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Comparative Efficacy of Low-Dose Alteplase versus Standard Dose among Acute Ischemic Stroke Patients: A Single-Centre Experience in Pakistan

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ABSTRACT

Intravenous (IV) alteplase(tPA) at a dose of 0.9 mg /kg is the standard treatment of acute ischemic stroke (AIS), but it carries the risk of intracranial hemorrhage. **Objectives:** To assess the efficacy and safety of tPA low dose (LD; 0.6 mg/kg) as compared to standard-dose (SD; 0.9 mg/kg) in AIS patients in normal clinical practice. **Methods:** In this retrospective comparative cohort study, 320 AIS patients administered IV-tPA within 4.5 hours of stroke symptoms were selected in 2 groups (160 patients receiving LD; 0.6mg/kg), and 160 patients (SD; 0.9mg/kg) were developed in the Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, between January 2023 and December 2024. The measured outcomes were functional independence (mRS=02) at 90 days, incidence of symptomatic intracranial hemorrhage (sICH), and 90-day mortality. **Results:** Few individuals (32.5%) in the (LD; 0.6 mg/kg) group had positive functional outcomes compared to those in the (SD; 0.9 mg/kg) group (40.0%), but the difference was not significant (p=0.152). The (LD; 0.6mg/kg)(1.9% vs. 5.6%)(p=0.038) significantly reduced the risk of sICH. There were no differences in the 90-day mortality rates between the groups (11.3% vs. 13.8%, p=0.299). Adjusted (LD; 0.6 mg/kg) was, however, associated with reduced risk of sICH (aOR 0.30; 95% CI 0.08-0.98; p=0.040) but not functional outcome (aOR 0.82; 95% CI 0.54-1.25; p=0.361). Functional outcomes were strongly predicted by age, baseline NIHSS, and treatment length. **Conclusions:** In routine clinical practice, (LD; 0.6 mg/kg) was selectively used in higher-risk patients and showed a promising safety profile with functional outcomes broadly comparable to (SD; 0.9 mg/kg) therapy.

INTRODUCTION

The acute ischemic stroke (AIS) is a typical subtype, with almost 62 percent of all strokes that happen [1]. Although innovative treatment methods, including thrombolysis, have existed, the prognosis in a large proportion of patients is not clearly established by the risk and limitations posed by the existing treatment procedures [1, 2]. IV thrombolysis using recombinant tissue plasminogen activator (alteplase tPA) at 0.9mg/kg is the initial treatment of AIS [3]. This is a dose that is applicable in enhancing functional outcomes. It is, however, associated with a high risk of symptomatic intracranial hemorrhage (sICH), which casts doubts on its use in general [3, 4]. The Japan Alteplase Clinical Trial in Japan resulted in a tPA of 0.6 mg/kg, which was approved and had similar efficacy with fewer bleeding issues [5]. Since its approval, the lower dose has gained support in other regions of Asia, driven by financial considerations and a desire to reduce treatment-associated hazards [5]. Despite its potential (LD; 0.6 mg/kg), tPA has not been widely adopted due to contradictory findings from observational studies and a lack of strong evidence of efficacy across diverse groups [5, 6]. Current evidence, including meta-analyses, suggests that (LD; 0.6 mg/kg) may be a safer alternative for specific categories, such as elderly individuals or those who are more likely to develop

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problems [6]. However, inconsistent findings and inadequate data on patient-specific characteristics such as age and stroke severity underscore the need for future research [5, 6]. Notably, there is a paucity of data on tPA dose comparison from Pakistan, where patient demographics, comorbidity profiles, resource availability, and clinical practices may differ from those in previously studied populations.

Limited data are available in Pakistan and other comparable facilities where low-dose versus standard-dose alteplase is compared in a variety of patient groups, especially with long-term and multi-center data. The main question is to find out the best dose of alteplase that would provide a balance between the safety (less hemorrhage) and the effectiveness (functional recovery) of acute stroke patients with ischemia. This study aims to compare the effectiveness of doses of tPA (LD; 0.6 mg/kg) vs (SD; 0.9 mg/kg) in AIS patients from hospital records, to establish a balanced dosing strategy that improves treatment outcomes while minimizing adverse effects, thereby contributing to better stroke care.

