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Effect of thrombolytic therapy with rt-PA at different times on neurological function and complications in patients with acute cerebral infarction

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Abstract: This study investigates the effects of rt-PA thrombolytic therapy at varying times on neurological function and complications in acute cerebral infarction (ACI) patients. A total of 120 ACI patients admitted between August 2019 and July 2021 were divided into three groups based on the timing of rt-PA treatment: <3h (40 patients), 3–4.5h (55 patients), and >4.5h (25 patients). All received standard treatment and rt-PA IV thrombolysis. Key comparisons included cerebral oxygen metabolism, oxidative stress, neural markers, hemodynamics, coagulation function, NIHSS scores, ADL, clinical efficacy, and complications. Results showed that 48 hours post-treatment, SjvO2 levels were significantly higher in the <3h and 3-4.5h groups compared to the >4.5h group. SOD levels were also higher in the earlier groups, while MDA levels were lower. Three months after treatment, NIHSS scores were significantly lower and ADL scores higher in the <3h and 3-4.5h groups, with lower complication rates. Efficacy was similar within 3 hours and 3–4.5 hours, but complications increased significantly after 4.5 hours.

Keywords: Different times, rt-PA thrombolysis, acute cerebral infarct (ACI), neurological function, complications.

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INTRODUCTION

Recombinant Human tissue plasminogen activator for injection (rt-PA), a commonly used thrombolytic agent in the clinic, is widely used in acute myocardial infarction, pulmonary embolism, deep vein thrombosis and other vascular diseases. It is also the most effective drug for treating acute cerebral infarct (ACI), canalizing occluded vessels and restoring cerebral blood perfusion (Edwards *et al*., 2021). "The earlier the better" is the principle of thrombolytic therapy for ACI. However, the time window of thrombolytic therapy for ACI has been controversial in the medical field. At the early stage of study, most scholars believed that thrombolysis could be performed within 6 hours after the onset of ACI in the absence of obvious contraindications (Jin *et al*., 2021). With the development of clinical research, the National Institute of Neurological Disorders and Stroke (NINDS) reported that patients with rt-PA administered intravenously within 3 hours after the onset of ACI had significantly higher neurological function after 3 months than those in the placebo group (Kato *et al*., 2021). However, the European Cooperative Acute Stroke Study (ECASS) and most clinical studies in China in recent years have shown that the administration of rt-PA thrombolysis within 3~4.5 hours after the onset of ACI still has a significant effect, and some studies believe that there is no significant difference between the effects of IV thrombolysis within 3 hours and IV thrombolysis within 4.5 hours (Wu *et al*., 2020; Kannan *et al*., 2021).

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At the same time, with the continuous updates of thrombolytic drugs, some patients can even extend the time window for thrombolysis to within 6 hours (Fu *et al*., 2022). Approximately 80% of patients with ACI experience varying degrees of neurological dysfunction after onset, such as hemiplegia, memory decline and impairments in executive function and learning ability. However, whether extending the time window will necessarily increase disability and mortality rates remains a matter of debate (Kitaura *et al*., 2019). Additionally, the poor efficacy of rt-PA intravenous thrombolysis in ACI patients is closely related to secondary conditions such as anxiety, depression, cognitive dysfunction, pressure injuries, and urinary tract infections (Li *et al*., 2019). Therefore, selecting the appropriate timing for thrombolysis in ACI is crucial for the prevention and treatment of related conditions and for improving patient prognosis. Based on this, this study investigates the effects of rt-PA thrombolysis at different time points in treating ACI, providing more insights for clinical improvement of neurological function and reduction of complication rates.

MATERIALS AND METHODS

Study subjects

120 ACI patients admitted to the Neurology Department and the Emergency Department of our hospital from August 2019 to July 2021 were selected as the study subjects. According to rt-PA treatment at different times after the onset of ACI, the patients were divided into 40 patients with Disease <3h (Disease <3h group), 55

patients with disease 3~4.5h (Disease 3~4.5h group), and 25 patients with disease >4.5h (Disease >4.5h group). Disease <3h group: 23 males and 17 females; Age: 36~72 years old, with an average of (54.43±6.75) years old; Weight: 48~77kg, with an average of (53.19±4.58)kg; Underlying diseases: 14 cases with hypertension, 8 cases with coronary heart disease, 5 cases with diabetes, 3 cases with hyperlipidemia and 10 cases with other diseases. Disease <3~4.5h group: 31 males and 24 females; Age: 38~74 years old, with an average of (55.12±6.29) years old; Weight: 46~80kg, with an average of (53.75±4.30)kg; Underlying diseases: 19 cases with hypertension, 10 cases with coronary heart disease, 7 cases with diabetes, 4 cases with hyperlipidemia and 15 cases with other diseases. Disease >4.5h group: 15 males and 10 females; Age: 35~73 years old, with an average of (54.96±7.10) years old; Weight: 49~78kg, with an average of (52.96±5.13)kg; Underlying diseases: 9 cases with hypertension, 5 cases with coronary heart disease, 3 cases with diabetes, 2 cases with hyperlipidemia, and 6 cases with other diseases. There was no statistical difference in general data among these three groups (P>0.05), so they were comparable.

Case selection

ACI diagnosis (Edwards *et al*., 2021): (1) Sudden onset, with varying degrees of dizziness, tinnitus and headache, nausea and vomiting, sensory and motor dysfunction; (2) Imaging examination showed cerebral ischemic penumbra, infarction, cerebral edema, vascular stenosis and occlusion.

