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OUTCOMES OF TISSUE PLASMINOGEN ACTIVATOR AT DOSE OF 0.6 MG/KG AS INTRAVENOUS THROMBOLYSIS FOR ISCHEMIC STROKE AT 03 MONTHS AT PEMH RAWALPINDI

Original Research

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ABSTRACT

Background: Low-dose intravenous thrombolysis using tissue plasminogen activator (tPA) at 0.6 mg/kg has emerged as a potential alternative to the standard regimen in acute ischemic stroke (AIS), particularly in populations at higher risk for bleeding complications. This strategy may offer comparable efficacy with a lower incidence of symptomatic intracranial hemorrhage (sICH), although evidence on its functional outcomes and safety remains limited in real-world settings.

Objective: To evaluate 3-month functional outcomes and safety profiles following low-dose intravenous tPA in AIS patients and to identify predictors of functional independence and sICH.

Methods: This cross-sectional study was conducted on 160 patients with AIS treated with intravenous alteplase (0.6 mg/kg) within 4.5 hours of symptom onset at a tertiary care center between July and December 2024. Clinical variables, stroke severity using the NIH Stroke Scale (NIHSS), time-to-treatment, and stroke subtype were recorded. Functional independence was defined as a modified Rankin Scale (mRS) score of 0–2 at 3 months. Primary safety outcomes included sICH, defined by SITS-MOST criteria, and all-cause mortality.

Results: At 3-month follow-up, 113 patients (71%) achieved functional independence (mRS 0–2), with 73 (46%) attaining favorable outcome (mRS 0–1) and 43 (27%) experiencing complete recovery (mRS 0). sICH occurred in 6 patients (4%), while all-cause mortality was reported in 9 patients (6%). Independent predictors of poor functional outcome included increased age (OR 0.96, $p = 0.003$), higher baseline NIHSS (OR 0.79, $p < 0.001$), delayed treatment time (OR 0.98, $p = 0.038$), and hypertension (OR 0.53, $p = 0.041$). Predictors of sICH included higher NIHSS (OR 1.19, $p = 0.009$), elevated blood glucose (OR 1.02, $p = 0.027$), and advanced age (OR 1.06, $p = 0.013$).

Conclusion: Low-dose intravenous tPA (0.6 mg/kg) is a safe and effective therapeutic option for AIS in carefully selected patients. Age, stroke severity, blood glucose, and treatment delays significantly influence both recovery and risk of sICH. Emphasis on early intervention and individualized risk stratification is key to optimizing outcomes.

Keywords: Alteplase; Blood Glucose; Intracranial Hemorrhages; Ischemic Stroke; Neurologic Recovery; Risk Factors; Thrombolytic Therapy.

INTRODUCTION

Stroke remains a critical global health burden, ranking among the leading causes of mortality and long-term disability worldwide. According to the World Health Organization, approximately 15 million individuals suffer from stroke annually, with nearly one-third resulting in death and another third in permanent disability (1). Among the various subtypes, ischemic stroke is by far the most prevalent, accounting for nearly 80% of all cases. It typically results from the occlusion of a cerebral artery due to a thrombus or embolus, leading to reduced cerebral perfusion, tissue infarction, and subsequent neurological deficits (2,3). Prompt restoration of blood flow is essential to minimize irreversible brain damage and improve long-term neurological recovery (4). Recombinant tissue plasminogen activator (rt-PA) remains the cornerstone of acute ischemic stroke (AIS) management. Its mechanism of action involves catalyzing the conversion of plasminogen to plasmin, facilitating the breakdown of fibrin-rich clots and re-establishing cerebral blood flow (4,5). The pivotal NINDS trial demonstrated that intravenous rt-PA, when administered within 3 hours of stroke onset, significantly reduces disability by approximately 30% at 90 days post-stroke (6,7). Subsequently, the therapeutic window was extended to 4.5 hours in the ECASS III trial, thereby increasing the proportion of patients eligible for treatment (8). Despite these advances, real-world utilization of rt-PA remains suboptimal due to multiple barriers, including delayed hospital presentation, strict eligibility criteria, and concerns regarding symptomatic intracranial hemorrhage (sICH).