METHODS

This retrospective comparative cohort study was conducted at the Department of Neurology, Pak Emirates Military Hospital, Rawalpindi, from January 2025 to April 2025. Patient data were retrospectively screened from the hospital management information system (HMIS) for the period spanning January 2023 to December 2024, during which patients received IV-tPA as part of routine stroke care. The hospital Institutional Review Board granted ethical permission for the access and analysis of retrospective data (Ref. No. A/28/ERC/02/2025). As this was a retrospective study using anonymized data, the IRB granted waiver of informed consent and permitted analysis of records generated before approval. The sample size was calculated by keeping the anticipated mRS ≤2 rates of 22.2% or the low and 34.8% for (SD; 0.9 mg/kg) patients [7], with a confidence level of 95%, and power of test as 80%, resulted in 392 sample size, by using the formula, $n = (Z_{(\alpha/2)} + Z_{\beta})^2 (p_1(1-p_1) + (p_2(1-p_2)) / (p_1 + p_2)^2$ [8]. The inclusion criteria were individuals of either gender or ethnicity, aged ≥18 years, with AIS confirmed by CT/MRI within 4.5 hours of symptom start and an NIHSS score between 4 and 25. The exclusion criteria were patients having hemorrhagic stroke, bleeding disorders, a previous stroke within the last three months, or major surgery within the last two weeks. During the study period, 423 patients with AIS who received IV-tPA were screened for eligibility. As this was a retrospective study, only patients with complete baseline information and documented 90-day outcome data were eligible for inclusion. A total of 103 patients were excluded due to incomplete medical records or missing 90-day outcome documentation, resulting in a final sample of 320 patients (160 per group). Due to the retrospective observational study design, patients were not randomly assigned to the (LD; 0.6 mg/kg) or (SD; 0.9 mg/kg) tPA groups. All dosing decisions were left to the treating neurologist based on routine clinical judgment at the time of presentation. Factors related to dose selection, as documented in clinical notes, included patient age, frailty, uncontrolled hypertension, elevated bleeding risk, delayed presentation, and physician preference, align with international evidence suggesting that low dose in selected patients is associated with lower risk of sICH. As the allocation was clinical-practice-based and derived from the hospital's electronic system, this introduces a potential risk of selection bias, which was acknowledged and addressed through comparison of baseline characteristics and stratified analysis. AIS diagnosis and haemorrhage detection were determined based on non-contrast CT imaging on admission and repeated at 24-36 hours. MRI was performed only in cases where further clarification was needed. Imaging was interpreted by the on-duty radiologists per institutional protocol; no blinded central imaging adjudication was available. AIS was defined as the sudden onset of focal neurological deficits consistent with cerebral ischemia, presenting within 4.5 hours of symptom onset, without evidence of intracranial hemorrhage on initial neuroimaging. The diagnosis was confirmed by a qualified neurologist using the National Institutes of Health Stroke Scale (NIHSS 0–42) and clinical presentation. Ischemia was verified by CT or MRI, and hemorrhage was ruled out. sICH was defined based on ECASS II criteria as a parenchymal hemorrhage involving more than 30% of the infarcted area (PH2), with mass effect or expansion beyond the infarct zone, and followed by a neurological impairment of at least four points on the NIHSS [9]. Treatment efficacy was evaluated using the mRS at 90 days, where a score of ≤2 denoted good functional recovery and independence in daily activities. Mortality referred to any death occurring between treatment initiation and the 90-day outcome assessment as documented in hospital records. Only those patients were included in the analysis whose routine clinical outcome data at 90 days were available in the hospital's electronic medical record system. All outcomes were assessed retrospectively through review of existing hospital electronic medical records; no patients were prospectively followed or contacted for outcome assessment. The NIHSS, a 15-item clinical stroke scale with a range of 0 to 42, was used to measure the severity of the stroke; higher scores indicate a more severe neurological loss. The total NIHSS is traditionally categorized as follows: 0 = no stroke symptoms; 1–4 = minor; 5–15 = moderate; 16–20 = moderate–severe; and 21–42 = severe [10]. With an