Contraindications to rt-PA thrombolysis (Rodríguez-Pardo, 2020): (1) Intracranial tumors, arteriovenous malformations or arteriovenous tumors; (2) Active bleeding tendency, subarachnoid hemorrhage or epileptic seizure, old cerebral infarction, bacterial endocarditis; (3) Abnormal laboratory test results, such as abnormal activated partial thromboplastin time (APTT) and platelet count $<100\times10^9$, etc.; (4) Grade 3 hypertension (systolic blood pressure ≥180mmHg or diastolic blood pressure ≥100mmHg); (5) CT showed multiple lobe infarcts, that is, craniocerebral low-density shadow>cerebral hemisphere; (6) Arterial puncture that is not easy for hemostasis by compression was carried out in the last week.

Inclusion criteria: (1) Approved by the Ethics Committee of Hunan Provincial People's Hospital (the First Affiliated Hospital of Hunan Normal University), informed consent was obtained from the patients or their relatives; (2) Patients, 18 to 75 years old, were not transferred from other hospitals; (3) Conforming to ACI diagnosis, with obvious neurological impairment; (4) Patients had their first onset of ACI, with the disease time<6h; (5) No interventional therapy or spinal canal operation for craniocerebral and cerebral blood supply arteries and veins was conducted within 6 months before onset; (6) No drugs affecting hemodynamics and blood coagulation function have been used in the past 2 weeks.

Exclusion criteria: (1) With severe craniocerebral trauma or skull fracture in the past 3 months; (2) Having contraindications to rt-PA thrombolysis; (3) Comorbidity with acute abdomen and shock symptoms; (4) Severe decline in liver and kidney function, heart failure, respiratory failure or blood system diseases; (5) Cognitive dysfunction, mental illness and nervous system lesions not caused by ACI; (6) Having undergone major abdominal or thoracic surgery in the past 1 week; (7) Diabetes mellitus complicated with micro angiopathy.

Removal criteria: (1) Patients and family members conceal their medical history or use other drugs that affect hemodynamics due to emergencies, resulting in deviations in the research results; (2) Those who withdraw, transfer to other hospitals, or lose follow-up or have not been re-examined after discharge; (3) Patients with incomplete clinical data, or who died without rt-PA thrombolysis; (4) Those who are allergic to the drug and its active ingredients in this study.

Methods

Three groups of patients all received conventional treatment and rt-PA intravenous (IV) thrombosis

Conventional treatment: high-flow oxygen inhalation, keep the respiratory tract unobstructed, and give endotracheal intubation and mechanical ventilation when necessary. For patients with intracranial pressure >200mmH_2O and cerebral edema, Mannitol (Sichuan Kelun Pharmaceutical Co., Ltd., SFDA Approval No. H20043783, Batch number: J20190708, Specification: 50ml: 10g) was administered, and the solution was prepared at concentration of 15~25% according to the weight of 1~2g/kg (ivgtt within 30~60min, q.d.); For weak patients, the dose of mannitol was reduced to 0.5g/kg. If the dehydration and intracranial pressure reduction effect of mannitol is poor, glycerin candy or furosemide can be used. According to the laboratory inspection results, drugs for anti-platelet aggregation and neuroprotection should be given as appropriate, such as Aspirin Enteric-coated Tablets (Bayer HealthCare Manufacturing, SFDA Approval No.: HJ20160685, Batch number: J20190612, Specification: 100mg*30 tablets), which was administered before meal with warm water (100mg at a time, q.d.) or clopidogrel bisulfate can be selected; Edaravone injection (Nanjing Simcere Dongyuan Pharmaceutical Co., Ltd., SFDA Approval No.: H20050280, Batch number: J20190720, Specification: 20ml:30mg), (30mg at a time, b.i.d., ivgtt within 30min after being diluted with 250ml 0.9% sodium chloride solution). At the same time, the liver and kidney functions, blood lipids and blood glucose of patients were closely monitored; In combination with blood pressure monitoring results, medical history, etc., we should carefully use such antihypertensive drugs as Sacubitril Valsartan Sodium Tablets and Valsartan Capsules to adjust the patients' blood pressure and Low

Molecular Weight Heparin Sodium (LMWH-Na) to prevent and treat pulmonary embolism and lower extremity deep vein thrombosis. Active prevention of respiratory tract and urinary system infection and low sodium, low fat, high fiber diet should be taken. After the patients' conditions were stable, turned them over and moved their limbs every 2 hours, and gave them psychological and daily care (Hutten *et al*., 2024).

rt-PA thrombolysis: Alteplase (Boehringer-Ingelheim, SFDA Approval No.: S20020034, Batch number: J20190711, Specification: 50mg/bottle) is preferred, preparing the solution at a concentration of 1mg/ml with the attached water for injection, or preparing the solution at a concentration of 0.5mg/ml by diluting it with normal saline and 5% glucose injection; The recommended standard dose is 0.9mg/kg, with 10% of the total dose administered as an intravenous bolus within 1 minute, followed by a slow infusion of the remaining 90% over 1 hour, the maximum dose should not exceed 90mg. The specific dose was adjusted according to the patient's weight and hemodynamics. If heparin is needed, the use of heparin should be postponed until 2 hours after the treatment of alteplase. Precautions should be taken to prevent the risk of hemorrhagic transformation during the first 24 hours after thrombolysis. If alteplase is not appropriate, other thrombolytic drugs such as tenecteplase can also be used (Chung *et al*., 2019).

