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Research Article

Efficacy, Influencing Factors, and Safety of Alteplase Intravenous Thrombolysis in Patients with Acute Ischemic Stroke Combined with Atrial Fibrillation

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Ischemic stroke is the most common type of stroke. Intravenous thrombolytic therapy with alteplase is currently the most effective method to improve the prognosis of patients with acute cerebral infarction. The purpose of this study was to investigate the efficacy and safety of intravenous thrombolysis with alteplase in patients with acute ischemic stroke combined with atrial fibrillation and to analyze the related influencing factors. It turns out, alteplase intravenous thrombolysis is effective for patients with ICS combined with atrial fibrillation, and the incidence of sICH are lower than those without alteplase intravenous thrombolysis, but the efficacy is worse than that of patients without atrial fibrillation. At the same time, the baseline NHISS score and systolic pressure before the thrombolytic were independent risk factors affecting the efficacy of intravenous thrombolysis with alteplase in ICS patients with atrial fibrillation. This study has provided a scientific basis for making an active decision to perform ultraearly intravenous thrombolysis in our hospital to reduce the mortality and disability rate of stroke in the region.

1. Introduction

Acute ischemic stroke (CIS) is the infarction of brain tissue caused by the occlusion of a cerebral artery, accompanied by the damage of neurons, astrocytes, and oligodendrocytes, which has the characteristics of high morbidity, high mortality, and a high disability rate [1, 2]. Evidence-based medical evidence indicates that ultraearly intravenous thrombolysis is currently the most effective drug therapy for CIS. Intravenous recombinant tissue plasminogen activator (rt-PA) within 4.5 hours of onset has been the preferred recommendation in the 2013 American Stroke Association (ASA) guidelines for the diagnosis and treatment of acute ischemic stroke and in the 2014 guidelines for the diagnosis and treatment of acute ischemic stroke in China [3, 4].

Atrial fibrillation is a common arrhythmia and an independent risk factor for CIS. The occurrence of atrial fibrillation not only increases the severity of CIS but also increases the incidence of other complications and poor prognosis [5]. However, the efficacy and safety of intravenous thrombolysis for CIS patients with atrial fibrillation are controversial, as is whether atrial fibrillation affects the efficacy of intravenous thrombolysis for CIS patients [6]. This study analyzed the efficacy, influencing factors, and safety of intravenous thrombolysis with alteplase in patients with CIS complicated with atrial fibrillation, aiming to provide theoretical support for making a positive decision of ultraearly intravenous thrombolysis and reduce the mortality and disability rate of stroke in this region, which was reported as follows.

2. Information and Methods

2.1. General Information. A total of 355 CIS patients admitted to our hospital from January 2019 to July 2020 were selected as the research objects. There were 198 patients with atrial fibrillation and 157 patients without atrial fibrillation. According to whether to accept alteplase intravenous thrombolysis therapy, 198 patients with atrial fibrillation were divided into group A ($n = 106$) and group B ($n = 92$). And 157 patients without atrial fibrillation were divided into group C.

2.2. Inclusion Criteria. The inclusion criteria were as follows: all patients who were confirmed to have ICS by head CT and/or MRI [7]; patients with neurologic impairment symptoms caused by ischemic stroke; patients whose intracranial hemorrhage has been excluded by cerebral CT without imaging changes of early massive cerebral infarction [8]; patients aged > 18 years; patients whose onset time reaches the admission time ≤ 4.5 h; and the patient or family members who have signed the informed consent form for intravenous thrombolysis. This study was approved by the ethics committee, and the informed consent form was signed by the patient or his/her family.

2.3. Exclusion Criteria. The exclusion criteria were as follows: patients with subarachnoid hemorrhage indicated by medical history and physical examination; Patients who have a history of head trauma, or cerebral infarction, or myocardial infarction within the last 3 months; patients with gastrointestinal or urinary bleeding within the last 3 weeks; patients who had major surgery within the last 2 weeks; patients with a history of artery puncture at the site of hemostasis that is not easy to compress within the past 1 week; patients with a previous history of cerebral hemorrhage; patients with active bleeding or trauma (e.g. fracture) detected by physical examination; patients who were on anticoagulants (INR > 1.7 or PT > 15 s) or who had been on low molecular weight heparin within 24 hours before stroke onset or who had been on thrombin inhibitors or factor Xa inhibitors within 48 hours before stroke onset; patients with platelet count $<100\times10^9$/L; patients with blood glucose < 2.8 mmol/L or >22.22 mmol/L; CT scan results showed the presence of early large lesions, i.e., in patients with lesion size greater than 1/3 of the MCA distribution or ASPECTS score < 5; and patients in pregnancy.

