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Efficacy and Safety of Alteplase in the Acute Ischemic Stroke Patients with Different NIHSS-time Scores

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Abstract: This study investigates the efficacy and safety of alteplase in acute ischemic stroke (AIS) patients with different NIHSS-time scores. 208 AIS patients admitted to the second people's hospital from 1 March 2019 to 31 May 2022 who received standard doses of intravenous thrombolysis of alteplase (rt-PA) were divided into the NIHSS-time ≤20 group (n=142), the NIHSS-time 20-40 group (n=49) and the NIHSS-time >40 group (n=17). The early neurological improvement (ENI) scores 24 h after thrombolysis, the ENI scores 7 d after thrombolysis, and the modified Rankin scale (mRS) score 90 days after onset were statistically significant among the three groups (P< 0.05). Compared with the NIHSS-time ≤20 group, both the P values of sICH within 7 days after thrombolysis and systemic bleeding within 7 days after thrombolysis are >0.05 in the NIHSS-time 20-40 group, and the differences are not statistically significant. Compared with the NIHSS-time ≤20 group, all the P values of sICH within 7 days after thrombolysis, systemic bleeding within 7 days after thrombolysis, and all-cause death within 90 days after thrombolysis are <0.05 in the NIHSS-time >40 group, and the differences are statistically significant. Compared with the NIHSS-time 20-40 group, the P value for the occurrence of both the sICH within 7 days after thrombolysis and all-cause death within 90 days after thrombolysis are <0.05, and the differences are statistically significant, while the P value for systemic bleeding within 7 days after thrombolysis is >0.05, and the difference is not statistically significant. This single-center retrospective study indicates that NIHSS-time score can predict the efficacy and safety of standard-dose rt-PA intravenous thrombolysis in patients with AIS. It needs to be further confirmed by a large-sample multicenter randomized controlled test.

1. Introduction

Stroke has become a major public health problem due to its high rate of incidence, mortality, and disability in China. It is urging to be solved. Epidemiological data shows that the incidence of

stroke increased year by year in China from 2013 to 2019 [1]. Therefore, the prevention and treatment of stroke are facing great challenges and of important social significance. Acute ischemic stroke (AIS) is the most common type of stroke, accounting for approximately 69.6%-70.8% of all stroke cases. Intravenous thrombolysis is the most effective treatment measure to restore cerebral blood flow in AIS [2]. Recombinant tissue plasminogen activator (rt-PA), also called alteplase, is the main drug for intravenous thrombolysis in AIS internationally [3]. However, the prognosis of intravenous rt-PA thrombolysis in AIS treatment is not the same. Many factors may be related to its prognosis, and there is still some controversaries [4]. Aoki et al. found that the NIHSS-time score has a certain predictive effect on the prognosis of AIS patients after low-dose rt-PA intravenous thrombolysis [5]. This study compares the effectiveness and safety of intravenous thrombolytic treatment with standard dose rt-PA in AIS patients with different NIHSS-time scores in order to provide a reference for thrombolytic decision-making in AIS within the clinical time window.

2. Patients and Methods

2.1. Patients

AIS patients who admitted to the Stroke Green Channel and accepted intravenous rt-PA thrombolysis were colleceted from 1 March 2019 to 31 May 2022 in the Second Peoples's Hospital of Hunan province. Inclusion criteria: Cases met the diagnostic criteria of AIS, with the indications and without contraindications for rt-PA intravenous thrombolysis according to the "2018 Guidelines for the early management of patients with acute ischemic stroke" [2]. ≥18 years old. Patients received intravenous thrombolytic treatment with standard-dose rt-PA (0.9 mg/kg, the maximum dose was 90mg) within 4.5 hours after onset. Consents were given by the patients or their close relatives before thrombolysis. Modified Rankin scale (mRS) score was 0 to 1 before stroke. Secondary preventions were carried out according to the guideline after thrombolysis [2]. General information is accurate and complete. Exclusion criteria: The symptoms of stroke were found after waking up or the time of onset was unknown. Patients who have undergone endovascular treatment after thrombolysis. Patients with cerebrovascular malformation or intracranial aneurysm. Patients with acute coronary syndrome. Patients with acute and chronic conditions inflammatory diseases, tumors, autoimmune diseases or important organ dysfunction. Patients combined with tissue and organ necrosis. Patients receiving anti-inflammatory or immunosuppressive treatment. Patients combined with psychiatric diseases. Recurrent stroke within 3 months. Patients couldn't be followed-up within 3 months after the intravenous thrombolytic treatment. This research has gotten the ethics committee review approval (Study on the Effect of Regional Stroke Screening and Follow up Management System Construction Based on Medical Consortium. No.: 2024K026).

