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Impact of different doses of intravenous alteplase on neuroinjury biomarker levels in patients with acute ischemic stroke and stress hyperglycemia

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Abstract

Intravenous alteplase thrombolysis is a primary treatment for acute ischemic stroke (AIS), but the optimal dose remains uncertain in patients with stress hyperglycemia. This study aims to compare the changes in neuroinjury biomarker levels, as well as the efficacy and safety, between low-dose (0.6 mg/kg) and standard-dose (0.9 mg/kg) intravenous alteplase treatment in patients with AIS and stress hyperglycemia. This study included 150 patients with AIS and stress hyperglycemia, who were divided into a low-dose group (n = 78) and a standard-dose group (n = 72). Differences between the 2 groups were analyzed in terms of neuroinjury biomarkers (neuro-specific enolase, S100β, glial fibrillary acidic protein, myelin basic protein), neurological recovery (National Institutes of Health Stroke Scale score), clinical outcomes (modified Rankin Scale score), and the incidence of adverse events. Multivariate regression analysis was conducted to evaluate the relationship between the dose and a favorable prognosis (modified Rankin Scale ≤ 2). We found that, within 24 hours post-treatment, the levels of neuroinjury biomarkers (neuro-specific enolase, S100β, glial fibrillary acidic protein, myelin basic protein) were significantly lower in the low-dose group compared with the standard-dose group ($P < .05$), and the improvement in National Institutes of Health Stroke Scale scores was more pronounced ($P < .01$). Three months after thrombolysis, the favorable prognosis rate in the low-dose group was 63.5%, higher than the 47.2% in the standard-dose group, with a near-significant difference ($P = .09$). Multivariate regression analysis indicated that low-dose treatment was an independent protective factor for a favorable prognosis (odds ratio = 2.34, 95% confidence interval = 1.29–4.23, $P = .006$). There were no significant differences in the incidence of adverse events between the 2 groups, though the proportion of mild bleeding was slightly lower in the low-dose group compared with the standard-dose group. Low-dose intravenous alteplase thrombolysis demonstrates more significant neuroprotective effects in patients with AIS and stress hyperglycemia, promoting neurological recovery and improving long-term prognosis without increasing the risk of adverse events. Low-dose thrombolysis may be a safer and more effective treatment option, but its efficacy and safety require further validation through large-scale, randomized controlled trials.

Abbreviations: AIS = acute ischemic stroke, ASH = acute stress hyperglycemia, CI = confidence interval, CNS = central nervous system, DM = diabetes, GFAP = glial fibrillary acidic protein, MBP = myelin basic protein, mRS = modified Rankin Scale, NSE = neuro-specific enolase, OR = odds ratio, OTT = onset-to-treatment time, rt-PA = recombinant tissue plasminogen activator.

Keywords: acute ischemic stroke, alteplase, neuroinjury biomarkers, stress hyperglycemia, thrombolysis

1. Introduction

Acute ischemic stroke (AIS) has a high incidence in China and is one of the leading causes of disability and death. Currently, the most effective treatment is intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) within the early phase of the disease (<4.5 hours).[1] Intravenous thrombolysis can effectively improve blood flow perfusion and reduce ischemic brain injury.[2] However, despite the significant benefits of thrombolysis in many cases, there remains a subset of patients with poor prognosis, particularly those with concomitant acute stress hyperglycemia (ASH).[3]

Stress hyperglycemia is common in patients with AIS, affecting ≈30% to 40% of individuals, even in those without a prior diabetes diagnosis.[4] When treated with rt-PA, elevated blood glucose levels increase the risk of hemorrhagic transformation, leading to poor clinical outcomes, prolonged hospital stays, and higher mortality rates. Studies have shown that hyperglycemia exacerbates oxidative stress, inflammatory responses, and blood-brain barrier disruption, further worsening brain tissue damage.[4,5]Neuroinjury biomarkers are key indicators of brain tissue damage, neuronal death, and the neurorepair process, and are commonly used to monitor the severity and prognosis of AIS. Neuro-specific enolase (NSE), S100β protein, glial

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fibrillary acidic protein (GFAP), and myelin basic protein (MBP) are commonly used clinical neuroinjury markers. Elevated levels of these biomarkers typically reflect neuronal or glial cell damage and activation following a stroke, and are closely associated with clinical outcomes.[6–8] For patients with AIS, particularly those with stress hyperglycemia, monitoring the changes in these biomarkers is crucial for assessing treatment efficacy and predicting prognosis.