In response to these concerns, research from Asian populations has highlighted the potential benefits of a lower rt-PA dose of 0.6 mg/kg, particularly among individuals with lower body mass and higher risk of hemorrhagic transformation. Although the standard recommended dose remains 0.9 mg/kg, several studies conducted in Japan and China have reported comparable functional outcomes with the reduced dose, along with a trend toward decreased rates of sICH (10–14) (9). These findings have informed regional clinical guidelines, with countries such as Japan officially adopting the 0.6 mg/kg regimen for AIS thrombolysis (10,11). The adjustment not only addresses safety concerns but also contributes to reduced treatment costs—an important consideration for health systems with limited resources. Despite the growing body of evidence, there remains a need for robust, real-world data to evaluate the clinical effectiveness and safety of low-dose rt-PA in diverse settings (12). This study aims to assess the functional outcomes and complications associated with the administration of intravenous rt-PA at 0.6 mg/kg in patients with acute ischemic stroke. Specifically, it investigates 3-month functional independence, identifies predictors of favorable and unfavorable outcomes, and evaluates the incidence of thrombolysis-related complications, thereby contributing to a more nuanced understanding of dosage optimization in AIS management.

METHODS

This cross-sectional study was conducted at the Pakistan Emirates Military Hospital, Rawalpindi, over a six-month period from July 2024 to December 2024. A total of 160 patients with acute ischemic stroke (AIS) were included, following ethical approval from the Institutional Review Board under Notification No. RTMC#NEU-2022-124-756. Informed consent was obtained from patients or their legal guardians prior to the initiation of treatment, ensuring adherence to ethical research practices and patient autonomy. Patients were eligible for inclusion if they presented with a clinical diagnosis of AIS and received intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of symptom onset. Diagnosis was confirmed through detailed clinical evaluation and corroborated by neuroimaging. The study excluded individuals younger than 18 years, those with incomplete clinical records or missing follow-up data, patients with a pre-stroke modified Rankin Scale (mRS) score greater than 2, those with intracerebral hemorrhage (ICH) evident on baseline computed tomography (CT) imaging, and individuals who underwent endovascular thrombectomy or intra-arterial thrombolysis. These exclusion criteria were employed to eliminate confounding variables and ensure homogeneity of the study population (13).

All eligible patients were administered intravenous alteplase (rt-PA) at a dose of 0.6 mg/kg, with a maximum dose not exceeding 60 mg. The dosing protocol followed standardized institutional stroke management guidelines, whereby 15% of the total dose was delivered as a rapid intravenous bolus, and the remaining 85% was infused over a period of 60 minutes. This low-dose protocol was specifically chosen to evaluate safety and effectiveness in a real-world South Asian clinical setting, where body mass index and hemorrhagic risk factors may differ from those in Western populations. Data were collected prospectively using a structured data collection form by trained clinical staff. The recorded variables included demographic information (age and sex), vascular risk factors (e.g., hypertension,

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diabetes mellitus), baseline stroke severity assessed using the National Institutes of Health Stroke Scale (NIHSS), initial blood pressure and random blood glucose levels, stroke etiology as categorized by the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification, and the time interval from symptom onset to thrombolysis. Thrombolysis-related complications, including both symptomatic and asymptomatic intracranial hemorrhage, were systematically documented.

The primary safety outcomes assessed were symptomatic intracerebral hemorrhage (sICH) within 36 hours, defined in accordance with the SITS-MOST criteria as parenchymal hemorrhage type 2 accompanied by a neurological decline of at least four points on the NIHSS, as well as all-cause mortality at three months post-treatment (mRS score = 6). Functional independence at three months, defined as an mRS score of 0–2, was the principal efficacy outcome. Secondary outcomes included complete recovery (mRS = 0), favorable outcome (mRS = 0–1), and any intracerebral hemorrhage (including asymptomatic cases identified on follow-up imaging). Statistical analysis was performed using SPSS version 25.0. Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, as appropriate. Categorical variables were presented as absolute frequencies and percentages. To assess associations between baseline clinical variables and outcomes, both univariate and multivariate logistic regression analyses were applied. The student's t-test was employed for comparison of continuous variables between groups.

