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Effects of Ultra-early Alteplase Intravenous Thrombolysis in Patients with Acute Cerebral Infarction and the Influencing Factors of Deterioration After Improvement

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Abstract

Objective: To analyze the effects of ultra-early alteplase (rt-PA) intravenous thrombolysis in patients with Acute Cerebral Infarction (ACI) and the influencing factors of deterioration after improvement.

Methods: A total of 70 patients with ACI treated by rt-PA intravenous thrombolysis in our hospital from January 2014 to December 2016 were selected as the observation group, and another 90 patients with ACI who only received conventional treatment were selected as the control group. The status of neurological impairment was evaluated with the National Institutes of Health Stroke Scale (NIHSS) and the prognosis was evaluated with the Barthel Index (BI) and modified Rankin Scale (mRS). The incidence of complications was statistically analyzed. Patients in the observation group were divided into the deterioration group (n=9) and the non-deterioration group (n=61). the clinical data were collected for univariate analysis and factors with significant differences were analyzed by Logistic regression analysis.

Results: Before treatment, there were no significant differences between the two groups in NIHSS score, BI and mRS score, while after treatment, the above-mentioned indexes were significantly improved, and the improvement was more obvious in the observation group than the control group. Multivariable Logistic regression analysis showed that age, previous history of atrial fibrillation, late thrombolysis, high NIHSS score before thrombolysis, low white blood cell count and total anterior circulation infarction were independent risk factors for deterioration after improvement.

Conclusion: Ultra-early rt-PA intravenous thrombolysis can quickly correct the status of cerebral ischemia and hypoxia and save the damaged neurological function in patients with ACI, and attention should be paid to the independent risk factors for deterioration after improvement.

Keywords: Acute cerebral infarction; Ultra-early rt-PA intravenous thrombolysis; Deterioration

Introduction

Acute Cerebral Infarction (ACI) is recognized as one of the critical emergencies with high mortality and high disability rate, the aim of its clinical treatment is to dredge the infarct area as quickly as possible, recovery of responsible vascular perfusion to save ischemic penumbra, minimization or termination of secondary brain necrosis and softening due to hypoxia and ischemia and restore the injured nerve as much as possible, so that the patient benefit from greater survival [1-4]. Rt-PA, as a recombinant tissue

plasminogen activator, has been listed as a first-line drug for the treatment of aci in European countries. However, in clinical application, the timing and prognosis of the drug are often different [3,5,6]. In view of this, 70 cases of ACI patients who were treated with super early rt-PA in our hospital were included in the study scope. On the basis of determining the efficacy of thrombolytic therapy, logistic regression analysis was used to analyze the risk factors that might lead to the deterioration of thrombolytic improvement. The purpose of this study is to provide high value clinical reference data for rt-PA intravenous thrombolytic therapy in patients with ACI.

Data and Methods

General data: Selection From January 2014 to December 2016, 70 ACI patients treated with rt-PA intravenous thrombolytic therapy were selected as observation group and 90 patients with ACI received routine therapy as control group. In the observation group, there were 45 males and 25 females, the age of 39-72 year-old (55.57 ±16.32) years, the average time spent from onset to admission to hospital (2.12 ±0.71) h, 35 cases with hypertension, 25 cases with diabetes mellitus and 10 cases with hyperlipidemia. The control group consisted of 65 males and 25 females with an age of 38-73 year-old (56.04 ±15.96) years, the average time spent from onset to admission to hospital was (2.27 ±0.58) h, 40 cases with hypertension, 35 cases with diabetes mellitus and 15 cases with hyperlipidemia. There was no significant difference in sex, age, onset time and complications between the two groups ($p > 0.05$).

Inclusion and exclusion criteria

Inclusion criteria

1. According to the relevant descriptions of the guidelines for the diagnosis and treatment of Acute Ischemic Stroke in China 2010 and the guidelines for the diagnosis and treatment of Acute Ischemic Stroke in China 2014.
2. The time from onset to admission to hospital is less than 3 hours.
3. All can control blood pressure, blood sugar, blood lipid.
4. According to the indication of thrombolysis and without thrombolytic related contraindication.
5. This study was approved by the Hospital Ethics Committee when it was carried out.
6. All patients voluntarily chose intravenous thrombolytic therapy or non-venous thrombolytic therapy and knew the contents of the study.