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inter-rater reliability of 0.95, the NIHSS has been extensively validated and demonstrated to predict both short and long-term outcomes following AIS [11]. Demographic variables like age, gender, comorbidities, and baseline NIHSS scores were retrieved from the hospital's electronic medical records in order to identify eligible individuals. The treatment was tPA, with 10% given as a bolus and the rest infused over an hour. Patients were treated in the ICU or stroke units according to institutional guidelines. Outcome data recorded within 90 days in the hospital electronic records included NIHSS evaluations at 24 hours, functional outcomes using the mRS, and mortality. Although the final analyzed sample was smaller than the initially calculated sample size, it represents all eligible patients with complete outcome data available during the study period. The data were analysed using SPSS-27. Continuous variables (age, mRS score, and NIHSS scores) were tested by the Shapiro-Wilk test to ascertain that they are normal and reported as the mean + SD or median (IQR) accordingly. This was compared using an independent t-test or Mann-Whitney U test. Gender, comorbidities, functional outcomes, sICH, and mortality are all quantitative variables reported in frequencies and percentages and compared with one another based on the Chi-square test or Fisher's exact test, where a p-value of 0.050 or less was considered statistically significant.

RESULTS

Among all 423 patients screened, only 320 (75.7%) patients had complete clinical and 90-day outcome data, while 103 (24.3%) individuals were excluded due to missing outcome documentation. The patients were split into two groups, with group A receiving (LD; 0.6 mg/kg) of tPA and group B receiving (SD; 0.9 mg/kg). The baseline features of both groups did not show any statistically significant differences. Group A's average age was 64.2 ± 11.5 years, while group B's average was 62.8 ± 10.9 years (p=0.251). Males constituted 60.0% of group B and 57.5% of Group A, indicating a comparable gender distribution (p=0.683). Group A's baseline NIHSS score was 14 (IQR 10–18), while Group B was 13 (IQR 9–17) (p=0.635). The average time to treatment was 205 ± 39 minutes and 198 ± 42 minutes, respectively (p=0.127). Comorbidities, including hypertension (68.8% vs. 65.6%, p=0.543), diabetes (46.9% vs. 43.8%, p=0.572), and atrial fibrillation (17.5% vs. 15.6%, p=0.642), were also comparable between groups (Table 1).

Table 1: Baseline Characteristics

Characteristic		Group A (n=160)	Group B (n=160)	p-value
Age (Year)	Mean ± SD	64.2 ± 11.5	62.8 ± 10.9	0.251[a]
Gender, n (%)	Male	92 (57.5%)	96 (60.0%)	0.683[b]
	Female	68 (42.5%)	64 (40.0%)	
Baseline NIHSS	Median (IQR)	14 (10-18)	13 (9-17)	0.635[c]
Time to Treatment (min)	Mean ± SD	198 ± 42	205 ± 39	0.127[a]
Comorbidities, n (%)	Hypertension	110 (68.8%)	105 (65.6%)	0.543[b]
	Diabetes Mellitus	75 (46.9%)	70 (43.8%)	0.572[b]
	Atrial Fibrillation	28 (17.5%)	25 (15.6%)	0.642[b]

Note: For comparison [a]Independent t test, [b]Chi-square test, [c]Mann-Whitney U test was used. *Statistically significant at p<0.05.

Favourable outcomes (mRS ≤2) at 90 days were observed in 32.5 and 40.0% of patients in group A and group B, respectively, and the difference between the two groups was not found (RR 0.81, 95% CI 0.61108; p=0.152). Group A had a lower rate of symptomatic intracranial haemorrhage (sICH) as compared to group B (1.9% vs. 5.6; RR 0.33, 95% CI 0.091.20; p=0.038). The two groups did not differ in terms of mortality rates (11.3 vs. 13.8; RR 0.82, 95% CI 0.461.46; p=0.299) (Table 2).