2.4. Methodology. The patient was given multifunctional monitoring and oxygen inhalation immediately after weighing. At the same time, bilateral vein channels were established and the vital signs of patients were monitored. The blood pressure of both upper limbs was measured first, and then the upper limb with the higher blood pressure was selected for blood pressure monitoring. All patients had their blood pressure controlled at or below 180/105 mmHg. Patients above this level were given intravenous urapidil to control their blood pressure. And the oxygen saturation should be kept above 95%. Patients in groups A and C received intravenous thrombolysis with alteplase. The dosage was determined according to the standard of 0.9 mg/kg, and 10% of the total dose was initially measured. The intravenous injection was performed within 1 min, and the remaining dose was administered within 60 min. After 24 hours, the head CT scan was reexamined, and the patient was given routine treatment for ischemic stroke if there was no bleeding. Patients in group B were treated with routine treatment for ischemic stroke after admission.

Patients' clinical data were collected, including basic demographic information such as age, gender, and weight; previous medical history such as hypertension, diabetes, atrial fibrillation, stroke, acute myocardial infarction, heart failure, and smoking; concomitant medication before thrombolysis; emergency examination data such as systolic blood pressure, diastolic blood pressure, blood glucose value, platelet value, LDL value, INR value, NIHSS score, time from admission to intravenous thrombolysis (DNT), and time from onset to intravenous thrombolysis (ONT).

2.5. Clinical Efficacy Evaluation

2.5.1. Short-Term Prognosis. The NIHSS scores of all patients on day 1 and day 7 after treatment were counted. The neurological changes on days 1 and 7 were observed. Compared with the baseline NIHSS score, a NIHSS score reduction of ≥4 points or a NIHSS score of 0–1 is effective, a NIHSS score of ±3 points showed no change, and a NIHSS score increase of ≥ 4 points, or the death turned for the worse [9].

2.5.2. Long-Term Prognosis. The modified Rankin scale (mRS) scores of all patients within 3 months after treatment were counted. Three months later, the score of mRS ≤ 1 was classified as a good prognostic outcome, while the score of mRS ranged from 2 to 6 was a poor prognostic outcome [10].

2.6. Safety Evaluation of Thrombolytic Therapy

(1) Evaluation of intracranial hemorrhage transformation: hemorrhage transformation was evaluated 24 h after treatment and, according to the secondary analysis Asian acute stroke study (ECASS ii) criteria, it was divided into four types of hemorrhagic infarction-1 (HI-1), HI-2, cerebral parenchymal hemorrhage-1 (PH-1), and PH-2 [11]

(2) The basis for judging symptomatic intracranial hemorrhage (sICH): cerebral parenchymal hematoma was determined by head CT/MRI examination 24 h after treatment, accompanied by a worsening of clinical symptoms (NIHSS score increase ≥ 4 points) [12]

(3) The case fatality rate within 3 months was observed

2.7. Statistical Methods. SPSS26.0 statistical software was used for analysis. The measurement data were expressed as the mean ± standard deviation, and independent sample *t*-test was conducted. The enumeration data were subjected to

χ^2 test. The level of statistical significance was defined as a two-sided test. In univariate analysis, variables with $P \leq 0.05$ were included in the multivariate logistic regression model, and the independent risk factors for poor prognosis were analyzed by multivariate logistic regression.

3. Results

3.1. Comparison of Short-Term and Long-Term Prognosis among the Three Groups. There were differences in the improvement rate and unchanged rate in the short-term prognosis among the three groups ($P < 0.05$), but there was no difference in the deterioration rate among the three groups ($P > 0.05$). There were differences in long-term prognosis among the three groups ($P < 0.05$; Table 1).

3.2. Comparison of Safety among the Three Groups. The bleeding rate in groups A and C was higher than that in group B after thrombolysis for 24 h ($P < 0.05$). The new hemorrhage within 7 days rate of groups A and B was higher than that of group C ($P < 0.05$), but there was no significant difference between group A and group B ($P > 0.05$). The incidence of sICH in groups A and C was lower than that in group B ($P < 0.05$). The mortality of group C was lower than that of group B ($P < 0.05$), but the mortality of group A was not statistically significant compared with that of group B ($P > 0.05$ Table 2).