Exclusion criteria

1. In the last 3 months, there was a history of major head trauma or stroke (cerebral hemorrhage, cerebral infarction).
2. Suspected subarachnoid hemorrhage.
3. In the last 1 week, there is an artery puncture which is not easy to compress and stop bleeding.
4. There were intracranial tumors, intracranial arteriovenous malformations and intracranial aneurysms.
5. Recent intracranial or spinal canal surgery.
6. Having a history of hemorrhagic hematological diseases or acute bleeding tendencies (including platelet count < 90 × 109 / L or other conditions).
7. Heparin was treated within 48 hours [Activated Partial prothrombin Time (APTT) exceeded normal range].
8. Recently, anticoagulants were taken and the International Standardized Ratio (INR) was more than 1.7 or the Plasma thrombin reduction Time (PT) was more than 15s.
9. Pre-treatment systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg, except for blood pressure that can be reduced to 160/90 mmHg after treatment.
10. Blood glucose < 2.7 mmol/l.
11. Major surgery or severe trauma in the last 2 weeks.
12. Bleeding of digestive or urinary systems during the last 3 weeks.
13. A history of myocardial infarction in the last 3 months.
14. Cranial CT showed infarction in (MCA) area of middle cerebral artery with low density > 1/3.
15. NIHSS score > 25.
16. Allergy to atropase (rt-PA).
17. Patients or family members refuse intravenous thrombolytic therapy.

Methods

Patients in both groups were treated with routine ACI [6], on admission, such as respiratory support, anti-brain edema, control of intracranial pressure and hypertension, diabetes and other complications, the observation group was given rt-PA (Unit of production: Boehringer Ingelheim Pharma GmbH & amp; Co.KG, Germany, registration number: S20110051, specification: 50mg/ branch) intravenous thrombolytic therapy. Take 0.9 mg/Kg as the

standard and calculate the dosage, the maximum dose is 90 mg, the concentration of the original solution is 1 mg/mL, 10% of the drug was injected intravenously at 1st min, and the remaining dose was pumped into the vein at 60 min with the infusion pump. Close monitoring of vital signs after thrombolytic therapy, CT was performed 24 hours later, coagulation function, blood routine examination and so on. If there was no intracranial hemorrhage, antiplatelet therapy could be given. The control group was treated with aspirin enteric-coated tablets (Bayer S.p.A, Italy, 100mg/ tablet), clopidogrel (Sanofi Pharma Bristol-Myers Squibb SNC, France, 75mg/tablet) at the discretion of the physician according to the condition of the disease. The dosage of the drug was given at the doctor's discretion.

Observation indicators

Intravenous thrombolytic effect of rt-PA in patients with acute cerebral infarction

1. Improvement of nerve function defect: before treatment, 2 hours after treatment, 24 days after treatment and 3 months after treatment, (NIHSS) was used to evaluate the neurological impairment of the patients. The scale includes patients' consciousness, limb movement, reflex and other neurological function behaviors. The higher the score is, the more serious the nerve defect is.
2. Prognosis situation: Barthel (BI) index was used to evaluate ADL before and 3 months after treatment, the improved Rankin (mRS) scale was used to evaluate the recovery of neurologic function in patients, the higher the score of BI index, the more daily behavior, such as daily, food, clothing, housing and transportation, etc. The mRS scale is a comprehensive evaluation of the patients' physical movement, sensation, vision, cognition and so on. The higher the score, the worse the recovery of neurological function.

Factors influencing the deterioration of patients with acute cerebral infarction after the improvement of thrombolytic therapy in rt-PA at the very early stage

70 patients who received intravenous thrombolytic therapy with rt-pa were divided into two groups according to whether the thrombolysis had deteriorated after thrombolytic improvement (n=9) and no deterioration (n=61). The clinical data such as demography, past history, thrombolytic index, laboratory index, OCSP classification, TOAST classification and so on were collected.

Statistical methods

The data involved in this study were statistically analyzed by spss19.0 software. The measurement was expressed in $\bar{x}\pm s$, the t test was used, the percentage standard was used to count the data, the X2 test was carried out, and the logistic regression analysis of multiple factors was carried out, $p<0.05$ was statistically significant.

Results

Comparison of changes in NIHSS scores between the two groups before and after treatment

Before treatment, there was no difference in NIHSS score between the two groups ($p>0.05$). After treatment, the NIHSS score of the two groups decreased, and the NIHSS score of the observation group was lower than that of the control group at 2h and 24h after treatment, and the difference was statistically significant ($p< 0.05$) (Table 1).