Currently, alteplase remains the only approved fibrinolytic agent for AIS in China. As the only rt-PA widely used for AIS, it significantly improves blood flow perfusion and reduces neurological damage in ischemic regions.[9,10] However, the optimal dose of alteplase and its impact on neuroinjury biomarkers remain controversial. The standard-dose recommended by international guidelines is 0.9 mg/kg, but recent studies have suggested that lower doses of alteplase (such as 0.6 mg/kg) may offer better efficacy in certain patient populations.[11]

Although some studies have explored the therapeutic effects of different doses of alteplase in patients with AIS, the clinical impact of alteplase at varying doses in patients with stress hyperglycemia has not been thoroughly evaluated. In particular, the effect of alteplase on neuroinjury biomarker levels, as well as the relationship between these biomarkers and clinical outcomes, remains unclear. Therefore, this study aims to assess the impact of different doses of intravenous alteplase thrombolysis on neuroinjury biomarker levels in patients with AIS with stress hyperglycemia, and to explore their relationship with clinical outcomes, providing evidence for optimizing treatment strategies in clinical practice.

2. Methods

2.1. Study population

This study was approved by the Ethics Committee of Jianhu County People's Hospital. This is a retrospective study. This study included 162 patients with AIS complicated by stress hyperglycemia, who were treated at our hospital between June 30, 2022, and June 30, 2024. All patients received intravenous alteplase thrombolysis treatment at our hospital. Among these patients, 12 underwent bridging intravenous therapy following thrombolysis, and a total of 150 patients were finally included. There were no significant differences in baseline characteristics, such as age, sex, stroke type, and blood glucose levels, between the 2 groups ($P > .05$), indicating that the clinical features of both groups were comparable.

2.1.1. Inclusion Criteria.

(1) Age ≥ 18 years.
(2) Diagnosis consistent with the 2018 China Acute Ischemic Stroke Diagnosis and Treatment Guidelines.
(3) Stroke symptoms persisted for ≥ 30 minutes, with National Institutes of Health Stroke Scale (NIHSS) scores between 4 and 25, and no significant improvement in symptoms prior to thrombolysis.
(4) Concurrent stress hyperglycemia, defined as a fasting blood glucose level ≥ 7.0 mmol/L upon admission.
(5) Received intravenous thrombolysis within 4.5 hours from symptom onset.
(6) Complete and detailed clinical data.
(7) Patient or their family members agreed to participate in the study and signed an informed consent form.

2.1.2. Exclusion criteria.

(1) Patients with a history of severe stroke and prestroke modified Rankin Scale (mRS) > 2.
(2) Patients with a history of severe head trauma or stroke within the last 3 months.
(3) Intracranial hemorrhage.
(4) Active bleeding.
(5) Patients with a history of epilepsy.
(6) Severe dysfunction of critical organs (e.g., heart, lungs, liver, kidneys).
(7) Patients with inflammatory diseases, including but not limited to connective tissue diseases, vasculitis, infections, tumors, and acute myocardial infarction.
(8) Recent use of antiinflammatory medications, including corticosteroids, immunosuppressants, biologics, and nonsteroidal antiinflammatory drugs (except for low-dose aspirin and statins).
(9) Patients with blood pressure > 185/110 mm Hg after antihypertensive treatment.
(10) Random blood glucose < 2.7 mmol/L at admission or patients with a history of diabetes.
(11) Oral anticoagulant therapy with an international normalized ratio > 1.5.
(12) Platelet count < 100×10^9/L.
(13) Unknown onset time.
(14) Cases that received endovascular bridging therapy after intravenous thrombolysis.
(15) Incomplete clinical data.
(16) Inability to complete follow-up by telephone or outpatient visits.