Indexes observed

Cerebral oxygen metabolism-related indexes: Blood oxygen saturation of jugular vein bulb ($SjvO_2$), cerebral O_2 extraction rate ($CERO_2$) and arteriovenous oxygen content difference ($AVDO_2$) of patients were recorded before treatment and 48 hours after treatment using FORE-SIGHT Oximeter, the cerebral oxygen saturation monitor (SFDA Device (Imported) 2013 No. 2214690) of Shanghai Hanfei Medical Instruments Co., Ltd.

Oxidative stress indexes: Before treatment and before discharge, 5ml venous blood of the patient was extracted and centrifuged at 3000r/min for 10min (radius of centrifugation: 15cm). The upper serum was extracted (erythrocyte sedimentation rate (ESR) was kept at -20ºC). Superoxide dismutase (SOD) was examined by xanthine oxidase method, while malonic dialdehyde (MDA) was evaluated by chemiluminescence immunoassay. The kits used in this study were all from Shanghai mlbio Co., Ltd., and the analysis was conducted using PUZS-600A Fully Automatic Biochemical Analyser (Beijing Perlong New Technology Co., Ltd., Beijing M.D.R.C. 20182220295).

Neural indexes: Serum was extracted before treatment and before discharge and S100B protein and brain-derived neurotrophic factor (BDNF) were examined by radioimmunoassay.

Cerebral vascular hemodynamic indexes: The mean blood flow velocities (Vm) of bilateral anterior cerebral arteries (BACA), middle cerebral arteries (MCA), bilateral vertebral arteries (BVA) and basilar arteries (BA) were measured by Doppler ultrasound before treatment and before discharge.

Coagulation function: ESR was extracted before treatment and before discharge for coagulation function measurement, including prothrombin time (PT), thrombin time (TT), APTT and fibrinogen (FIB).

NIH Stroke scale (NIHSS): NIHSS was evaluated before treatment and 3 months after treatment, including level of consciousness (7 points), gaze (2 points), visual fields (3 points), facial palsy (3 points), motor left arm (4 points), motor right arm (4 points), motor left leg (4 points), motor right leg (4 points), ataxia (2 points), sensory (2 points), language (3 points), dysarthria (2 points) and neglect (2 points). The higher the total score, the more serious the neurological impairment.

Activity of daily living scale (ADL): ADL was evaluated before treatment and 3 months after treatment, including bathing (5 points) and grooming (5 points), eating (10 points), dressing (10 points), toileting (10 points), stool control (10 points), urination control (10 points), going up and down stairs (10 points), bed-chair transfer (15 points) and walking (15 points). The higher the total score, the better the living ability.

Clinical efficacy: Cured: NIHSS reduced by more than 90%, and daily living ability returned to normal; Markedly effective: NIHSS reduced by 46%~90%, ADL increased by 50% or more, or ADL>80 points; Effective: NIHSS reduced by 18%~45%, ADL increased by 30%~49%; Ineffective: None of the above has reached or worsened or died.

ETHICAL APPROVAL

This study was approved by the Ethics Committee of Hunan Provincial People's Hospital (the First Affiliated Hospital of Hunan Normal University), with the approval No.2024-389.

STATISTICAL ANALYSIS

EpiData3.1 was used to correct all data, and SPSS22.0 statistical software was used to process all data. The counting data were entered in the form of "n(%)" and were tested by χ^2 and the rank data were verified by rank sum test; The measurement data were entered in the form of "x±s" and the results were tested by t, and the comparison of multiple groups was verified by Chi-square test; Test level: $P<0.05$ indicated statistically significant difference.

Table 1: Comparison of cerebral oxygen metabolism-related indexes among three groups (x ± s)

Group		$SjvO_2$ (%)	$CERO_2$ (%)	$AVDO_2$ (mL/dL)
Disease <3h group (n=40)	Before treatment	50.43±4.47	35.02±3.48	7.31±0.89
	48h after treatment	64.25±6.51*	30.19±2.25*	5.74±0.65*
Disease 3~4.5h group (n=55)	Before treatment	51.02±4.16	34.87±3.39	7.29±0.84
	48h after treatment	62.89±5.93*	30.72±2.43*	5.85±0.68*
Disease >4.5h group (n=25)	Before treatment	50.86±4.73	35.13±3.27	7.28±0.87
	48h after treatment	57.34±5.20	33.54±3.16	6.40±0.75
F	Before treatment	0.21	0.06	0.01
	48h after treatment	10.93	14.69	7.79
P	Before treatment	0.808	0.946	0.989
	48h after treatment	<0.001	<0.001	<0.001

Compare with the Disease >4.5h group, $^{*}P<0.05$.

Table 2: Comparison of oxidative stress indexes among three groups (x ± s)

Group		SOD(nU/ml)	MDA(mmol)
Disease <3h group (n=40)	Before treatment	62.34±5.26	13.28±2.57
	Before discharge	76.45±6.78*	6.45±1.09#*
Disease 3~4.5h group (n=55)	Before treatment	61.86±5.45	13.10±2.46
	Before discharge	75.73±6.24*	7.03±1.32*
Disease >4.5h group (n=25)	Before treatment	62.05±5.51	12.97±2.40
	Before discharge	70.38±5.87	9.85±1.87
F	Before treatment	0.09	0.13
	Before discharge	7.98	50.49
P	Before treatment	0.913	0.880
	Before discharge	<0.001	<0.001

Compare with the Disease 3~4.5h group, $^{\#}P<0.05$; Compare with the Disease >4.5h group, $^{*}P<0.05$.