3.3. Single Factor Analysis Affecting the Efficacy of Intravenous Thrombolysis with Alteplase in Patients with ICS Combined with Atrial Fibrillation. Gender, cycle type, history of hypertension, diabetes, hyperlipidemia, medical history, history of stroke, DNT, ONT, LDL-C, HDL-C, homocysteine, diastolic blood pressure before thrombolysis, random blood glucose, glycosylated hemoglobin, white blood cell count, platelet, neutrophil count, PT, APTT, INR, fibrinogen, and combined drug use before thrombolytic therapy had no correlation with intravenous thrombolytic efficacy of alteplase in ICS patients with atrial fibrillation ($P > 0.05$).

Age, weight, history of heart failure, baseline NHISS, systolic blood pressure before thrombolytic, hemoglobin, and red blood cells were single factors influencing the efficacy of intravenous thrombolysis with alteplase in ICS patients with atrial fibrillation ($P < 0.05$; Table 3).

3.4. Variable Assignment. Clinical efficacy (long-term prognosis) was taken as a dependent variable, and the factors with significant differences in Table 3 were taken as independent variables to be included in the logistic regression model. The assignments of the dependent variable and independent variable are shown in Table 4.

3.5. Analysis of Multiple Factors Affecting the Efficacy of Intravenous Thrombolysis with Alteplase in Patients with ICS Combined with Atrial Fibrillation. Baseline NHISS score and systolic pressure before thrombolytic were independent risk factors affecting the efficacy of intravenous thrombolysis with alteplase in ICS patients with atrial fibrillation ($P < 0.05$; Table 5).

4. Discussion

Previous studies have shown that ICS occurring in the presence of atrial fibrillation leads to a higher rate of dysfunction and mortality than in patients without atrial fibrillation. ICS is a dynamic process, and restoring blood supply to the ischemic penumbra is the primary objective in the treatment of ICS. However, despite the efficacy of conventional antiplatelet or anticoagulant therapy in ICS, evidence-based medicine indicates that intravenous thrombolytic therapy with retissue-type plasminogen activator remains the dominant approach for ultraearly treatment of ICS [13].

Alteplase can effectively reverse the pathological process of ischemic penumbra after thrombolysis and has become the most widely used intravenous thrombolytic drug in clinical practice [14]. Alteplase has the effect of promoting the activity of the fibrinolytic system in vivo. However, unlike streptokinase and urokinase, since the two cyclic structures have strong affinity for fibrin, they can specifically convert plasminogen in thrombus into plasmin to exert the effect of dissolving thrombus. At present, there are still differences in intravenous thrombolytic therapy of alteplase for patients with acute ischemic stroke complicated with atrial fibrillation at home and abroad, but most studies tend to benefit from thrombolytic therapy [15]. Our study showed that the long-term good prognosis rate of groups A and C was higher than that of group B ($P < 0.05$), confirming the effectiveness of intravenous thrombolysis with alteplase in ICS. The long-term good prognosis rate of group C was higher than that of group A ($P < 0.05$), indicating that the efficacy of alteplase intravenous thrombolysis for patients with ICS combined with atrial fibrillation was worse than that for patients without combined atrial fibrillation [16]. The possible reasons were as follows: The collateral circulation established by the body before thrombolysis is beneficial to reduce the infarct area after thrombolysis, and protecting the brain tissue by reducing the flow and intensity of hypoperfusion [17]. ICS patients with atrial fibrillation or arterial embolism have a worse ability to establish collateral circulation at the obstruction site than those with large artery thrombosis. Patients with ICS with atrial fibrillation are more likely to develop large and old thrombi, and the reaction of large and old thrombi to thrombolytic therapy is lower [18]. Early recanalization after thrombolysis is considered to be a good prognostic indicator for patients with stroke, while atrial fibrillation is associated with lower early recanalization after thrombolysis, which may result in poorer efficacy [19]. Meanwhile, the new hemorrhage within 7 days in group A and group B was not statistically different ($P > 0.05$), and the sICH in group A and group C was significantly smaller than that in group B ($P < 0.05$). Studies have shown that the pharmacological effect of alteplase on plasma free plasmin is not very strong and systemic fibrinolysis will not occur, thus effectively controlling the occurrence of bleeding and intracranial hemorrhage [20].

Further factors influencing the efficacy of intravenous thrombolytic therapy in patients with ICS with atrial

Table 1: Comparison of short-term and long-term prognosis among the three groups.