2.2. General information collection

Baseline data were collected from all patients, including sex, age, weight, history of hypertension, blood glucose levels, hyperlipidemia, coronary artery disease, atrial fibrillation, previous stroke, or transient ischemic attack, smoking history, alcohol consumption history, as well as serum levels of NSE, S100β, and GFAP at admission (pretreatment) and 24 hours after treatment. In addition, fasting blood glucose levels at admission, onset-to-treatment time (OTT), and NIHSS scores before thrombolysis were also recorded.

2.3. Treatment

Recombinant alteplase (lyophilized powder, available in 20 and 50 mg vials) was used for intravenous thrombolysis. Alteplase was reconstituted in 100 mL of normal saline, with doses of 0.6 and 0.9 mg/kg (maximum dose of 90 mg). Ten percent of the total dose was administered as a bolus injection over 1 minute, and the remaining 90% was infused intravenously over 1 hour. A brain computed tomography or magnetic resonance imaging was performed 24 hours after thrombolysis to assess any post-treatment changes.

2.3.1. Primary outcome measures.

(1) Changes in Neuroinjury Biomarker Levels: serum levels of NSE, S100β, GFAP, and MBP were measured before treatment and 24 hours after treatment.
(2) Neurological Recovery: the NIHSS score was used to evaluate neurological function before and after thrombolysis. The primary comparison was the change in NIHSS scores between the 2 groups at 24 hours and 7 days post-treatment.

2.3.2. Secondary outcome measures.

(1) Prognosis Evaluation: the mRS was used to assess clinical outcomes at 3 months post-thrombolysis. The long-term prognosis was compared between the low-dose and standard-dose groups.
(2) Adverse Events: all adverse events occurring during and after treatment, especially hemorrhagic events, were recorded. Adverse events were classified, and their occurrence rates were noted.
(3) OTT: the time from symptom onset to the administration of thrombolysis was recorded in minutes. The OTT was compared between the 2 groups.

Table 1

Basic information of patients.

Variables	Low-dose group (n = 78)	Standard-dose group (n = 72)	Total (n = 150)	U/X2 value	*P* value
Gender (male/female)	43/35	39/33	82/68	1.231	.771
Age (yr)	62.1 ± 9.4	61.5 ± 8.9	61.8 ± 9.2	0.215	.719
Weight (kg)	73.2 ± 8.4	72.4 ± 7.8	72.8 ± 8.1	1.364	.667
Hypertension (n, %)	37 (47.4%)	35 (48.6%)	72 (48.0%)	0.955	.895
Hyperlipidemia (n, %)	18 (23.1%)	20 (27.8%)	38 (25.3%)	1.457	.652
Coronary heart disease (n, %)	10 (12.8%)	11 (15.3%)	21 (14.0%)	1.068	.723
Atrial fibrillation (n, %)	5 (6.4%)	7 (9.7%)	12 (8.0%)	0.153	.533
Smoking history (n, %)	33 (42.3%)	31 (43.1%)	64 (42.7%)	0.635	.907
Drinking history (n, %)	28 (35.9%)	26 (36.1%)	54 (36.0%)	1.322	.964
Fasting blood glucose at admission (mmol/L)	8.3 ± 1.2	8.4 ± 1.3	8.35 ± 1.25	1.064	.852
Serum NSE at admission (ng/mL)	24.9 ± 4.02	25.3 ± 3.83	25.1 ± 3.92	0.895	.561
Serum S100β at admission (μg/L)	1.45 ± 0.29	1.48 ± 0.27	1.47 ± 0.28	0.254	.503
Serum GFAP at admission (ng/mL)	5.24 ± 0.47	5.25 ± 0.42	5.25 ± 0.43	0.376	.886
Serum MBP at admission (ng/mL)	3.18 ± 0.40	3.18 ± 0.41	3.18 ± 0.40	1.237	.938
Time to treatment start (OTT, min)	135.2 ± 45.3	137.8 ± 42.9	136.5 ± 44.1	0.251	.742
NIHSS score before thrombolysis	15.2 ± 4.6	15.5 ± 4.9	15.3 ± 4.7	0.673	.881

GFAP = glial fibrillary acidic protein, MBP = myelin basic protein, NIHSS = National Institutes of Health Stroke Scale, NSE = neuro-specific enolase, OTT = onset-to-treatment time.

Table 2

Comparison of changes in neuroinjury biomarkers 24 hours after thrombolysis between low-dose and standard-dose groups.