Group	NIHSS			
	Prior treatment	2 hours after treatment	24 hours after treatment	2 weeks after treatment
Observation group (n=70)	13.34±4.17	10.24±5.49	8.69±5.23	6.84±5.35
Control group (n=90)	13.22±4.46	12.86±5.61	11.93±5.78	9.52±5.59
t	0.713	2.964	3.665	3.065
P	0.862	0.003	0.0003	0.002

Table 1: Comparison of changes in NIHSS score between two groups before and after treatment ($\bar{x}\pm s$, score).

Comparison of BI index and mRS score before and after treatment between the two groups

Before treatment, there was no significant difference in BI index and mRS score between the two groups ($p > 0.05$). After treatment, the BI index increased and the mRS score decreased in both groups. The BI index score of the observation group was higher than that of the control group at 2 weeks and 3 months after treatment, and the mRS score was lower than that of the control group ($p < 0.05$) (Table 2).

Group	Time	BI	mRS
Observation group (n=70)	prior treatment	26.01±8.64	3.58±0.34
	3 months after treatment	49.15±18.01[1) 2)]	2.17±1.69[1) 2)]
Control group (n=90)	prior treatment	26.48±8.27	3.60±0.29
	3 months after treatment	36.28±15.17[1)]	3.01±0.97[1)]
1）Compared with pre-treatment: $p < 0.05$ **; 2**）Compared with control group: $p < 0.05$			

Table 2: Comparison of BI index and mRS score between two groups before and after treatment ($\bar{x}$±s, score).

Univariate analysis of the deterioration after the improvement of intravenous thrombolytic therapy in the ultra-early stage of ACI with rt-PA

The average age, thrombolytic time, NIHSS score, WBC count and the proportion of patients with complete anterior circulation infarction in the group with good prognosis were lower than those in the control group ($p < 0.05$) (Table 3).

Variable	No deterioration group (n=61)	Deterioration group (n=9)	Statistic (t/ x^2)	P
General information				
sex（M/F)	49/12	6/3	0.869	0.351
age	45.17±4.68	56.37±10.55	3.124	0.002
Past history				
hypertension	41	4	1.770	0.183
diabetes	17	3	0.114	0.734
hyperlipemia	8	2	0.531	0.466
smoking	10	3	1.488	0.222
alcohol	13	4	2.282	0.130
AF	5	7	10.728	0.001
Thrombolytic related index				
Thrombolysis time (min)	124.38±11.45	167.25±10.09	11.702	0.000
NIHSS score before thrombolysis (score)	8.37±0.11	12.95±2.14	6.379	0.000
Blood pressure before thrombolysis (mmHg)				
SBP	139.28±19.72	140.25±19.44	0.139	0.889
DBP	83.16±11.64	84.25±11.36	0.267	0.789
Laboratory index				
Blood glucose before thrombolysis (mmol/L)	7.65±2.47	8.01±2.23	0.446	0.656
WBC (×109/L)	10.91±5.14	8.27±3.34	2.054	0.043
NEU-R (%)	0.83±0.24	0.86±0.23	0.363	0.717
Hb (g/L)	148.66±16.87	145.78±17.01	0.474	0.636
PLT (×109/L)	214.37±61.25	220.18±62.17	0.262	0.794
INR	1.10±0.32	1.19±0.35	0.727	0.469
PT (s)	13.39±1.27	13.50±1.17	0.260	0.795

APTT (s)	35.25±6.87	35.04±6.90	0.125	0.900
Fbg (g/L)	3.41±1.49	3.24±1.32	0.354	0.723
TC (mmol/L)	5.48±1.01	5.18±1.13	0.752	0.454
LDL (mmol/L)	3.41±0.95	3.21±0.96	0.584	0.561
Urinary protein positive	2	6	32.006	0.000
Oxfordshire community stroke project (OCSP) classification				
Complete anterior circulation infarction	5	5	14.365	0.000
Partial anterior circulation infarction	30	7	2.574	0.108
Posterior circulation infarction	10	2	0.187	0.664
Lacunar infarction	9	1	0.085	0.770
Stroke (TOAST) classification				
Atherosclersis	34	6	0.382	0.536
Cardiogenic embolism	2	1	1.172	0.278
Arteriolar lesion	33	7	1.795	0.180
Others	7	1	2.535	0.111

Table 3: Univariate analysis of deterioration after the improvement of intravenous thrombolytic in the ultra-early stage of ACI with rt-PA (n=70).