Table 3: Comparison of neural indexes among three groups (x ± s, ng/mL)

Group		S100B	BDNF
Disease <3h group (n=40)	Before treatment	2.67±0.55	3.20±0.48
	Before discharge	1.15±0.29*	4.95±0.62*
Disease 3~4.5h group (n=55)	Before treatment	2.65±0.53	3.07±0.45
	Before discharge	1.22±0.31*	4.88±0.57*
Disease >4.5h group (n=25)	Before treatment	2.69±0.52	3.15±0.46
	Before discharge	1.87±0.40	4.16±0.50
F	Before treatment	0.05	0.95
	Before discharge	43.97	17.05
P	Before treatment	0.951	0.392
	Before discharge	<0.001	<0.001

Compare with the Disease >4.5h group, $^{*}P<0.05$.

RESULTS

Comparison of cerebral oxygen metabolism-related indexes among three groups

48h after treatment, the levels of $SjvO_2$ were significant higher in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, while the levels of $CERO_2$ and $AVDO_2$ were significantly lower in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the differences were statistically significant (P<0.05); There was no statistically significant difference in $SjvO_2$, $CERO_2$ and $AVDO_2$ between Disease <3h group and Disease 3~4.5h group (P>0.05) (table 1).

Comparison of oxidative stress indexes among three groups

Before discharge, the levels of SOD were significant higher in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the levels of MDA were significant lower in the Disease <3h group than in the Disease 3~4.5h group and Disease >4.5h group, the differences were statistically significant (P<0.05); There was no statistically significant difference in SOD between

Disease <3h group and Disease 3~4.5h group (P>0.05) (table 2).

Comparison of neural indexes among three groups

Before discharge, the levels of S100B were significant lower in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the levels of BDFN were significant higher in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the differences were statistically significant (P<0.05); There was no statistically significant difference in S100B and BDNF between Disease <3h group and Disease 3~4.5h group (P>0.05) (table 3).

Comparison of cerebral vascular hemodynamic indexes among three groups

Before discharge, the levels of BACA-Vm, MCA-Vm, BVA-Vm and BA-Vm were significant higher in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the differences were statistically significant (P<0.05); There was no statistically significant difference in BACA-Vm, MCA-Vm, BVA-Vm and BA-Vm between Disease <3h group and Disease 3~4.5h group (P>0.05) (table 4).

Comparison of coagulation function between two groups

Before discharge, the levels of PT, TT and APTT of the three groups were compared and there was no statistically significant difference in FIB between Disease <3h group and Disease 3~4.5h group (P>0.05); The levels of FIB were significant higher in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the differences were statistically significant (P<0.05) (table 5).

Comparison of NIHSS and ADL among three groups

Three months after treatment, the NIHSS scores were significant lower in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group and the ADL scores were significant higher in the Disease <3h group and Disease 3~4.5h group than in the Disease >4.5h group, the differences were statistically significant (P<0.05); There was no statistically significant difference in NIHSS and ADL scores between Disease <3h group and Disease 3~4.5h group (P>0.05) (table 6).

Comparison of clinical efficacy among three groups

The total effective rate in Disease <3h group (85.00%) and the total effective rate in Disease 3~4.5h group (83.64%) were significant higher than that in Disease >4.5h group (60.00%), the differences were statistically significant (P<0.05); There was no statistically significant difference in the total effective rate between Disease <3h group and Disease 3~4.5h group (P>0.05) (table 7).

Comparison of complications among three groups

In the onset <3h group, there were 5 deaths, with 5 cases of limb paralysis and motor dysfunction, 2 cases of cognitive impairment and 1 case of emotional disturbance, resulting in a complication rate of 22.85% (8/35). In the onset -4.5h group, there were 7 deaths, with 4 cases of limb paralysis and motor dysfunction, 3 cases of cognitive impairment, 2 cases of emotional disturbance, 2 cases of pneumonia and 1 case of cerebral infarction, leading to a complication rate of 25.00% (12/48). In the onset >4.5h group, there were 8 deaths, with 5 cases of cerebral infarction, 2 cases of pneumonia and 2 cases of pressure sores, resulting in a complication rate of 52.94% (9/17), which was significantly higher than that of the onset <3h group and the onset 3–4.5h group, with statistically significant differences (χ^2=4.706, P=0.030; χ^2=4.482, P=0.034).

DISCUSSION

The main component of rt-PA is glycoprotein, which primarily binds to fibrin through lysine residues, activating plasminogen that is bound to fibrin, converting it into plasmin and thereby activating the fibrinolytic system to remove excess thrombus from the vasculature (Wen *et al*., 2021). However, if the optimal timing for rt-PA thrombolysis in ACI is missed, it can not only increase the bleeding risk in the skin and mucous membranes but also heighten the risk of secondary cerebral infarction, potentially leading to elevated intracranial pressure and the occurrence of brain herniation (Zhai *et al*., 2021).

The results of this study indicate that the cerebral oxygen metabolism indicators improved significantly in all three treatment groups 48 hours after therapy. This improvement is attributed to conventional treatments such as mannitol and enteric-coated aspirin, which effectively reduce intracranial pressure, prevent brain edema and lower the risk of transient ischemic attacks and secondary strokes (Santos *et al*., 2022). Edaravone can effectively penetrate the blood-brain barrier, diffuse into brain tissue, alleviate vascular endothelial injury and protect neural function (Chen *et al*., 2020). Additionally, rt-PA intravenous thrombolysis can enhance blood flow in occluded or narrowed cerebral vessels, thereby reducing mortality in ACI patients (Xu *et al*., 2021). SjvO2 primarily reflects cerebral oxygen consumption and delivery, relying on cerebral blood flow; lower levels indicate more severe ischemia in brain tissue and higher oxygen demand and consumption (Liberman *et al*., 2019).