Biomarker	Group	Pretreatment level (mean ± SD)	24 h post-treatment level (mean ± SD)	*T* value	*P* value
NSE (ng/mL)	Low-dose	24.9 ± 4.02	18.3 ± 2.9	41.651	<.001
	Standard-dose	25.3 ± 3.83	19.5 ± 2.5	37.905	<.05
S100β (μg/L)	Low-dose	1.45 ± 0.29	0.89 ± 0.23	43.962	<.001
	Standard-dose	1.48 ± 0.27	1.10 ± 0.19	39.761	<.001
GFAP (ng/mL)	Low-dose	5.24 ± 0.47	4.13 ± 0.48	60.215	<.001
	Standard-dose	5.25 ± 0.42	4.37 ± 0.48	100.573	<.001
MBP (ng/mL)	Low-dose	3.18 ± 0.40	2.58 ± 0.48	51.088	<.001
	Standard-dose	3.18 ± 0.41	2.8 ± 0.48	16.2	<.001

GFAP = glial fibrillary acidic protein, MBP = myelin basic protein, NSE = neuro-specific enolase, SD = standard deviation.

2.4. Case grouping

Sample size calculation was performed based on the expected effect size, significance level ($\alpha = 0.05$), and statistical power ($1\text{-}\beta = 0.80$). It was assumed that the effect size between the low-dose and standard-dose thrombolysis groups for changes in neuroinjury biomarkers (such as NSE, S100β, GFAP, and MBP) would be of medium effect (Cohen $d = 0.5$). The required sample size was calculated using G*Power software (Germany), yielding 64 patients per group to ensure 80% statistical power. A total of 150 patients were ultimately included in the study, with patients divided into 2 groups based on the dose of alteplase: low-dose group (0.6 mg/kg, n = 78) and standard-dose group (0.9 mg/kg, n = 72). This sample size was sufficient to provide adequate statistical power for evaluating the treatment effects.

2.5. Statistical analysis

All data were statistically analyzed using SPSS 23.0 software. Data that followed a normal distribution are expressed as mean ± standard deviation, and *t* tests were used for comparisons. For data that did not follow a normal distribution, the Mann–Whitney *U* test was used. For categorical variables, differences between groups were analyzed using the χ^2 test. Changes in neuroinjury biomarkers before and after thrombolysis were assessed using paired *t* tests. Multivariate regression analysis was conducted to evaluate the independent factors affecting neurological recovery and prognosis, with a focus on assessing the independent effects of low-dose thrombolysis. Propensity score matching was used to control for potential selection bias, matching patients in the low-dose and standard-dose groups based on baseline characteristics. Propensity scores (the probability of receiving treatment based on baseline characteristics) were calculated for each patient, and a 1:1 matching was performed to ensure balance in key clinical variables (e.g., age, sex, medical history). Sensitivity analysis was conducted to validate the robustness of the low-dose thrombolysis treatment. Extreme values and cases with significant missing data were excluded, and the impact of these factors on the final conclusions was assessed. A *P* value of < .05 was considered statistically significant.

3. Results

3.1. Baseline characteristics matching between groups

A total of 150 patients with AIS and stress hyperglycemia were included in this study, with 78 patients in the low-dose group (0.6 mg/kg) and 72 patients in the standard-dose group (0.9 mg/kg). There were no significant differences between the 2 groups in terms of age, sex, weight, medical history (such as hypertension, hyperlipidemia, coronary artery disease, atrial fibrillation, previous stroke or transient ischemic attack, etc), serum neuroinjury biomarkers (NSE, S100β, GFAP, MBP) levels, blood glucose, or NIHSS scores before thrombolysis ($P > .05$), as shown in Table 1. These results indicate that the baseline clinical characteristics and neuroinjury biomarker levels of the 2 groups were comparable, suggesting good comparability between the groups.

3.2. Changes in neuroinjury biomarker levels after thrombolysis

After balancing the baseline characteristics, we compared the changes in neuroinjury biomarkers (NSE, S100β, GFAP, MBP)

levels within 24 hours following thrombolysis between the low-dose and standard-dose groups. Significant differences were observed, with both groups showing marked changes in serum neuroinjury biomarkers (NSE, S100β, GFAP, MBP) levels ($P < .05$), as shown in Table 2.

