharmacopoeia Commission with unique ID numbers IN-IPC-300837063, IN-IPC-300837061, IN-IPC-300837062, IN-IPC-300837063, IN-IPC-300837064. As the HTF occurred after administering tPA, it followed a temporal relationship. Furthermore, it cannot be explained by any other drugs or disease. Hence, after assessment of causality, the event came out to be probably/likely to be associated with tPA therapy.

Case report

Case 1

A 82-year-old male presented with dizziness, left-sided limb weakness, and slurred speech. He was diagnosed with an acute infarct in the right perisylvian region. Thrombolysis with Tenecteplase was performed, but post-treatment, he became drowsy (GCS- E2V2M5), required intubation. CT showed HTF with mass effect (Refer to Table 1). The patient was discharged with a GCS score of E4V1M6. He later returned with slurred speech, focal seizure, and low Glasgow Coma Scale (GCS) (NIHSS: 11) due to subacute infarct with hemorrhagic transformation. Unfortunately the patient did not survive.

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Case 2

A 52-year-old male with a history of hypertension, diabetes, and ischemic heart disease presented with right-sided weakness, imbalance, difficulty swallowing, and drooling. CT Brain showed possibility of acute infarct in left temporal region. He was then thrombolysed with Inj. Alteplase 50 mg. After thrombolysis CT brain showed hyperdense area in left parietal and temporal region, possibility of acute infarct with HTF & subarachnoid haemorrhage(Refer to Table 1). However, with supportive treatment, the patient improved, and was discharged with GCS- E4M6V5 indicating neurological recovery.

Case 3

A 72-year-old hypertensive male missed his morning Atenolol dose and developed sudden right-sided weakness, speech loss, and left facial deviation. A CT scan revealed a dense left middle cerebral artery (MCA) (Refer to Figure 1). He was then thrombolysed with Inj. Alteplase 44 mg (0.9 mg/kg) 4 mg bolus dose, followed by remaining 40 mg infused over 1 hour. The following day, he became drowsy, requiring intubation due to respiratory distress. Subsequent imaging showed an acute infarct with HTF in various brain regions(Refer to Table 1) (Refer to Figure 2). However, with supportive treatment, the patient improved, and he was discharged with an NIHSS score of.¹⁰

Case 4

A 71-year-old male with a history of heart disease and

a prior stroke presented with right-sided gaze deviation, left hemiparesis, and facial weakness. He received thrombolysis with Alteplase for a suspected lacunar infarct. Inj. Alteplase 67.5mg (0.9mg per kg) was given as a bolus dose of 6.75mg (10%) and the rest 60.75mg (90%) was infused over 1 hour. However, 24 hours later, a CT scan showed significant HTF, mass effect, and worsening cerebral edema(Refer to Table 1). The patient's condition deteriorated despite conservative management and non-surgical interventions, leading to uncal and transtentorial herniation. The patient's neurological status remained poor, with a GCS score of E3V4M5 (NIHSS - 14), until he suddenly collapsed.

Case 5

A 32-year-old male with a history of ischemic heart disease presented with right-sided hemiparesis and speech difficulties. CT brain revealed an acute infarct in the left frontoparietotemporal region, which was treated with thrombolysis using Alteplase. He was thrombolysed with Inj. Alteplase 63mg (0.9mg per kg). 6.3mg (10%) was given as a bolus dose and the rest 56.7mg (90%) was infused over 1 hour. Post-thrombolysis CT showed HTF (Refer to Figure 3), midline shift, and cerebral edema(Refer to Table 1). The patient was managed conservatively and discharged on the fourth day with improved GCS score E4V4M5, indicating neurological recovery.

CT scan findings before and after treatment of all 5 cases have been shown in Table 1.

Table 1: Demographic and Clinical Characteristics of Stroke Patients: Age, CT scan Findings, NIHSS Score, Hospital Stay Duration, and Outcome

	Age (Years)	CT Scan (On Presentation)	CT Scan (Post Thrombolysis)	NIHSS Score	Duration of Hospital stay (Days)	Outcome
Case 1	82	Acute infarct in right perisylvian region	Subacute infarct with HTF in right fronto-parietal region, right centrum semiovale, right external capsule and right insular cortex.	11	30	Death
Case 2	52	Acute infarct in left temporal region	Hyperdense area in left parietal and temporal region, possibility of acute infarct with HTF & subarachnoid haemorrhage.	12	4	Recovery
Case 3	72	Acute infarct in left fronto-parietal region	HTF in the left fronto-parietal region	10	4	Recovery
Case 4	71	Hypodense area in right high parasagittal frontal lobe, possibility of lacunar infarct.	Large acute infarct with internal hyperdense (HTF) areas in cortex and subcortical white matter of right fronto-parieto-temporal region, centrum semiovale, insular cortex, head of caudate nucleus and right half of genu and body of corpus callosum	17	17	Death
Case 5	32	Acute infarct in left frontoparietotemporal region, corona radiata and ganglio-capsular region.	Acute to subacute infarct with HTF in the left ganglio-capsular region + midline shift of 3.5 mm to right side + cerebral edema.	10	4	Recovery