Groups	Short-term prognosis			Long-term prognosis	
	Effective	No change	Worse	Good	Poor
Group A ($n = 106$)	55 (51.89)	39 (36.79)	12 (11.32)	50 (47.17)	56 (52.83)
Group B ($n = 92$)	15 (16.30)	59 (64.13)	18 (19.56)	27 (29.35)	65 (70.65)
Group C ($n = 157$)	91 (57.96)	51 (32.48)	15 (9.55)	95 (60.51)	62 (39.49)
χ^2	43.220	25.517	5.503	22.652	
P	<0.001	<0.001	0.064	<0.001	

Table 2: Comparison of complications and deaths among the three groups.

Groups	Hemorrhage occurred within 24 hours	New hemorrhage within 7 days	sICH	Death
Group A ($n = 106$)	21 (19.81)	24 (22.64)	3 (2.83)	18 (16.98)
Group B ($n = 92$)	4 (4.35)	20 (21.74)	8 (8.70)	20 (21.74)
Group C ($n = 157$)	13 (8.28)	14 (8.92)	2 (1.27)	14 (8.92)
χ^2	14.052	11.370	9.353	8.286
P	0.001	0.003	0.009	0.016

Table 3: Single factor analysis of intravenous thrombolysis of alteplase in ICS patients with atrial fibrillation.

Factor	Good group ($n = 50$)	Poor group ($n = 56$)	χ^2/t	P
Gender				
Male	40 (80.00)	37 (66.07)	2.579	0.108
Female	10 (20.00)	19 (33.93)		
Age (years)	72.50 ± 10.55	77.91 ± 8.49	2.922	0.004
Weight (kg)	63.20 ± 11.62	58.48 ± 11.92	2.057	0.042
Circulation type				
Anterior	39 (78.00)	46 (82.14)		
Posterior	9 (18.00)	7 (12.50)	0.689	0.709
Anterior + posterior	2 (4.00)	3 (53.60)		
History of hypertension				
No	16 (32.00)	14 (25.00)	0.638	0.424
Yes	34 (68.00)	42 (75.00)		
History of diabetes				
No	36 (72.00)	43 (76.79)	0.319	0.572
Yes	14 (28.00)	13 (23.21)		
History of hyperlipidemia				
No	33 (66.00)	38 (67.86)	0.041	0.839
Yes	17 (34.00)	18 (32.14)		
History of stroke				
No	48 (96.00)	53 (94.64)	0.108	0.742
Yes	2 (4.00)	3 (5.36)		
History of heart failure				
No	34 (68.00)	24 (42.86)	6.739	0.009
Yes	16 (32.00)	32 (57.14)		
DNT (min)	56.44 ± 26.49	57.64 ± 23.58	0.247	0.805
ONT (min)	154.62 ± 57.46	156.43 ± 48.49	0.176	0.861
Baseline NHISS (points)	9.32 ± 6.10	15.48 ± 7.96	4.433	<0.001
LDL (mmol/L)	2.58 ± 0.95	2.64 ± 0.95	0.312	0.756
HDL (mmol/L)	1.07 ± 0.27	1.07 ± 0.27	0.023	0.982
Homocysteine (μmol/L)	15.50 ± 13.39	15.77 ± 13.60	0.099	0.921
Systolic pressure before thrombolytic (mmHg)	149.78 ± 28.39	163.29 ± 26.94	2.512	0.014
Diastolic pressure before thrombolytic (mmHg)	83.80 ± 16.06	88.70 ± 18.64	1.440	0.153
Random blood glucose (mmol/L)	7.69 ± 2.94	7.98 ± 3.13	0.490	0.625
Hemoglobin (%)	6.22 ± 1.09	6.18 ± 0.89	0.180	0.858
White blood cell count ($\times 10^9$/L)	7.43 ± 2.08	7.55 ± 2.23	0.304	0.762
Red blood cell count ($\times 10^9$/L)	4.55 ± 0.58	4.26 ± 0.63	2.501	0.014
Neutrophil count ($\times 10^9$/L)	4.80 ± 1.74	4.65 ± 1.98	0.402	0.689
Hemoglobin (g/L)	141.78 ± 18.04	131.68 ± 19.64	2.747	0.007
Platelet count ($\times 10^9$/L)	167.72 ± 46.43	187.30 ± 56.35	1.939	0.055
PT (s)	11.44 ± 0.92	11.37 ± 1.34	0.345	0.731

Table 3: Continued.