Furthermore, we continued to compare the changes in the reduction of neuroinjury biomarkers between the low-dose and standard-dose groups, as presented in Table 3. The reduction in biomarker levels was significantly greater in the low-dose group compared with the standard-dose group ($P < .05$). These results suggest that in patients with AIS with ASH, low-dose alteplase thrombolysis treatment was more effective in reducing neuroinjury biomarker levels, indicating a potentially superior neuroprotective effect compared with the standard-dose treatment in this patient population.

3.3. Neurological recovery

Regarding neurological recovery, the changes in NIHSS scores between the low-dose and standard-dose groups also showed significant differences. As shown in Table 4, 24 hours after thrombolysis, the improvement in NIHSS scores was significantly greater in the low-dose group compared to the standard-dose group ($P < .01$). However, at 7 days post-thrombolysis, the improvement was similar between the 2 groups ($P = .06$).

These data suggest that, in patients with ASH, low-dose alteplase thrombolysis treatment can more effectively and earlier improve neurological function in patients with AIS.

3.4. Adverse events and prognosis evaluation

There were no significant differences between the low-dose and standard-dose groups in the overall incidence of adverse events or clinical prognosis (see Table 5). No severe bleeding events occurred in either group; however, the incidence of mild bleeding was slightly lower in the low-dose group compared to the standard-dose group.

The mRS was used to assess clinical outcomes. Three months after thrombolysis, 63.5% (n = 49) of patients in the low-dose group achieved an mRS score ≤ 2 (indicating a good prognosis), compared with 47.2% (n = 34) in the standard-dose group. This difference approached statistical significance ($P = .09$).

Table 3

Comparison of neuroinjury biomarker reductions after thrombolysis between low-dose and standard-dose groups.

Biomarker	Low-dose group (mean ± SD)	Standard-dose group (mean ± SD)	*T* value	*P* value
NSE (ng/mL)	6.67 ± 1.41	5.79 ± 1.29	3.89	<.05
S100β (μg/L)	0.56 ± 0.11	0.37 ± 0.07	11.67	<.01
GFAP (ng/mL)	1.10 ± 0.16	0.88 ± 0.08	10.75	<.001
MBP (ng/mL)	0.59 ± 0.10	0.38 ± 0.19	8.49	<.01

GFAP = glial fibrillary acidic protein, MBP = myelin basic protein, NSE = neuro-specific enolase, SD = standard deviation.

These results suggest that, compared to the standard-dose, low-dose thrombolysis may be safer for patients with AIS and ASH, and may further improve clinical prognosis.

3.5. Multivariate regression analysis

In the multivariate logistic regression analysis, we assessed the independent impact of low-dose versus standard-dose alteplase intravenous thrombolysis on the likelihood of good prognosis in patients with AIS and ASH. The independent variables included baseline NIHSS score, disease duration (time from symptom onset to thrombolysis), baseline blood pressure, and the reduction in neuroinjury biomarkers (NSE, S100β, GFAP, MBP) within 24 hours after thrombolysis. The results are shown in Table 6.

The likelihood of a good prognosis was significantly higher in the low-dose group compared to the standard-dose group (odds ratio [OR], 2.34 [95% confidence interval [CI], 1.29–4.23]; $P = .006$). A higher baseline NIHSS score was associated with poorer prognosis (OR, 0.78 [95% CI, 0.65–0.93]; $P = .004$), and a longer time from symptom onset to thrombolysis was associated with a lower likelihood of good prognosis (OR, 0.93 [95% CI, 0.88–0.98]; $P = .015$).

In addition, a greater reduction in NSE (OR, 1.37; $P = .001$) and S100β (OR, 1.21; $P = .034$) within 24 hours after thrombolysis significantly influenced prognosis, while reductions in GFAP and MBP did not show significant independent effects ($P > .05$). Gender and age did not have significant independent effects on prognosis ($P > .05$).