RESULTS

A total of 160 patients with acute ischemic stroke received low-dose intravenous rt-PA (0.6 mg/kg), and their baseline characteristics, clinical outcomes at 3 months, and predictors of both functional recovery and thrombolysis-related complications were analyzed. Functional independence (defined as mRS 0–2 at 3 months) was achieved by 71% of patients, with significantly better outcomes observed among those who were younger (mean age 67 ± 13 years vs. 73 ± 9 years, $p = 0.004$), had milder baseline stroke severity (NIHSS 7 ± 4 vs. 11 ± 6, $p < 0.001$), and received treatment earlier (148 ± 47 minutes vs. 178 ± 58 minutes, $p = 0.028$). No statistically significant differences were found between the favorable and unfavorable outcome groups in terms of sex, hypertension, diabetes, atrial fibrillation, hyperlipidemia, history of prior stroke or TIA, or smoking status. However, small vessel occlusion was numerically more common among those with favorable outcomes. At 3-month follow-up, 27% of patients showed complete recovery (mRS 0), 46% achieved favorable outcomes (mRS 0–1), and the incidence of symptomatic intracerebral hemorrhage (sICH) was 4%. All-cause mortality was observed in 6%, and any ICH was reported in 10%, including 7% classified as asymptomatic, indicating an acceptable safety profile of low-dose thrombolysis in this population.

Multivariate regression analysis identified four independent predictors of functional independence at 3 months: younger age (OR 0.96, 95% CI: 0.93–0.99, $p = 0.003$), lower baseline NIHSS score (OR 0.79, 95% CI: 0.74–0.85, $p < 0.001$), shorter time to treatment (OR 0.98, 95% CI: 0.97–0.99, $p = 0.038$), and absence of hypertension (OR 0.53, 95% CI: 0.27–0.97, $p = 0.041$). Conversely, predictors of sICH included higher NIHSS score (OR 1.19, $p = 0.009$), elevated blood glucose levels (OR 1.02, $p = 0.027$), and advanced age (OR 1.06, $p = 0.013$), all of which were significantly associated with increased hemorrhagic risk. Outcomes varied across stroke subtypes. Patients with small vessel occlusion demonstrated the most favorable prognosis, with 79% achieving functional independence, 1.5% experiencing sICH, and 2.9% mortality. In contrast, strokes of undetermined cause had the lowest rate of functional recovery (48%) and higher complication rates. Large artery atherosclerosis and cardioembolic strokes yielded intermediate results, suggesting that stroke mechanism influenced both treatment response and safety.

Baseline stroke severity, as measured by NIHSS, was strongly associated with clinical outcomes. Patients with mild strokes (NIHSS ≤ 5) exhibited a 92% rate of functional independence, 0% sICH, and no mortality. In comparison, those with severe strokes (NIHSS ≥ 15) had only a 30% likelihood of achieving mRS 0–2, along with the highest sICH rate (9.1%) and mortality (15%). These findings underscored the prognostic utility of initial stroke severity in determining both efficacy and risk of complications associated with thrombolysis. Subgroup analysis revealed important trends in functional outcomes across key patient characteristics. While not statistically significant in the univariate analysis, male sex, diabetes mellitus, and atrial fibrillation demonstrated noticeable variations in recovery. Among male patients, 55.8% achieved functional independence compared to 70.2% among those with unfavorable outcomes, suggesting a possible sex-based disparity in stroke recovery. Similarly, diabetic patients represented 29.2% of those with favorable outcomes but a markedly higher 44.7% among those with unfavorable outcomes, indicating a potential negative influence of diabetes on recovery. Atrial fibrillation was present in 20.4% of patients with favorable outcomes and 36.2% with unfavorable outcomes, pointing to its role as a potential risk factor for poorer post-thrombolysis prognosis. These findings highlight the need for further focused studies to explore these trends and validate their clinical significance in guiding individualized treatment strategies.

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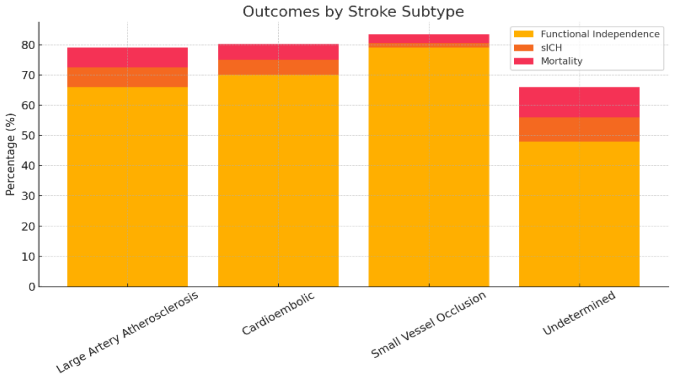

