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Opinion

"Risk and Efficacy of tPA in Acute Ischemic Stroke: Implications of Antiplatelet Therapy and Hemorrhagic Complications"

Abdul Wahid*, Amna Tariq, Yusra Khan and Abdul Ahad

Department of Medicine, Karachi medical and dental college, Pakistan

***Corresponding Author:** Abdul Wahid, Department of Medicine, Karachi medical and dental college, Pakistan.

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Ischemic stroke, the second leading cause of death globally, results from interrupted cerebral blood flow due to thrombosis or embolism. Key risk factors include diabetes, smoking, hyperlipidemia, and hypertension. It causes significant neuronal and glial cell damage symptoms include sudden unilateral weakness, numbness, diplopia, slurred speech, ataxia, and non-orthostatic vertigo. Neurons in the ischemic core undergo cell death, while those in the penumbra show various stress responses. Increased blood-brain barrier permeability allows immune cells to infiltrate, which can release both protective and harmful factors affecting brain tissue [1].

The FDA's only approved initial treatment for acute ischemic stroke (AIS) is tissue plasminogen activator (tPA), demonstrated as effective within a 3-hour window by the National Institute of Neurological Disorders and Stroke trial and later extended to 4.5 hours by the ECASS III study [2,3].

tPA, primarily produced by endothelial cells and normally absent in healthy blood, converts plasminogen into plasmin, which then breaks down fibrin to initiate fibrinolysis. tPA's activity is typically regulated and occurs mainly when bound to fibrin, ensuring local fibrinolysis. However, in acute myocardial infarction trials, IV tPA's low fibrin specificity has caused plasminogen conversion even in the presence of circulating fibrinogen, leading to fibrinogen degradation coagulopathy. This condition, marked by a ≥200 mg/dL decrease in fibrinogen levels 6 hours after IV tPA infusion, was observed in 20% of acute ischemic stroke patients, correlating with a higher risk of hemorrhagic events [4].

While intravenous tPA (IV tPA) improves neurological outcomes, its thrombolytic properties necessitate careful administration due to the risk of symptomatic intracranial hemorrhage (sICH), defined by a significant NIHSS score increase of 4 points or more [3].

In clinical trials, symptomatic intracranial hemorrhage (SICH) is the primary adverse event assessed following tPA treatment for acute ischemic stroke. For adults, tPA is associated with a 6.4% SICH rate per NINDS guidelines. However, in 26 treated children, no SICH cases were reported. Bayesian beta-binomial modeling estimates the genuine risk of SICH in children to be below 15%, likely under 10%, with a 68% to 88% chance it is less than 5%, suggesting minimal risk when administered within 4.5 hours of symptom onset [5].

A meta-analysis of randomized controlled trials found that 32.9% of patients receiving IV tPA within 3 hours of acute ischemic stroke (AIS) onset achieved a modified Rankin Scale score of 0-1 at 3 months, compared to 23.1% in the placebo group. For large-vessel occlusions in the anterior circulation, combining endovascular therapy (EVT) with IV tPA significantly improved disability outcomes at 3 months compared to IV tPA alone. Hemorrhagic complications from reperfusion therapies can range from minor petechial hemorrhagic infarctions to severe intracerebral hemorrhage (ICH), often associated with higher morbidity and mortality, making it a critical safety measure in AIS trials [6].

The research concluded that thrombolysis-related hemorrhage rates are low, indicating no need to delay potentially life-saving treatment for ischemic stroke in emergency settings. IV tPA should

be administered within 4.5 hours of symptom onset to reduce stroke-related harm, though the impact of pre-stroke antiplatelet therapy on symptomatic intracerebral hemorrhage (sICH) risk remains uncertain. The study, involving 321,819 participants from the GWTG-Stroke registry, found that from 2013 to 2021, the use of single antiplatelet therapy (SAPT) decreased while dual antiplatelet therapy (DAPT) increased. Adjusted analyses revealed that SAPT was associated with a 13% higher risk of sICH, and DAPT with a 28% higher risk compared to no antiplatelet therapy. Absolute sICH risks were 0.9% higher for SAPT and 1.2% higher for DAPT. Despite higher sICH rates in patients on DAPT, thrombolysis should not be withheld if needed [7].

Conflict of Interest

All authors declare no conflict of interest.

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