The SjvO2 levels after rt-PA thrombolysis at >4.5 hours were significantly lower than those in the onset <3h and 3-4.5h groups, while CERO2 and AVDO2 levels were significantly higher than in the earlier onset groups. This can exacerbate irreversible damage following cerebral infarction, leading to further increases in CERO2 and AVDO2, and intensifying the body's oxidative stress response, resulting in neutrophil inflammatory infiltration, increased protease secretion and the generation of

numerous oxidative intermediates, thereby promoting disease progression (Schmidt-Pogoda *et al*., 2019). However, thrombolysis performed within 4.5 hours after ACI can help control disease progression. SOD can scavenge excess free radicals in the body, reduce the levels of lipid oxidants in the blood, slow cellular aging, and prevent atherosclerosis, regulate lipid levels, and inhibit the progression of hyperlipidemia-related cardiovascular and cerebrovascular diseases (Ho *et al*., 2022).

MDA is the final product of lipid peroxidation caused by free radicals, leading to cross-linking and polymerization of macromolecules such as proteins and nucleic acids, which accelerates tissue damage and promotes neuronal apoptosis after ACI (Rajeev *et al*., 2021). Before discharge, the SOD levels in the onset <3h group and the 3-4.5h group were significantly higher than those in the >4.5h group, while the MDA levels in the onset <3h group were significantly lower than those in the 3-4.5h group and the >4.5h group. This indicates that performing rt-PA thrombolysis within 3 hours of onset can enhance SOD levels and minimize the production of MDA.

Before discharge, S100B protein levels significantly decreased in all three groups, but the levels in the >4.5h group and the 3-4.5h group were notably lower. This is likely related to the ability of thrombolysis performed within 4.5 hours to block the NO-dependent pathway that induces neuronal death or the release of neurotoxins (Langeh *et al*., 2021; Wu *et al*., 2020).

BDNF is a protein mainly expressed in the central nervous system, with the highest content in hippocampus and cortex, which can increase synaptic plasticity and strengthen cognitive function; It can also assist cell survival, such as maintaining and promoting the development, differentiation and growth of serotonergic (5-hydroxytryptamine, 5-HT) and dopaminergic (dopamine, DA) neurons (Lima Giacobbo *et al*., 2019; Di Carlo *et al*., 2019). The function of serotonergic and dopaminergic neurons is closely related to the occurrence and development of emotional disorders. This suggests that early rt-PA thrombolysis can reduce the occurrence of emotional disorder in ACI patients to a certain extent. Furthermore, as a neurotrophic factor with high content in the body, BDNF can also bind to multiple receptors such as tyrosine kinase A (TrkA), TrkB and TrkC, so as to improve neurologic function, expand information and activate a series of biochemical reactions in cells (Mosconi *et al*., 2022).

The anterior cerebral artery (ACA) supplies the medial surface of the cerebral hemisphere and a portion of the bottom surface of the frontal lobe in front of parieto-occipital sulcus and the superior cortices of outer surface of the frontal and parietal lobes (Jeromel *et al*., 2020); The middle cerebral artery (MCA) is a direct continuation of the internal carotid artery, its branches supply the internal capsule and the basal ganglia and involve multiple brain functional areas including the motor area, somatosensory area, auditory area and association area (Miura *et al*., 2019). For example, the bleeding of central branches of MCA (internal capsule hemorrhage) may cause paralysis of the contralateral limbs, lower half of the facial muscles and tongue muscles and hemidysesthesia. The patient with vertebral-basilar artery insufficiency will develop a clinical syndrome with dizziness as the main symptom, often accompanied by temporal headache, memory and vision deterioration, and mental weakness. In severe cases, cataplexy may occur (Warach *et al*., 2020). The cerebral hemodynamic improvements in the <3h and 3-4.5h groups before discharge were significantly better than those in the >4.5h group, indicating that early thrombolysis can maximize cerebral perfusion and reduce neurological dysfunction. Before discharge, there were no significant differences in PT, TT and APTT among the three groups, as early rt-PA thrombolysis inhibits platelet aggregation and enhances fibrinolysis. However, FIB levels in the >4.5h group were significantly higher than in the other two groups. It is important to note that when performing thrombolysis in ACI patients, coagulation markers should not be reduced excessively. Special caution should be exercised when treating patients over 65 years of age or those with severe neurological deficits, as they are at higher risk for hemorrhagic transformation.

Three months after treatment, NIHSS scores in the <3h and 3–4.5h groups were significantly lower, and ADL scores were significantly higher than in the >4.5h group. This can be attributed to several factors (Liu *et al*., 2020; Çakal *et al*., 2020): (1) rt-PA thrombolysis within 4.5 hours results in a higher recanalization rate of occluded cerebral vessels; (2) adequate blood supply from the anterior cerebral artery, middle cerebral artery and vertebrobasilar arteries improves functions such as learning, memory, execution and language, enhancing patients' quality of life; (3) early rt-PA thrombolysis effectively regulates neuroendocrine function, reduces microcirculation disturbances and damage to the basement membrane and neurons, promoting early recovery and better prognosis. However, studies suggest that the thrombolysis timing and effectiveness can vary depending on the affected vascular circulation during cerebral infarction (Liu *et al*., 2020). For example, compared to posterior circulation infarction (vertebrobasilar system), acute occlusion or stenosis in the anterior circulation (internal carotid artery system) often shows a lower thrombolysis success rate (Ota *et al*., 2019). In such cases, interventional therapy may be needed, extending the treatment window beyond 4.5 hours. Additionally, different drugs may influence the safety, efficacy, and timing of recanalization.