Figure 1 Outcomes by Stoke Subtype

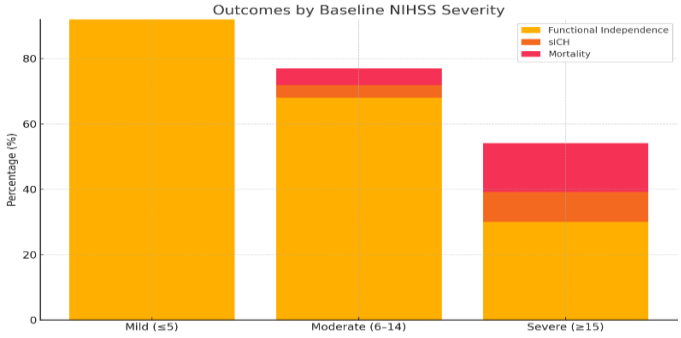

Figure 2 Outcomes by Baseline NIHSS Severity

Table 1: Baseline characteristics (n = 160)

Characteristic	Favorable Outcome (mRS 0–2) (n = 113)	Unfavorable Outcome (mRS >2) (n = 47)	p-value
Demographics			
Age (years, mean ± SD)	67 ± 13	73 ± 9	0.004
Sex (Male), n (%)	63 (58)	33 (47)	0.052
Vascular Risk Factors			
Hypertension, n (%)	73 (67)	42 (60)	0.591
Diabetes Mellitus, n (%)	33 (30)	21 (30)	0.943
Atrial Fibrillation, n (%)	23 (21)	17 (24)	0.618
Hyperlipidemia, n (%)	41 (38)	27 (39)	0.902
Prior Stroke/TIA, n (%)	11 (10)	9 (13)	0.655
Smoking (Current/Former), n (%)	36 (33)	22 (31)	0.852
Stroke Characteristics			
Baseline NIHSS Score (mean ± SD)	7 ± 4	11 ± 6	<0.001
Time to Treatment (minutes)	148 ± 47	178 ± 58	0.028
Stroke Subtype (TOAST)			0.183
Large Artery Atherosclerosis	31 (28)	16 (23)	
Cardioembolic	26 (24)	11 (16)	
Small Vessel Occlusion	42 (39)	26 (37)	
Other/Undetermined	14 (13)	17 (24)	

Table 2: Outcomes at 3 Months

Outcome	n (%)	95% CI
Primary Outcome		
Functional Independence (mRS 0–2)	113 (71)	(64, 77)
Primary Safety Outcomes		
sICH	6 (4)	(1, 8)
All-Cause Mortality	9 (6)	(2, 11)
Secondary Outcomes		
Complete Recovery (mRS 0)	43 (27)	(20, 34)
Favorable Outcome (mRS 0–1)	73 (46)	(38, 54)
Any ICH	16 (10)	(6, 15)
Asymptomatic ICH	11 (7)	(4, 12)

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Table 3: Predictors of favorable outcome

Variable	Odds Ratio (OR)	95% CI	p-value
Age (per year increase)	0.96	(0.93, 0.99)	0.003
Baseline NIHSS Score (per point)	0.79	(0.74, 0.85)	0.001
Time to Treatment (per minute)	0.98	(0.97, 0.99)	0.038
Hypertension (Yes vs. No)	0.53	(0.27, 0.97)	0.041

Table 4: Predictors of sICH

Variable	Odds Ratio (OR)	95% CI	p-value
Baseline NIHSS Score (per point)	1.19	(1.04, 1.36)	0.009
Blood Glucose (per mg/dL increase)	1.02	(1.01, 1.03)	0.027
Age (per year increase)	1.06	(1.02, 1.11)	0.013

Table 5: Subgroup Analysis of Functional Outcomes

Subgroup	Favorable Outcome (n=113)	Unfavorable Outcome (n=47)	Total (%) Favorable	Total (%) Unfavorable
Male Sex	63	33	55.8	70.2
Diabetes Mellitus	33	21	29.2	44.7
Atrial Fibrillation	23	17	20.4	36.2

DISCUSSION

This study evaluated the clinical outcomes and safety profile of low-dose intravenous thrombolysis in patients with acute ischemic stroke (AIS), with a particular focus on functional independence and the occurrence of symptomatic intracerebral hemorrhage (sICH). The findings demonstrated that increased age, higher baseline NIHSS score, and delayed treatment initiation were independently associated with poorer functional outcomes at 3 months. Additionally, higher stroke severity, elevated admission blood glucose levels, and advanced age were found to be significant predictors of sICH (14). These observations contribute to the growing body of evidence on the complexities of thrombolytic therapy and underscore the necessity of personalized risk stratification in AIS management. The association between advanced age and reduced functional recovery is consistent with previously published data (15). Older patients often have a higher burden of comorbidities, diminished physiological resilience, and altered pharmacodynamic responses to thrombolytics, all of which may attenuate the beneficial effects of treatment (16). Despite the proven efficacy of rt-PA in improving outcomes across age groups, the magnitude of benefit appears to be reduced in the elderly, who are simultaneously at greater risk for adverse events. This reinforces the importance of judicious clinical decision-making when considering thrombolysis in older individuals.