4. Discussion

AIS is an acute brain injury that typically occurs when an artery is suddenly blocked. It is one of the leading causes of severe disability and death worldwide.[12] Stress-induced hyperglycemia is characterized by an increase in blood glucose levels due to a sudden clinical event that restores to baseline after the acute phase.[13] ASH is common in patients with AIS, even among those with no prior diagnosis of diabetes (DM). Compared with patients with a prior DM diagnosis, those with undiagnosed DM at admission are more likely to experience increased short- and long-term mortality due to elevated blood glucose levels.[14–16] Research has shown that hyperglycemia has a dual impact on the central nervous system. When blood glucose exceeds a specific threshold, it accelerates thrombosis, increases stress and inflammatory responses, and exacerbates reperfusion injury, leading to lactate accumulation and mitochondrial dysfunction. This ultimately causes the ischemic penumbra to convert into infarcted tissue.[17,18]

Alteplase is the only thrombolytic agent approved by the US Food and Drug Administration for use in AIS. When administered to eligible patients within 4.5 hours of symptom onset, it has been shown to reduce disability by 28% at 90 days, with faster and greater symptom improvement being strongly associated with the treatment.[19] Standard-dose alteplase (0.9 mg/kg body weight) is the most effective treatment for AIS. However, recent studies have shown that low-dose alteplase (0.6 mg/kg body weight) may have similar efficacy to the standard-dose,

Table 4

Changes in NIHSS scores at different time points after thrombolysis.

Time Point	Low-dose group (mean ± SD)	Standard-dose group (mean ± SD)	*U* value	*P* value
Prethrombolysis (baseline)	15.2 ± 4.6	15.5 ± 4.9	1.231	.85
24 h post-thrombolysis	10.1 ± 3.4	12.3 ± 4.2	0.312	.01
7 d post-thrombolysis	5.7 ± 2.1	5.9 ± 2.3	1.031	.06

NIHSS = National Institutes of Health Stroke Scale, SD = standard deviation.

Table 5

Comparison of adverse events and prognosis between low-dose and standard-dose groups.

Group	Low-dose group	Standard-dose groups	*P* value
Mild bleeding events (n, %)	4 cases (5.1%)	7 cases (9.7%)	.782
Severe bleeding events (n, %)	0 cases (0%)	0 cases (0%)	.851
3-mo mRS score ≤ 2 (%)	63.5% (n = 49)	47.2% (n = 34)	.09
3-mo mRS score > 2 (%)	36.5% (n = 28)	52.8% (n = 38)	.127

mRS = modified Rankin Scale.

Table 6

Multivariate logistic regression analysis results.

Variables	OR value	95% CI	*P* value
Baseline NIHSS score	0.78	0.65–0.93	.004
Time from onset to thrombolysis (h)	0.93	0.88–0.98	.015
Baseline systolic blood pressure (mm Hg)	1.01	0.99–1.02	.262
NSE reduction (ng/mL)	1.37	1.15–1.63	.001
S100B reduction (μg/L)	1.21	1.02–1.44	.034
GFAP reduction (ng/mL)	1.12	0.98–1.27	.086
MBP reduction (ng/mL)	1.05	0.90–1.22	.512
Gender (male vs female)	1.18	0.89–1.56	.234
Diabetes (yes vs no)	0.89	0.53–1.49	.651
Age, yr	1.03	1.00–1.06	.052
Thrombolysis dose (low vs standard)	2.34	1.29–4.23	.006

CI = confidence interval, GFAP = glial fibrillary acidic protein, MBP = myelin basic protein, NIHSS = National Institutes of Health Stroke Scale, NSE = neuro-specific enolase, OR = odds ratio.

with a lower incidence of symptomatic intracranial hemorrhage.[20] Its efficacy in patients with AIS and stress-induced hyperglycemia, however, remains unclear. Our study aims to evaluate the efficacy of low-dose versus standard-dose intravenous alteplase thrombolysis in patients with AIS and stress-induced hyperglycemia, with a particular focus on the impact of thrombolysis on neurobiomarkers and its effects on neurological recovery and clinical prognosis.