Table 4: Comparison of cerebral vascular hemodynamic indexes among three groups (x ± s, cm/s)

Group		BACA-Vm	MCA-Vm	BVA-Vm	BA-Vm
Disease <3h group (n=40)	Before treatment	39.02±3.14	51.49±4.53	27.54±3.28	33.27±3.59
	Before discharge	44.36±4.28*	57.85±6.26*	32.48±4.36*	39.85±4.71*
Disease 3~4.5h group (n=55)	Before treatment	38.87±3.10	51.03±4.72	28.02±3.41	32.91±3.64
	Before discharge	43.75±3.96*	57.12±5.89*	31.87±4.29*	38.72±4.20*
Disease >4.5h group (n=25)	Before treatment	39.08±3.17	51.64±4.48	27.96±3.58	33.05±3.37
	Before discharge	41.26±3.68	53.41±5.22	29.13±3.70	36.24±3.78
F	Before treatment	0.05	0.20	0.25	0.12
	Before discharge	4.90	4.79	5.28	5.48
P	Before treatment	0.953	0.822	0.781	0.889
	Before discharge	0.009	0.010	0.006	0.005

Compare with the Disease >4.5h group, $^{*}P<0.05$.

Table 5: Comparison of coagulation function between two groups (x ± s)

Group		PT(s)	TT(s)	APTT(s)	FIB(g/L)
Disease <3h group (n=40)	Before treatment	12.28±2.60	15.23±2.37	27.35±3.79	3.77±0.62
	Before discharge	19.15±3.57	20.48±4.15	34.56±4.75	2.16±0.54*
Disease 3~4.5h group (n=55)	Before treatment	12.31±2.45	15.47±2.20	27.16±3.51	3.81±0.64
	Before discharge	18.72±3.29	19.76±3.95	34.80±4.62	2.22±0.50*
Disease >4.5h group (n=25)	Before treatment	12.09±2.37	15.68±2.34	27.59±3.64	3.79±0.65
	Before discharge	17.88±2.90	19.21±4.08	33.29±4.12	2.83±0.57
F	Before treatment	0.07	0.31	0.12	0.05
	Before discharge	1.14	0.81	0.97	14.45
P	Before treatment	0.932	0.734	0.884	0.955
	Before discharge	0.325	0.449	0.381	<0.001

Compare with the Disease >4.5h group, $^{*}P<0.05$.

Table 6: Comparison of NIHSS and ADL among three groups (x ± s, scores)

Group		NIHSS	ADL
Disease <3h group (n=40)	Before treatment	25.32±3.45	61.40±5.28
	3 months after treatment	11.49±2.12	74.65±6.70
Disease 3~4.5h group (n=55)	Before treatment	24.75±3.58	62.07±5.65
	3 months after treatment	24.68±3.31	73.48±6.32
Disease >4.5h group (n=25)	Before treatment	12.35±2.40	62.17±5.48
	3 months after treatment	15.80±3.19	68.60±6.13
F	Before treatment	0.05	0.95
	3 months after treatment	43.97	7.33
P	Before treatment	0.951	0.392
	3 months after treatment	<0.001	0.001

Compare with the Disease >4.5h group, $^{*}P<0.05$.

Table 7: Comparison of clinical efficacy among three groups (cases (n %))

Group	Cured	Markedly effective	Effective	Ineffective	Total effective rate (%)
Disease <3h group (n=40)	14	11	9	6	34(85.00)*
Disease 3~4.5h group (n=55)	10	16	20	9	46(83.64)*
Disease >4.5h group (n=25)	2	5	8	10	15(60.00)
Z		13.340			7.060
P		0.038			0.029

Compare with the Disease >4.5h group, $^{*}P<0.05$.

First-generation thrombolytic drugs like streptokinase and urokinase, while more effective than oral aspirin and other conservative treatments, often lead to mucosal bleeding and have lower thrombolytic efficacy and safety (Zeng *et al*., 2020). Second-generation thrombolytics, such as alteplase, are produced using recombinant DNA technology and act as physiological activators of the fibrinolytic system.

These drugs dissolve clots with high specificity, ensuring effective thrombolysis while minimizing systemic fibrinolysis, thus significantly reducing bleeding risks and improving safety (Valgimigli *et al*., 2023). Alteplase is more effective in intravenous thrombolysis compared to arterial routes and it works better on newly formed clots than older ones. However, once in the bloodstream, alteplase rapidly binds to plasminogen activator inhibitors, losing its activity quickly, leading to a short half-life that requires continuous infusion in clinical settings (Singh *et al*., 2024; Mannino *et al*., 2020). Additionally, the higher cost of alteplase compared to urokinase and streptokinase drives some patients to opt for first-generation thrombolytics. Third-generation thrombolytics, such as tenecteplase and reteplase, are primarily variants of tissue-type plasminogen activators (Rose *et al*., 2023).

However, many of these studies primarily involved patients with mild strokes and the standard dosage of tenecteplase for treating ischemic stroke remains unclear. Additionally, there is a lack of phase III studies proving that tenecteplase is superior or non-inferior to alteplase (Qu *et al*., 2022; Bouchal *et al*., 2021). Therefore, in clinical practice, alteplase is still the preferred choice for rt-PA thrombolytic therapy. For tenecteplase, international guidelines recommend using different doses for different stroke populations.