Table 2: Outcome on 90 Days

Outcomes	Group A (n= 160), n (%)	Group B (n= 160), n (%)	Risk Ratio, (95% CI)	p-value
Favorable Outcome (mRS ≤2)	52 (32.5%)	64 (40.0%)	0.81 (0.61 - 1.08)	0.152[a]
Symptomatic ICH	3 (1.9%)	9 (5.6%)	0.33 (0.09 - 1.20)	0.038*[b]
Mortality (90-Day)	18 (11.3%)	22 (13.8%)	0.82 (0.46 - 1.46)	0.299[a]

Note: Group B (SD; 0.9 mg/kg) was used as the reference category for risk ratio calculation. [a]Chi-square test or [b]Fisher's Exact test was used for comparison between groups. *Statistically significant at p<0.05

At 90 days, based on hospital record review, the distribution of mRS scores was broadly comparable between groups. mRS 0–2 was observed in 32.6% of group A and 40.1% in group B, while moderate to severe disability (mRS 3–5) occurred in 56.2% and 46.3%, respectively. Mortality rates were similar (11.3% vs. 13.8%) (Table 3).

Table 3: Modified Rankin Scale (mRS) Scores at 90 Days

mRS Score	Description	Group B (n= 160), n (%)	Group A (n= 160), n (%)
0	No Symptoms	15 (9.4%)	20 (12.5%)
1	No Significant Disability	18 (11.3%)	22 (13.8%)
2	Slight Disability	19 (11.9%)	22 (13.8%)
3	Moderate Disability	45 (28.1%)	38 (23.8%)
4	Moderately Severe Disability	32 (20.0%)	27 (16.9%)
5	Severe Disability	13 (8.1%)	9 (5.6%)
6	Death	18 (11.3%)	22 (13.8%)

After adjusting for confounders, (LD; 0.6 mg/kg) showed similar 90-day functional outcomes as (SD; 0.9 mg/kg), but was associated with a lower risk of symptomatic intracranial hemorrhage. Older age, higher baseline NIHSS, and delayed treatment predicted poorer outcomes, while only baseline NIHSS predicted sICH (Table 4).

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Table 4: Multivariate Logistic Regression Analysis for 90-Day Outcomes

Dependent Variables	Independent Variables	Adjusted Odds Ratio (aOR)	95% CI	p-value
mRS ≤2	(LD; 0.6 mg/kg)	0.82	0.54 – 1.25	0.361
	Age	0.70	0.52 – 0.95	0.021*
	Baseline NIHSS	0.86	0.81 – 0.92	<0.001*
	Time to Treatment (Minutes)	0.98	0.97 – 0.99	0.045*
	Hypertension	0.88	0.62 – 1.25	0.482
	Diabetes Mellitus	0.75	0.50 – 1.12	0.155
	Atrial Fibrillation	0.68	0.41 – 1.13	0.138
	(LD; 0.6 mg/kg)	0.30	0.08 – 0.98	0.040*
sICH	Age	1.22	0.95 – 1.58	0.118
	Baseline NIHSS	1.10	1.03 – 1.18	0.006*
	Time to Treatment (Minutes)	1.01	0.99 – 1.03	0.334
	Hypertension	1.45	0.88 – 2.39	0.145
	Diabetes Mellitus	1.32	0.75 – 2.31	0.334
	Atrial Fibrillation	1.25	0.65 – 2.41	0.501