2.2. Methods

The general information of the patients was collected retrospectively, including age, gender, BMI, cerebrovascular disease risk factors (hypertension, coronary heart disease, atrial fibrillation, diabetes, previous stroke history, smoking history, long-term alcohol abuse), history of taking antiplatelet drugs, history of taking coagulants, blood pressure on admission, NIHSS score before thrombolysis, time from onset to intravenous thrombolysis (ODT) and laboratory test (blood sugar, blood lipids). The calculation formula of NIHSS-time score is as follows [5]:

$$\text{NIHSS-time score} = \text{NIHSS score} \times \text{ODT (hour)}$$

Patients were divided into three groups according to their NIHSS-time scores: the NIHSS-time ≤20 group, the NIHSS-time 20-40 group and the NIHSS-time > 40 group.

2.3. Observation Indicators

The outcome indicators were set as follows: We use early neurological improvement (ENI) to evaluate the short-term prognosis and defined it like this: NIHSS score decreased by≥4 points or dropped to 0-1 points at 24h and 7d after intravenous thrombolysis of rt-PA [6]. We use the mRS score 90 days after onset to evaluate the long-term prognosis. The valuation criteria of mRS: 0-1 means good prognosis, ≥2 means poor prognosis. We use symptomatic intracranial hemorrhage (sICH) within 7 days after thrombolysis, systemic bleeding within 7 days after thrombolysis, and all-cause death within 90 days after thrombolysis to evaluate the safety of thrombolysis.

2.4. Statistical Methods

All data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows Version 22.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed as Mean±SD, and LSD t-tests were performed for comparisons among multiple groups. Count data were expressed as percentages (%), and Chi-Square ($\chi 2$) tests were performed for multiple comparisons. $P < 0.05$ is considered as a statistically significant difference.

3. Results

3.1. General Data Comparison

A total of 208 patients were included in this study, 127 males and 81 females, with an average age of (68.24±10.647) years old. The baseline data were compared among the three groups, and the defences are not statistically significant ($P > 0.05$). (see Table 1).

Table 1: Comparison of general information on admission among the three groups.

general information		the NIHSS-time ≤20 group (n=142)	the NIHSS-time 20-40 group (n=49)	the NIHSS-time >40 group (n=17)	χ^2 value	P value
ages (Mean±SD)		67.27±10.11	70.29±12.25	70.47±9.78	/	0.157
gender [n (%)]	male	91 (64.1)	26 (53.1)	10 (58.8)	2.933	0.241
	female	51 (35.9)	23 (46.9)	7 (41.2)		
BMI (kg/m^2) (Mean±SD)		21.96±2.28	21.77±2.91	21.56±2.49	/	0.793
history of hypertension [n (%)]	yes	50 (35.2)	17 (34.7)	5 (29.4)	0.592	0.752
	no	92 (64.8)	32 (65.3)	12 (70.6)		
coronary disease [n (%)]	yes	19 (13.4)	7 (14.3)	3 (17.6)	0.556	0.774
	no	123 (86.6)	42 (85.7)	14 (82.4)		
atrial fibrillation [n (%)]	yes	5 (3.5)	3 (6.1)	1 (5.9)	1.012	0.668
	no	137 (96.5)	46 (93.9)	16 (94.1)		
diabetes [n (%)]	yes	11 (7.7)	3 (6.1)	1 (0.0)	4.115	0.126
	no	131 (92.3)	46 (93.9)	16 (100)		
stroke history [n (%)]	yes	19 (13.4)	7 (14.3)	2 (11.8)	0.184	0.897
	no	123 (86.6)	42 (85.7)	15 (88.2)		
history of smoking [n (%)]	yes	17 (12.0)	5 (10.2)	2 (11.8)	0.191	0.911
	no	125 (88.0)	44 (89.8)	15 (88.2)		