CONCLUSION

In conclusion, there is no significant difference in the efficacy of rt-PA thrombolysis treatment within 3 hours of onset compared to the 3 to 4.5-hour window for ACI patients, with both showing significantly better outcomes than thrombolysis after 4.5 hours and fewer complications. However, there are numerous thrombolytic drugs with varying effectiveness, and this study did not compare the effects of other medications. Additionally, many factors influence the prognosis of ACI patients and whether the thrombolysis window could be extended with the continuous improvement of thrombolytic drugs, or how it relates to other underlying conditions in patients, still requires extensive clinical validation. In future practice, scholars should adhere to a realistic approach, optimizing individualized treatment plans based on specific patient conditions to reduce early mortality and improve long-term outcomes.

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REFERENCES

Bouchal S, Lamrani YA, Chtaou N, Maaroufi M and Belahsen F (2021). Repeated intravenous thrombolysis in early recurrent stroke secondary to carotid web: Case report. *Radiol. Case Rep.,* **16**(4): 843-846.

Cakal B, Kalcık M, Guner A, Yesin M, Gursoy MO, Gunduz S, Karakoyun S, Bayam E, Kalkan S and Ozkan M (2020). Improvement of endothelial function early after thrombolytic therapy in patients with prosthetic heart valve thrombosis. *Turk Kardiyol Dern Ars.,* **48**(6): 566-575.

Chen M, Zhang W, Wu H, Guang C and Mu W (2020). Mannitol: Physiological functionalities, determination methods, biotechnological production and applications. *Appl. Microbiol. Biotechnol.,* **104**(16): 6941-6951.

Chung HJ, Park HJ, Baek SY, Park JK, Lee WY, Kim KW, Jo YM, Hochi S, Kim YM, Choi TJ, Cho ES and Cho KH (2019). Production of human tissue-type plasminogen activator (htPA) using in vitro cultured transgenic pig mammary gland cells. *Anim. Biotechnol*., **30**(4): 317-322.

Di Carlo P, Punzi G and Ursini G (2019). Brain-derived neurotrophic factor and schizophrenia. *Psychiatr. Genet*., **29**(5): 200-210.

Edwards MD and Hughes TAT (2021). Managing blood pressure in acute cerebral infarction. *J. Neurol.,* **268**(6): 2294-2296.

Edwards MD and Hughes TAT (2021). Managing blood pressure in acute cerebral infarction. *J. Neurol.,* **268**(6): 2294-2296.

Fu Y, Zheng S, Kong H, Ying M, Chen H, Wang J and Yuan X (2022). Clinical value of combined detection of UA and MMP-9 in evaluating bleeding transformation and prognosis after thrombolysis in acute cerebral infarction. *Appl. Biochem. Biotechnol.,* **194**(11): 5236-5254.

Ho KM, Rogers FB and Chamberlain J (2022). Incremental cost of venous thromboembolism in trauma patients with contraindications to prophylactic anticoagulation: a prospective economic study. *J. Thromb. Thrombolysis,* **54**(1): 115-122.

Hutten EM, van de Ven AAJM, Mencke R, Pleijhuis RG (2024). Angioedema after use of recombinant tissue-type plasminogen activators in stroke. *Stroke,* **55**(8): 2193-2197.

Jeromel M, Milosevic ZV and Oblak JP (2020). Mechanical recanalization for acute bilateral cerebral artery occlusion - literature overview with a case. *Radiol. Oncol.,* **54**(2): 144-148.

Jin L, Wang Y, Lyu Z, Zhang C (2021). Application of

quantitative electroencephalogram monitoring in evaluating thrombolytic effect of acute cerebral infarction. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.*, **33**(2): 207-210.

Kannan A, Delgardo M, Pennington-FitzGerald W, Jiang EX, Christophe BR and Connolly ES Jr (2021). Pharmacological management of cerebral ischemia in the elderly. *Expert Opin. Pharmacother.*, **22**(7): 897-906.

Kato H, Murakami T, Tajiri Y, Yamaguchi N, Ugawa Y and Hanajima R (2021). Hemichorea in a patient with acute cerebral infarction of the somatosensory cortex. *Rinsho Shinkeigaku.*, **61**(5): 325-328.

Kitaura J, Mukai S, Morimoto H, Futagami D and Furuta A (2019). Mediastinal hematoma after intravenous thrombolytic therapy for cerebral infarction in a patient with a history of total aortic arch replacement. *Kyobu Geka.*, **72**(9): 673-676.

Langeh U and Singh S (2021). Targeting S100B protein as a surrogate biomarker and its role in various neurological disorders. *Curr. Neuropharmacol.*, **19**(2): 265-277.

Li L, Ren S, Hao X, Zhen Z and Ji H (2019). Efficacy of minimally invasive intervention in patients with acute cerebral infarction. *J. Cardiovasc. Pharmacol.*, **73**(1): 22-26.

Liberman AL, Pinto D, Rostanski SK, Labovitz DL, Naidech AM and Prabhakaran S (2019). Clinical decision-making for thrombolysis of acute minor stroke using adaptive conjoint analysis. *Neurohospitalist.*, **9**(1): 9-14.

Lima Giacobbo B, Doorduin J, Klein HC, Dierckx RAJO, Bromberg E and de Vries EFJ (2019). Brain-derived neurotrophic factor in brain disorders: Focus on neuroinflammation. *Mol. Neurobiol.*, **56**(5): 3295-3312.

Liu J, Huang J, Xu H and Dai H (2020). Nonatrial fibrillation was associated with early neurological improvement after intravenous thrombolysis with rt-PA in patients with acute ischemic stroke. *Neurologist*, **25**(2): 28-32.

Liu YP, Ju ML and Yu FQ (2020). Clinical significance of FSTL 1, Bax, Bcl-2 in acute cerebral infarction and its relationship with hemorrhagic transformation. *Eur. Rev. Med. Pharmacol. Sci.*, **24**(16): 8447-8457.