Multivariate logistic regression analysis on the deterioration of ACI after the improvement of intravenous thrombolytic therapy with rt-PA in the ultra-early stage of ACI

Multivariate logistic regression analysis showed that venerable age, history of atrial fibrillation, relatively late of thrombolytic time, and low NIHSS score before thrombolysis, Low WBC count and complete anterior circulation infarction are independent risk factors for deterioration of ACI after thrombolytic therapy. The history of atrial fibrillation is the most important risk factor (Table 4).

Variable	β	Waldχ^2	OR	95%CI	P
Age	0.343	9.220	2.136	0.467~5.643	0.002
History of AF	2.230	12.254	7.209	2.603~18.271	0.000
Thrombolytic time	1.411	12.357	4.135	1.267~8.556	0.000
NIHSS score before Thrombolysis	2.257	25.366	1.186	1.158~2.257	0.000
WBC	0.220	0.220	0.536	0.112~1.015	0.053
Complete anterior Circulation infarction	1.818	11.945	6.212	2.067~16.124	0.000

Table 4: Multivariate logistic regression analysis on the deterioration of ACI after the improvement of intravenous thrombolytic therapy with rt-PA in the ultra-early stage of ACI.

Comparison of complications between the two groups

During the treatment, one case of tongue edema appeared in the observation group, which could be caused by drug allergy through clinical comprehensive diagnosis and was cured after symptomatic treatment. Four patients in the observation group had bleeding symptoms after thrombolytic therapy, including 2 gingival cases, 2 skin bleeding cases, a case of bleeding gums with skin bleeding ,the total incidence was 8.33%; while in the control group 2 cases had gingival bleeding, the total incidence was 3.33%. There was no significant difference in bleeding complications between the two groups (x^2=1.365, P=0.242).

Discuss

Analysis of the effect of intravenous thrombolytic therapy on rt-PA in ultra-early stage of ACI

ACI is caused by multiple factors, such as atherosclerosis, cardiogenic embolism and so on. The course of ACI is accompanied by cerebral ischemia and anoxia. Irreversibility of nerve function in the perivascular tissue of the responsible vessel and formation of ischemic penumbra around the central necrotic region [7]. Clinical studies suggest that the ischemic penumbra is reversible, but if the ischemic and anoxic state of brain tissue is not released in time, the area of central necrosis will extend further with the prolongation of ischemia and hypoxia time. It eventually covers the entire ischemic penumbra, resulting in irreversible necrosis of the brain [8,9]. Meanwhile, due to ischemia and long time of hypoxia, a large number of toxic biochemical substances produced by brain tissue metabolism also lead to the cascade of malignant complications, and accelerate the progression of the disease, and then worsen the condition, endangering the life and health of the patient. Therefore, in the clinical treatment of ACI, how to relieve cerebral ischemia, hypoxia quickly and save ischemic penumbra has become a common understanding of treatment.

Intrvenous thrombolysis is one of the effective thrombolytic methods. It has high clinical value with the advntages of simple, fast, easy to use, no long time preparation and so on. In particular, the emergence of the third-generation thrombolytic drug rt-PA has greatly improved the specificity of previous thrombolytic drugs, such as urokinase, Anipase, etc., with a short half-life and high fibrinolytic blood circulation. It has longer drug half-life and better specificity and safety. It is highly specific to fibrin and can effectively avoid systemic anticoagulant thrombolytic state caused by non-selective fibrinolytic agent. Rt-PA can bind to cellulose in thrombus and form fibrinogen with strong affinity. It can dissolve thrombus in time by rapid degradation of fibrinase [10-12].

The results of this study are also reflected in our report, and the time of thrombolytic therapy was shortened to 3 hours after the onset of thrombolysis. The statistical analysis showed that there was no difference in NIHSS score, BI index and mRS score between the two groups before treatment. After treatment, the NIHSS score, bi index and mRS score at different time points in the observation group were better than those in the control group. Among the patients who were treated with rt-PA within 3 hours after the onset of the disease, the proportion of patients with good prognosis was as high as 60%, which suggests that rt-PA thrombolytic therapy at the very early stage is better for the improvement of neurological function defect in patients. At the same time, there were no severe symptoms of intracranial hemorrhage or fatal hemorrhage in both groups, and there was no significant difference between the two groups in gingival, skin and other bleeding cases.