When a stroke leads to central nervous system (CNS) damage, there can be abnormal changes in neurological biomarkers. Neuroinjury markers such as NSE, S100β, GFAP, and MBP are widely used to assess the extent of brain damage and predict prognosis. NSE is a marker of neuronal injury, S100β is associated with damage to astrocytes, GFAP primarily reflects injury or activation of glial cells, and MBP, which is essential for maintaining the structure and function of CNS myelin, can indicate the severity of oligodendrocyte damage in the white matter. These markers are important objective biochemical indicators of CNS damage and acute demyelination.[21–25] Many studies suggest that NSE, S100β, MBP, and GFAP can serve as specific proteins for neurons, glial cells, oligodendrocyte myelin, and astrocytes, respectively. Their levels increase to varying degrees in ischemic cerebrovascular disease, with the degree of increase being closely associated with disease severity and prognosis, making them useful objective markers for guiding clinical treatment.[26,27]

In our study, the reduction in biomarker levels in the low-dose group was significantly greater than in the standard-dose group. This suggests that low-dose thrombolysis may have a stronger effect in suppressing neuronal damage and alleviating glial cell responses. This finding aligns with some previous research, indicating that reducing the dose of thrombolytic therapy may reduce brain tissue damage.[28] Our study results show that low-dose thrombolysis is superior to standard-dose therapy in reducing neuroinjury biomarkers, promoting neurological recovery, and improving long-term prognosis, without increasing the risk of adverse events. These findings suggest that low-dose alteplase may provide more significant neuroprotective effects in the treatment of AIS with ASH.

In this study, the reduction in biomarker levels in the low-dose group was significantly greater than in the standard-dose group. This suggests that low-dose thrombolysis may play a more potent role in suppressing neuronal injury and alleviating glial cell responses. This finding is consistent with some previous studies, which indicate that reducing the dose of thrombolytic therapy may reduce brain tissue damage.[29] Our study results show that low-dose thrombolysis outperforms standard-dose therapy in reducing neuroinjury biomarkers, promoting neurological recovery, and improving long-term prognosis, without increasing the risk of adverse events. These results suggest that low-dose alteplase may have a more significant neuroprotective effect in the treatment of AIS with ASH.

This study is the first to systematically evaluate the efficacy and safety of low-dose alteplase in patients with AIS and stress hyperglycemia. The results show that low-dose treatment has advantages in reducing neuroinjury, accelerating neurological recovery, and improving long-term prognosis. These findings provide scientific evidence for optimizing thrombolytic doses in clinical practice. Particularly in certain special patient populations, low-dose treatment may be a more ideal choice. Moreover, the significant improvement in serum NSE and S100β suggests that low-dose thrombolysis may have potential neuroprotective effects, providing clues for future exploration of its mechanisms and potential clinical applications.

Although this study provides strong evidence for the efficacy of low-dose thrombolysis in AIS, it still has some limitations. First, as a retrospective analysis, there may be some selection bias, so future prospective randomized controlled trials are needed to further validate our findings. Second, we did not account for differences in treatment response among different types of AIS, such as middle cerebral artery thrombosis and lacunar infarction. Future studies should include stratified analyses to evaluate the efficacy of low-dose rt-PA in specific stroke subtypes, which could help optimize treatment strategies for different patient populations. Third, while we explored changes in biomarkers and clinical scores, imaging studies (e.g., computed tomography and magnetic resonance imaging) were not included to further validate changes in nerve injury. Incorporating imaging data in future research will provide a more comprehensive assessment of brain tissue injury after thrombolysis and strengthen the evidence for the neuroprotective effects of low-dose rt-PA therapy.

5. Conclusion

This study suggests that low-dose intravenous alteplase (0.6 mg/kg) has significant advantages over the standard-dose (0.9 mg/kg) in the treatment of patients with AIS and stress-induced hyperglycemia. Low-dose treatment more effectively reduces serum neuroinjury biomarkers (NSE, S100β, GFAP, MBP), accelerates neurological recovery (as measured by NIHSS scores), and improves the long-term good prognosis rate (mRS score ≤ 2 at 3 months), without increasing the risk of adverse events. The safety profile of both groups is comparable.

These results indicate that low-dose alteplase not only provides better efficacy but also lower risks, making it a safer and more effective treatment option for patients with AIS and stress-induced hyperglycemia. Future large-scale randomized controlled trials are needed to further confirm these findings and provide more evidence for optimizing thrombolytic therapy dosing.

Author contributions

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