history of alcohol [n (%)]	yes	11 (7.7)	3 (6.1)	2 (11.8)	1.476	0.478
	no	131 (92.3)	46 (93.9)	15 (88.2)		
history of taking antiplatelet drugs [n (%)]	yes	20 (14.1)	7 (14.3)	3 (17.6)	0.406	0.860
	no	122 (85.9)	42 (85.7)	14 (82.4)		
history of anticoagulant [n (%)]	yes	6 (4.2)	4 (8.2)	1 (5.9)	1.635	0.505
	no	136 (95.8)	45 (91.8)	16 (94.1)		
BP (Mean ±SD)	SBP	148.23 ±20.06	143.93 ±35.21	151.69 ±22.31	/	0.484
	DBP	84.01 ±12.19	81.69 ±20.37	85.41 ±10.65	/	
blood sugar (mmol/L) (Mean ±SD)		6.30 ±2.02	6.56 ±1.79	6.79 ±2.30	/	0.639
plasma lipids (mmol/L) (Mean ±SD)	TC	4.23 ±1.09	3.97 ±1.34	4.19 ±1.46	/	0.471
	TG	1.89 ±1.91	1.64 ±1.11	1.63 ±0.10	/	0.649
	LDL-C	2.69 ±0.89	2.60 ±1.09	2.89 ±1.42	/	0.599

3.2. Comparison of Efficacy among the Three Groups

Pairwise comparisons among the three groups were made. As for the good ENI 24 hours after thrombolysis: all the P values are< 0.05, and the differences are statistically significant. As for the good ENI 7 days after thrombolysis all the P values are <0.05, and the differences are statistically significant. As for the good long term prognosis 90 days after onset: all the P values are <0.05, and the differences are statistically significant (see Table 2).

Table 2: Comparison of efficacy among the three groups.

groups	prognosis 24h after thrombolysis		prognosis 7d after thrombolysis		prognosis 90d after thrombolysis	
	good	poor	good	poor	good	poor
the NIHSS-time ≤20 group n (%)	92 (64.8)	50 (35.2)	100 (70.4)	42 (29.6)	116 (81.7)	26 (18.3)
the NIHSS-time 20-40 group n (%)	23 (46.9)	26 (53.1)	24 (49.0)	25 (51.0)	26 (53.1)	23 (46.9)
the NIHSS-time >40 group n (%)	3 (17.6)	14 (82.4)	3 (17.6)	14 (82.4)	4 (23.5)	13 (76.5)
χ^2 value	16.249		43.538		58.640	
P value	<0.001		<0.001		<0.001	

3.3. Comparison of Safety among the Three Groups

Compared with the NIHSS-time ≤20 group, all the P values of sICH within 7 days after thrombolysis and systemic bleeding within 7 days after thrombolysis are >0.05 in the NIHSS-time 20-40 group, and the differences are not statistically significant (see Table 3).

Table 3: Comparison of safety between the NIHSS-time ≤20 group and the NIHSS-time 20-40 group.

groups	sICH within 7 days after thrombolysis		Systemic bleedings within 7 days after thrombolysis		all-cause death within 90 days after thrombolysis	
	yes	no	yes	no	yes	no
the NIHSS-time ≤20 group n (%)	4 (2.8)	138 (97.2)	10 (7.0)	132 (93.0)	0 (0)	142 (100)
the NIHSS-time 20-40 group n (%)	0 (0)	49 (100)	5 (10.2)	44 (89.8)	0 (0)	49 (100)
$\chi 2$ value	2.807		0.759		/	
P value	0.120		0.261		/	

Compared with the NIHSS-time ≤20 group, the P values of sICH within 7 days after thrombolysis, systemic bleeding within 7 days after thrombolysis, and all-cause death within 90 days after thrombolysis are all <0.05 in the NIHSS-time >40 group, and the differences are statistically significant (see Table 4).

Table 4: Comparison of safety between the NIHSS-time ≤20 group and the NIHSS-time >40 group.

groups	sICH within 7 days after thrombolysis		Systemic bleedings within 7 days after thrombolysis		all-cause death within 90 days after thrombolysis	
	yes	no	yes	no	yes	no
the NIHSS-time ≤20 group n (%)	4 (2.8)	138 (97.2)	10 (7.0)	132 (93.0)	0 (0)	142 (100)
the NIHSS-time >40 group n (%)	3 (17.6)	14 (82.4)	3 (17.6)	14 (82.4)	1 (5.9)	16 (94.1)
$\chi 2$ value	13.137		4.755		8.485	
P value	0.001		0.033		0.018	

Table 5: Comparison of safety between the NIHSS-time 20-40 group and the NIHSS-time >40 group.