Mannino M and Cottone S (2020). Early dual antiplatelet therapy in patients with acute minor stroke treated with intravenous Thrombolysis. *Eur. Neurol.*, **83**(1): 97-98.

Miura M, Yoshimura S, Sakai N, Yamagami H, Uchida K, Nagao Y and Morimoto T (2019). Endovascular therapy for middle cerebral artery M2 segment occlusion: Subanalyses of RESCUE-Japan Registry 2. *J. Neurointerv. Surg.*, **11**(10): 964-969.

Mosconi MG, Paciaroni M and Ageno W (2022). Investigational drugs for ischemic stroke: What's in the clinical development pipeline for acute phase and prevention? *Expert Opin. Investig. Drugs*, **31**(7): 645-667.

Ota T, Shigeta K, Amano T and Kaneko J (2019). Endovascular treatment for acute carotid T and carotid non-T occlusion: A retrospective multicentre study of 81 patients. *Interv. Neuroradiol.*, **25**(5): 497-501.

Qu T, Bao Y, Zhu W, Ding H, Wang L, Yang J and Huang D (2022). The influence of unexpected early termination of intravenous rt-PA treatment on clinical outcome in acute ischemic stroke patients. *Acta Neurol. Belg.*, **122**(5): 1329-1335.

Rajeev S and Katsumi T (2021). Microsurgical embolectomy in the current era of pharmacological and mechanical (Endovascular) thrombolysis-A reappraisal. *Neurol. India*, **69**(3): 567-572.

Rodríguez-Pardo J, Secades-García S, Riera-López N, Alonso de Leciñana M, Real-Martínez V, Carneado-Ruiz J, Díaz-Guzmán J, Díez-Tejedor E, Egido-Herrero J, Gil-Núñez A, Matute-Lozano MC, Trillo S, Vera-Lechuga R, Vivancos-Mora J, Ximénez-Carrillo Á and Fuentes B (2020). Contraindications to intravenous thrombolysis in prehospital triage of thrombectomy candidates. *Eur. J. Neurol.*, **27**(12): 2439-2445.

Rose D, Cavalier A, Kam W, Cantrell S, Lusk J, Schrag M, Yaghi S, Stretz C, de Havenon A, Saldanha IJ, Wu TY, Ranta A, Barber PA, Marriott E, Feng W, Kosinski AS, Laskowitz D, Poli S and Mac Grory B (2023). Complications of intravenous tenecteplase versus alteplase for the treatment of acute ischemic stroke: A systematic review and meta-analysis. *Stroke*, **54**(5): 1192-1204.

Santos M and de Sousa DA (2022). Cerebrovascular disease in pregnancy and postpartum. *Curr Opin Neurol.*, **35**(1): 31-38.

Schmidt-Pogoda A and Minnerup J (2019). Seltene Schlaganfallursachen im Alltag gar nicht so selten (Rare causes of stroke-a frequent stroke etiology). *Nervenarzt.*, **90**(10): 1013-1020.

Singh A, Singh MP, Gaikwad NR and Kannauje PK (2024). Tenecteplase versus alteplase in acute ischemic stroke: A systematic review and meta-analysis. *Ann. Neurosci.*, **31**(2): 132-142.

Valgimigli M, Aboyans V, Angiolillo D, Atar D, Capodanno D, Halvorsen S, James S, Jüni P, Kunadian V, Landi A, Leonardi S, Mehran R, Montalescot G, Navarese EP, Niebauer J, Oliva A, Piccolo R, Price S, Storey RF, Völler H, Vranckx P, Windecker S and Fox KAA (2023). Antithrombotic treatment strategies in patients with established coronary atherosclerotic disease. *Eur. Heart J. Cardiovasc. Pharmacother.*, **9**(5): 462-496.

Warach SJ, Dula AN and Milling TJ Jr (2020). Tenecteplase thrombolysis for acute ischemic stroke. *Stroke*, **51**(11): 3440-3451.

Wen H, Lv M. Correlation analysis between serum procalcitonin and infarct volume in young patients with acute cerebral infarction. *Neurol. Sci.*, **42**(8): 3189-3196.

Wu KJ, Wang W, Wang HD, Leung CH and Ma DL

(2020). Interfering with S100B-effector protein interactions for cancer therapy. *Drug Discov. Today*, **25**(9): 1754-1761.

Wu T, Li P and Sun D (2020). Assessing the clinical efficacy of recombinant tissue plasminogen activator on acute cerebral infarction. *J. Nanosci. Nanotechnol.*, **20**(12): 7781-7786.

Xu J, Wang A, Meng X, Yalkun G, Xu A, Gao Z, Chen H, Ji Y, Xu J, Geng D, Zhu R, Liu B, Dong A, Mu H, Lu Z, Li S, Zheng H, Chen X, Wang Y, Zhao X and Wang Y (2021). TASTE trial investigators. edaravone dexborneol versus edaravone alone for the treatment of acute ischemic stroke: A phase III, randomized, double-blind, comparative trial. *Stroke*, **52**(3): 772-780.

Zeng J, Wang F, Feng H, Chen F, Wang R, Chen Y, Chen X and Miao J (2020). Influencing factors of recanalization after intravenous thrombolysis with urokinase in acute cerebral infarction patients. *Eur. Neurol.*, **83**(2): 162-166.

Zhai Y, Wang H, Zhan S and Wu H (2021). Efficacy of intravenous thrombolysis for acute severe cerebral infarction and risk factors of poor prognosis: A randomized controlled trial in 152 cases. *Nan Fang Yi Ke Da Xue Xue Bao.*, **41**(9): 1426-1430.