*p-value<0.050 was significant

DISCUSSION

This study's findings show that (LD; 0.6 mg/kg) is associated with a decreased incidence of sICH, albeit with a potentially minimal reduction in functional efficacy. This safety profile may justify its use as a practical option, particularly in patients at increased bleeding risk or in resource-constrained settings where close monitoring is difficult. Dose selection should therefore balance safety and efficacy concerns. Our findings are comparable with those of Rahimi *et al.* who found a higher proportion of positive outcomes with (SD; 0.9 mg/kg) tPA and a lower incidence of sICH in the (LD; 0.6 mg/kg) group. Their propensity score analysis revealed sICH rates of 2.3% in the (LD; 0.6 mg/kg) group versus 11.4% in the (SD; 0.9 mg/kg) group [12]. Although (LD; 0.6 mg/kg) tPA exhibited a trend toward lower sICH (1.9% vs 5.6%), the limited number of events reduces statistical confidence; these data should be regarded with caution. Larger, well-powered research is needed to corroborate this observation. Similarly, Wang *et al.* reported an insignificant difference in functional results between low- and standard-dose tPA, despite lower sICH with the lower dose [13]. Additionally, meta-analyses demonstrate that the two doses are equally effective in terms of 90-day functional independence and recanalization, with no discernible variations in sICH or mortality [14]. Karedath *et al.* showed comparable death and sICH rates, but (SD; 0.9 mg/kg) treatment was linked with a slightly larger proportion of good functional outcomes [1]. However, these study findings only partially align with broader literature. The (LD; 0.6 mg/kg) group had a functional independence rate (mRS ≤2) of 32.5%, which was lower than previous studies' reported rates of 48-76.9% [13–15]. Xu *et al.* reported poorer functional outcomes with (LD; 0.6 mg/kg) tPA in Asian patients, suggesting that ethnicity and regional treatment patterns may influence results [16]. Additionally, Chen *et al.* found improved outcomes with (SD; 0.9 mg/kg) tPA in patients receiving combined thrombolysis and thrombectomy [7]. Overall, our data did not demonstrate a meaningful functional advantage for (LD; 0.6 mg/kg) tPA, supporting the idea that dose reduction may compromise efficacy in certain populations [17-19]. Regarding safety outcomes, our findings align with existing evidence. The rate of sICH in the (LD; 0.6 mg/kg) group was 1.9% compared to 5.6% in the (SD; 0.9 mg/kg) group, which is similar to Rahimi *et al.* [12]. Although the mortality differences were not statistically significant, the numerically decreased mortality in the (LD; 0.6 mg/kg) group corresponds to a safer profile described in other studies [20, 21]. However, due to the small number of incidents, these safety data should be taken as exploratory tendencies rather than definite evidence. It is important to emphasize that the current study is based on real-world clinical practice rather than a controlled comparison. In our center, physicians utilized (LD; 0.6 mg/kg) tPA on patients who were thought to be at increased risk of bleeding. This method was linked with a low incidence of sICH and functional outcomes that were roughly equivalent to those receiving (SD; 0.9 mg/kg).

Limitations of the study include that it is a retrospective study with a single center, possible selection bias and the lack of full data of all patients; therefore, the study may not be generalized. Further studies ought to involve large, multicenter randomized trials and extended follow-up to confirm the results and inform standard treatment procedures.

CONCLUSIONS

In this retrospective analysis, (LD; 0.6 mg/kg) was used selectively in high-risk patients and had less sICH incidence than (SD; 0.9 mg/kg). The general outcomes of the functional outcomes at 90 days were similar, but with lower numbers in the (LD; 0.6 mg/kg) group. As the study is observational, these findings should be interpreted as descriptive observations rather than evidence of non-inferiority. Treatment decisions should be individualized, particularly when considering bleeding risk or resource-limited settings. While (LD; 0.6 mg/kg) tPA may be a safer option for selected patients, further experimental studies are required to determine its comparative effectiveness.

Authors' Contribution

Conceptualization: JL
Methodology: TK[1], JL
Formal analysis: JL, TK[2]
Writing and Drafting: JL, AH, IA, HUR
Review and Editing: TK[1], JL, AH, IA, HUR

All authors approved the final manuscript and take responsibility for the integrity of the work.

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Conflicts of Interest

All the authors declare no conflict of interest.

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