Factor	Good group ($n = 50$)	Poor group ($n = 56$)	χ^2/t	P
APTT (s)	25.80 ± 2.56	25.95 ± 3.12	0.268	0.789
INR	0.98 ± 0.08	0.98 ± 0.11	0.197	0.844
Fibrinogen (g/L)	3.38 ± 2.24	3.28 ± 0.93	0.322	0.748
Na+ (mmol/L)	139.71 ± 2.27	139.40 ± 2.08	0.732	0.466
K+ (mmol/L)	3.68 ± 0.37	3.63 ± 0.49	0.584	0.560
Urea nitrogen (mmol/L)	6.77 ± 1.70	7.36 ± 3.43	1.097	0.245
Aspirin was taken before onset				
No	47 (94.00)	54 (96.43)	0.347	0.556
Yes	3 (6.00)	2 (3.57)		
Clopidogrel was taken before onset				
No	48 (96.00)	54 (96.43)	0.013	0.908
Yes	2 (4.00)	2 (3.57)		
Atorvastatin was taken before onset				
No	47 (94.00)	55 (98.21)	1.292	0.256
Yes	3 (6.00)	1 (1.79)		
Rosuvastatin was taken before onset				
No	49 (98.00)	56 (100.00)	1.131	0.288
Yes	1 (2.00)	0 (0.00)		

Table 4: Variable assignment of risk factors affecting the efficacy of intravenous thrombolysis with alteplase in ICS combined with atrial fibrillation.

Variable	The assignment
The dependent variable	
Clinical curative effect	effective = 0, ineffective = 1
The independent variables	
Age	Enter the actual value
Weight	Enter the actual value
History of heart failure	No = 0, Yes = 1
Baseline NHISS	Enter the actual value
Systolic pressure before thrombolytic	Enter the actual value
Hemoglobin	Enter the actual value
Red blood cell	Enter the actual value

Table 5: Binary logistic regression analysis of the influence on intravenous thrombolysis of alteplase in ICS patients with atrial fibrillation.

Variable	β	SE	Wald χ^2	P	OR	95% CI of OR
Age	0.019	0.026	0.510	0.475	1.019	0.968~1.072
Weight	−0.029	0.020	2.091	0.148	0.971	0.934~1.010
History of heart failure	−0.443	0.488	0.823	0.364	0.642	0.246~1.672
Baseline NHISS	0.146	0.040	12.960	0.000	1.157	1.069~1.252
Systolic pressure before thrombolytic	0.019	0.009	4.619	0.032	1.019	1.002~1.037
Hemoglobin	−0.018	0.028	0.409	0.552	0.982	0.929~1.038
Red blood cell	−0.497	0.855	0.338	0.561	0.608	0.114~3.253
Constant	0.656	3.269	0.040	0.841	1.928	–

fibrillation were investigated [21]. In this study, independent risk factors for the efficacy of intravenous thrombolysis with alteplase included baseline NHISS score and systolic pressure before thrombolytic. The NHISS score is a scale for evaluating the neurological functional recovery status of patients with stroke. A high NHISS score indicates how serious the nerve damage is, indicating that the recanalization rate after thrombolysis is low for patients [22]. Therefore, close observation of NHISS score changes in ICS patients with atrial fibrillation and early intervention in patients with high risk factors can help doctors effectively judge the severity of patients' disease and the outcome of curative effects and improve the effectiveness of clinical treatment. Increased blood pressure plays an important role in the prognosis and mortality of patients with ICS. Hypertension can lead to arteriosclerosis and increased fragility of the vascular wall, and increased irritability of blood pressure after cerebral ischemia. In addition, the increased systolic blood pressure will also increase the permeability of the blood-cerebrospinal fluid barrier and extracellular matrix, causing abnormal situations such as plasma extravasation and edema, and further inducing cerebral

hemorrhage. Therefore, we should strengthen the control of patients' blood pressure before thrombolytic therapy to maintain its relatively stable and normal level.

In summary, alteplase intravenous thrombolysis is effective for patients with ICS combined with atrial fibrillation, and the incidence of sICH are lower than those without alteplase intravenous thrombolysis, but the efficacy is worse than that of patients without atrial fibrillation. At the same time, the baseline NHISS score and systolic pressure before the thrombolytic were independent risk factors affecting the efficacy of intravenous thrombolysis with alteplase in ICS patients with atrial fibrillation. In order to improve the clinical application value of alteplase intravenous thrombolysis, targeted intervention for those combined with high-risk factors should be strengthened in clinics.

Data Availability

The datasets generated for this study are available from the corresponding author on reasonable request.

Ethical Approval

This study was approved by the Medical Ethics Committee of Ruian People's Hospital (LZM2018002).

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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