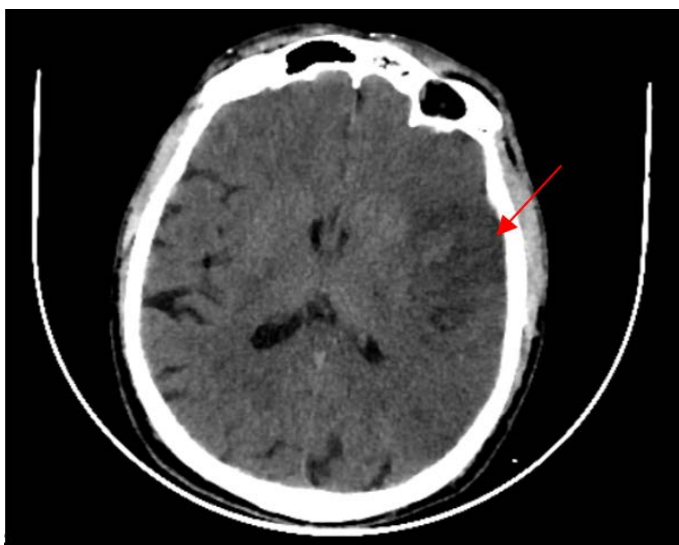


Figure:1 CT of patient(Case 3) showing acute infarct in left temporal region

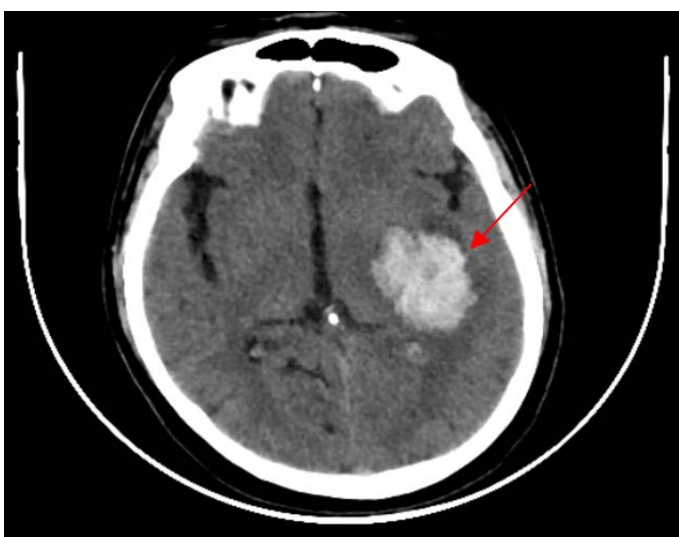


Figure:2 CT of patient(Case 3) showing HTF in the left fronto-parietal region

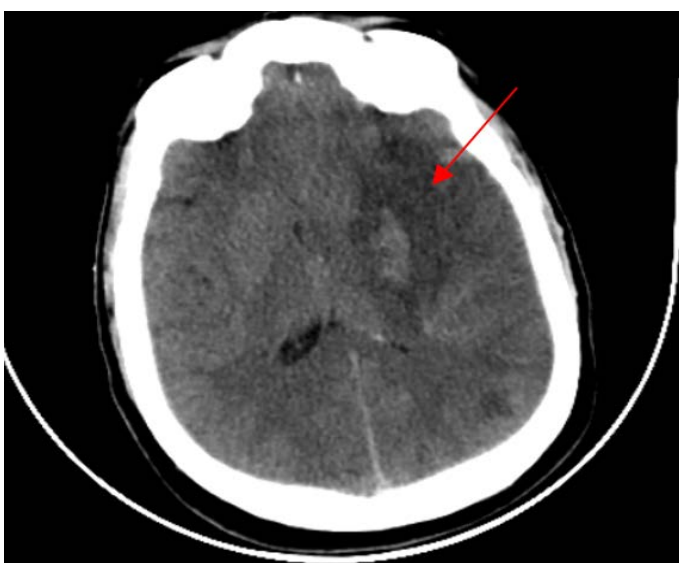


Figure:3 CT of patient showing acute to subacute infarct with HTF in the left ganglio-capsular region.

Discussion

Each year, approximately 14 million people worldwide suffer from strokes, with 5.5 million succumbing to the condition and an additional 5 million enduring debilitating complications.⁶ Among the two main stroke types, acute ischemic stroke occurs when blood flow to the brain is obstructed, necessitating swift intervention to salvage affected brain tissues. Early intervention is required to preserve the tissues where perfusion is decreased.⁷ Thrombolytic therapy, particularly with tissue plasminogen activators (tPA) like alteplase or tenecteplase, stands as the first-line treatment, but its effectiveness hinges on administration within 3-4.5 hours of symptom onset to restore blood flow to the affected area.^{8,9} tPA, a serine protease, becomes efficient at plasminogen activation when bound to fibrin, making it instrumental in dissolving obstructive clots in conditions like ischemic strokes, pulmonary embolism, myocardial infarction, and catheter clot clearance.

Thrombolytic therapy, while effective in recanalizing blood vessels presents risks, including a 30%-35% incidence of hemorrhagic transformation (HTF), primarily due to the disruption of the blood-brain barrier during reperfusion.¹⁰ Older patients are more susceptible to tPA-induced hemorrhage because of age-related vascular fragility, comorbidities, and weakened blood-brain barriers, necessitating individualized decision-making based on stroke severity and patient-specific factors. Hemorrhagic transformation is more likely in the ischemic penumbra due to free radical generation, blood-brain barrier disruption, and vessel stress during rapid blood flow restoration. Factors such as the timing of thrombolysis, initial infarct size, age, and comorbidities influence HTF risk, which is assessed using the National Institutes of Health Stroke Scale (NIHSS). Higher NIHSS scores justify tPA use for severe strokes, while milder strokes require careful evaluation. Early thrombolytic therapy is crucial to minimize brain damage, but vigilant monitoring of vital signs and post-treatment symptoms is imperative.¹¹

Conclusion

In conclusion, thrombolytic therapy, a critical intervention for acute ischemic stroke, carries the inherent risk of hemorrhagic transformation (HTF). Our case series underscores the complexity of managing HTF post-treatment. Balancing the benefits of timely thrombolysis with the potential risks requires careful consideration of patient-specific factors. Vigilant monitoring and individualized decision-making are essential to optimize outcomes in stroke management.

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