Baseline stroke severity emerged as a pivotal determinant of both clinical recovery and hemorrhagic risk. Patients with higher NIHSS scores at presentation were significantly less likely to regain functional independence and more prone to sICH, a trend that aligns with numerous large-scale registries and clinical trials (17,18). Severe strokes are frequently associated with larger infarct volumes and compromised blood-brain barrier integrity, which together increase the vulnerability to hemorrhagic transformation post-thrombolysis (19). These findings reaffirm the prognostic significance of initial stroke severity and highlight the need for enhanced monitoring and tailored interventions in patients with severe presentations. Timeliness of intervention continues to be a cornerstone of effective stroke therapy. In this cohort, prolonged onset-to-needle time was significantly associated with worse functional outcomes, reinforcing the principle that early reperfusion yields better neurological recovery. Each minute of delay increases the extent of irreversible neuronal injury, as supported by previous literature (20). These findings emphasize the urgent need to optimize stroke systems of care, both in prehospital and in-hospital settings. Implementation of streamlined stroke protocols, public education campaigns, and targeted logistical reforms are essential to reduce treatment delays.

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Hypertension was another variable linked with poorer functional outcomes. Although its relationship with hemorrhagic complications remains debated, the current study suggests that elevated blood pressure may contribute to suboptimal recovery, possibly through microvascular damage, impaired perfusion dynamics, or delayed thrombus clearance. Previous studies have reported mixed results on this association, reflecting a need for more nuanced understanding of blood pressure modulation in the context of thrombolysis (4,7). In contrast, hyperglycemia showed a clear independent relationship with sICH risk. Elevated glucose levels during the acute phase of stroke are known to promote oxidative stress, exacerbate ischemic injury, and compromise blood-brain barrier integrity, thereby predisposing to hemorrhagic transformation. This underscores the critical importance of vigilant glycemic control in the acute management of AIS patients undergoing thrombolysis. Despite offering important clinical insights, this study had several limitations. The cross-sectional design precludes establishment of causal relationships between predictors and outcomes. The relatively small sample size may have limited the statistical power to detect modest associations, especially in subgroup analyses. Additionally, the study was conducted at a single center, potentially limiting the generalizability of the findings. Nevertheless, the strength of this research lies in its real-world evaluation of low-dose rt-PA in an Asian population, where body composition and risk profiles may differ from Western populations, and where dose adjustments have important economic and clinical implications.

Future research should focus on larger, multicenter prospective studies to validate these findings and explore additional patient-specific modifiers of thrombolysis outcomes, such as frailty, renal function, and imaging biomarkers. There is also a need for randomized comparisons between standard and low-dose rt-PA in diverse populations to clarify optimal dosing strategies. Incorporating machine learning models to personalize thrombolysis risk-benefit assessments may further refine decision-making in acute stroke care. Overall, the findings highlight the multifactorial nature of thrombolysis outcomes and reinforce the importance of early intervention, individualized risk assessment, and aggressive management of modifiable physiological parameters such as blood pressure and glucose. Tailoring therapy based on patient-specific factors may offer the most effective path forward in improving functional outcomes and minimizing complications in AIS patients.

CONCLUSION

This study concluded that intravenous thrombolysis using low-dose alteplase in acute ischemic stroke presents a favorable balance of safety and effectiveness, supporting its use as a viable treatment approach in appropriately selected patients. The outcomes underscored the importance of early intervention and highlighted that, factors such as age, stroke severity, baseline glucose levels, and time to treatment significantly influence recovery and complication risks. Additionally, stroke subtype and initial clinical status emerged as important determinants of prognosis. These findings reinforce the need for individualized patient assessment and timely management to optimize outcomes and minimize risks in thrombolytic stroke therapy.

Author Contribution

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Munawar Khan*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Asif Hashmat	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Khurram Haq Nawaz	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Shabana Baloch	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Tayba Zain	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ayesha Zubair	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Nisar UL Haq	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Inayat Ullah	Writing - Review & Editing, Assistance with Data Curation

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