Analysis of the influencing factors on the deterioration of rt-PA after the improvement of intravenous thrombolysis in the Ultra-early stage of ACI

In view of the difference of the prognosis of rt-PA intravenous thrombolytic therapy in the ultra-early stage of ACI, it is helpful for the ACI patients treated with rt-PA to get more benefit. In this study, the patients in the observation group treated with rt-PA were divided into two groups, compared with demography, past history, laboratory index, OCSP, TOAST classification and so on, then showed that the age of patients with thrombolytic improvement was older than that of patients with no deterioration, and the proportion of patients with history of AF was higher, the onset time of thrombolysis was relatively late, and the NIHSS score and WBC count before thrombolysis were higher. The proportion of patients with complete anterior circulation infarction was higher than that of patients without deterioration after thrombolysis. Multivariate logistic regression analysis showed that old age, history of AF relatively late thrombolytic time, low NIHSS score before thrombolytic therapy, abnormal WBC count and complete anterior circulation infarction were independent risk factors for deterioration after the improvement of intravenous thrombolytic therapy on rt-PA in ultra-early stage of ACI. Among them, the history of AF has the strongest correlation. Analysis of its specific mechanism, elderly people induced a variety of vascular disease risk factors, because with age, the body's vascular wall elasticity, the higher the risk of microvascular disease, and blood flow after thrombolytic rapid recovery of vascular wall is difficult to tolerate which increased risk of bleeding. However, Af often leads to thrombus abscission and blood circulation after arrhythmia. Once circulating to the small blood vessels, it not only causes infarction, increases the infarct location, but also further destroys the function and structural integrity of blood vessels. After thrombolysis the fibrinogen in the embolus is dissolved and causes the thrombus to flow continuously with the blood and damage the damaged blood vessels causing it to rupture and bleed. Based on the analysis of the mechanism of complete anterior circulation infarction and deterioration after thrombolytic therapy, the author thinks it's possible that the complete anterior circulation infarction is caused by the infarction of the carotid artery supply area. The distal vessels in this part of the patients are relatively insufficient, the cerebral blood flow is low expression, and the thrombus load is relatively high in the occluded area. After thrombolytic therapy, the blood flow velocity in the stenotic part of the vessel becomes faster, which can also cause the thrombus to rupture and form a running embolus, causing secondary infarction or injury to the normal vascular wall or even causing it to rupture. At the same time, when the level of WBC count is increased, not only can a large number of blood vessels gather and attach to the blood vessel, resulting in stenosis of blood lumen, resulting in abnormal hemodynamic index, but also can destroy the normal structure and function of

vascular endothelium. The effects of excessive activation and release of oxygen free radicals and platelet activating factors on the establishment of collateral circulation resulted in poor compensability of collateral circulation and deterioration after thrombolytic improvement. The NIHSS score is a sensitive criterion for the expression of the degree of neurological deficit in patients. Its high score not only indicates that the nerve defect is relatively serious, but also indicates that the location or degree of cerebral infarction is relatively serious. Although intravenous thrombolytic therapy can relieve the degree of infarction quickly, the patients may be subjected to excessive vascular endothelial injury, residual thrombus exfoliation and other factors leading to re-infarction or bleeding symptoms. About the relationship between thrombolytic time and the deterioration after thrombolytic therapy, the author believes that the later the thrombolytic time, the more serious the injury caused by cerebral infarction. Although thrombolytic therapy can alleviate this situation, its effect is to save the ischemic penumbra zone, and with the prolongation of thrombolytic time, the irreversible damage caused by the expansion of the central necrotic area is further aggravated, and thrombolytic therapy may not benefit much. Therefore, in the clinical application of rt-PA, we still need to pay close attention to the above risk factors, and take timely measures to prevent and cure the disease, so as to make the patients with ACI get more benefit in treatment as far as possible.

To sum up, ultra-early rt-PA treatment in ACI patients not only significantly improved the neurological function defect and ADL, but also had good safety by advancing the thrombolytic time window to within 3 hours of onset, and did not increase the risk of bleeding at the same time. However, in the clinical application of rt-PA, the doctor should consider comprehensively the factors affecting the deterioration of rt-PA after the improvement of thrombolysis in the ultra early stage of ACI according to the actual condition of the patient and the factors reported in this paper, and select the appropriate treatment plan.

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