groups	sICH within 7 days after thrombolysis		systemic bleedings within 7 days after thrombolysis		all-cause death within 90 days after thrombolysis	
	yes	no	yes	no	yes	no
the NIHSS-time 20-40 group n (%)	0 (0)	49 (100)	5 (10.2)	44 (89.8)	0 (0)	49 (100)
the NIHSS-time >40 group n (%)	3 (17.6)	14 (82.4)	3 (17.6)	14 (82.4)	1 (5.9)	16 (94.1)
χ^2 value	18.406		1.670		5.883	
P value	<0.001		0.151		0.039	

Compared with the NIHSS-time 20-40 group, the P value for the occurrence of both the sICH

within 7 days after thrombolysis and all-cause death within 90 days after thrombolysis are <0.05, and the differences are statistically significant. The P value for systemic bleeding within 7 days after thrombolysis is >0.05, and the difference is not statistically significant (see Table 5).

4. Discussion

Intravenous rt-PA thrombolytic treatment within 4.5 hours after the onset of AIS is one of the effective methods, but the thrombolytic effects and risks vary in different patients. Some studies have found that a variety of factors may be related to the effectiveness of thrombolysis such as: age, gender, history of smoking, history of hypertension, history of atrial fibrillation, severity of neurological deficit, time from onset to thrombolysis, blood sugar level on admission, lesion size, brain Leukoaraiosis, hemorrhagic transformation, blood cell components and so forth, and some of these indicators are controversial in terms of their predictive value for thrombolytic effect [5, 7-15]. Aoki et al. proposed the calculation method of NIHSS-time score and found that it can help clinicians to predict the effect of low-dose rt-PA intravenous thrombolysis (0.6 mg/kg) in AIS patients. There is no other relevant literature on NIHSS-time evaluation of efficacy and safety. The therapeutic dose of this drug recommended by the AHA/ASA guidelines is the standard dose (0.9 mg/kg) [2]. This study aimed to investigate the value of NIHSS-time score in predicting the efficacy and safety of standard dose rt-PA intravenous thrombolysis with AIS patients.

ENI is an important factor affecting prognosis [16, 17]. The NIHSS scores 24h and 7d after thrombolysis are better indicators to evaluate ENI. mRS 90 days after thrombolysis is commonly used to evaluate the long-term efficacy of AIS treatment. The results of this study show that the P values of the improvement in NIHSS scores 24h after thrombolysis, 7d after thrombolysis and the improvement of mRS 90 days after onset between each two groups are <0.05, suggesting that the higher the NIHSS-time score is, the worse both the short-term and long-term efficacy after thrombolysis are.

sICH is associated with the poor prognosis of AIS patients [18]. Some studies have found that NIHSS score >10 on admission, ODT >50 minutes, and white blood cell count ≥9000/mm^3 are independent risk factors of sICH within 6 hours after intravenous thrombolysis in Chinese AIS patients [19]. The results of this study show that there is no statistical difference in sICH within 7 days of thrombolysis and systemic bleeding within 7 days of thrombolysis between the NIHSS-time score ≤20 group and the NIHSS-time score 20-40 group (P >0.05). But the NIHSS-time score >40 group shows significant incidence of sICH within 7 days after thrombolysis and all-cause mortality within 90 days after thrombolysis compared to the other two groups (P <0.05), suggesting that risk of sICH increased when the NIHSS-time score is >40. It may provide a reference for poor prognosis. In terms of systemic bleeding, there was no statistical significance among the three groups.

The NIHSS-time score is simple to operate, easy to calculate, highly feasible, and can help clinicians make quick decisions within the golden time window of "time is the brain". However, this study has the following limitations: Firstly, it is a single-center study. This center has the conditions to carry out endovascular treatment. Some cases with large vessel occlusions were excluded due to their choices of endovascular treatments alone or after intravenous thrombolysis. Therefore it was difficult to recruit a sufficient number of research objects. Secondly, due to the limited research time period, there were not enough research objects. Thirdly, low-dose rt-PA thrombolysis was given to some patients who were judged to have a high risk of bleeding based on clinical experience. Forthly, this study is a retrospective study and may be affected by recall bias. Fifthly, the calculation of NIHSS-time score only relies on the NIHSS score value and OTT, and does not include other factors that may cause adverse prognosis. It may affect the adverse prognosis

of some special populations. Poor prognosis for certain special populations cannot be assessed accurately. Therefore, large-sample, multi-center randomized controlled studies and the establishment of a more complete scoring system based on the NIHSS-time score are needed to further explore the predictive value of NIHSS-time scores for AIS patients after standard- dose rt-PA intravenous thrombolysis and to seek a more ideal prediction model.

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