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Original Article

Analysis of comparative observations on therapeutic effects of alteplase and urokinase in patients with acute cerebral infarction and the influence on inflammatory factors and MMP-9 levels

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Abstract: Objective: We aimed to compare the therapeutic effects of alteplase and urokinase in patients with acute cerebral infarction (ACI) and explore the influence on inflammatory factors (IF) and matrix metalloproteinase 9 (MMP-9) levels. Methods: In total, 72 patients who were diagnosed with ACI from May, 2018 to June, 2019 were selected as subjects of study and randomly divided into a urokinase group (UG) (n=36 cases) and an alteplase group (AG) (n=36 cases). In addition to the routine treatment and intervention performed in the two groups after admission, the UG was treated with urokinase through thrombolytic therapy (TT) and the AG was treated with alteplase through TT. After treatment, all patients were followed up for 3 months to compare the short-term curative effects, coagulation function, activity of daily living (ADL), IF level and treatment and prognosis between two groups. Results: After alteplase intervention, the short-term curative effect rate of the AG was 94.44%, which was higher than 75.00% of the UG (χ^2=6.391, P=0.025). After treatment, the prothrombin time (PT) and activated partial thromboplastin time (APTT) of coagulation factor (CF) in the AG were longer than those in the UG (P<0.05) and the fibrinogen (FIB) level and platelet (PLT) level of the AG were lower than those of the UG (P<0.05). In both groups, the NIHSS (National Institutes of Health Stroke Scale) scores after treatment were lower than those before treatment (P<0.05) and the ADL scores after treatment were higher than those before treatment (P<0.05). After treatment, the NIHSS scores of the AG were lower than those of the UG (P<0.05) and the ADL scores of the AG were higher than those of the UG (P<0.05). In both groups, the levels of high-sensitivity c-reactive protein (hs-CRP), amino-terminal fragment of pro-bnp (NT-pro-BNP) and interleukin-6 (IL-6) after treatment were lower than those before treatment (P<0.05). After treatment, the levels of hs-CRP, NT-pro-BNP and IL-6 in the AG were lower than those in the UG (P<0.05). The MMP-9 level of the AG was higher than that of the UG after treatment (P<0.05). The revascularization rate of the AG was higher than that of the UG after treatment (P<0.05); and the complication rate, bleeding rate and death rate of the AG were lower than those of the UG 3 months after treatment (P<0.05). Conclusion: The application of alteplase to ACI patients could achieve a better short-term curative effect, which was conducive to improving coagulation function, enhancing ADL, reducing IF level and obtaining favorable treatment and prognosis, so it is worthy of promotion and application.

Keywords: Alteplase, urokinase, acute cerebral infarction, inflammatory factor, coagulation function, activity of daily living, treatment and prognosis

Introduction

ACI is the sudden disruption of cerebral blood supply caused by various reasons, which leads to necrosis of brain tissue. For most patients, the thrombus or atherosclerosis is formed in arteries of the cerebral blood supply, which causes focal and acute insufficiency of the blood supply to brain tissue [1]. Meanwhile, if there is foreign matter in the blood circulation at the time of onset, this leads to the angiemphraxis, which affects the blood flow volume and thus causes ischemia and necrosis of the corresponding tissues [2]. Clinical research shows [3] that the pathogenesis of ACI is complicated and it is generally believed that the pathogenesis is related to hypertension, diabetes mellitus (DM), hyperlipidemia and smoking, etc. There can be sudden onset in patients, mostly manifesting as tinnitus, dizziness and

Table 1. Comparison of general data between the two groups

Clinical material		AG (n=36)	UG (n=46)	x^2	*P*
Gender	Male	23 (63.89)	22	1.294	0.059
	Female	13 (36.11)	14		
Age (years old)		65.39 ± 5.68	65.32 ± 5.69	0.194	0.537
Body mass (kg)		62.59 ± 4.69	63.11 ± 4.74	0.394	0.771
Time from onset to thrombolysis (h)		4.51 ± 0.71	4.53 ± 0.74	1.353	0.682
Complication	Hypertension	19 (52.78)	21 (58.33)	0.672	0.324
	DM	17 (47.22)	18 (50.00)		
	Hyperlipidemia	23 (63.89)	21 (58.33)		
Killip grading	Grade I	8 (22.22)	9 (25.00)	0.981	0.784
	Grade II	10 (27.78)	11 (30.56)		
	Grade III	12 (33.33)	11 (30.56)		
	Grade IV	6 (16.67)	5 (13.89)		

headache, etc. At present, the clinical treatment methods of ACI mainly include revascularization, recovery of cerebral blood perfusion and rescue of the ischemic penumbra. The symptomatic and supportive treatment can delay the progression of disease and reduce the clinical death rate, but the long-term prognosis is relatively poor [4].

With the continuous development of medical technologies, TT has been used in clinical practice, including arterial thrombolysis and intravenous thrombolysis [5]. The former needs the help of DSA and other devices. Furthermore, due to the disadvantages of a complicated operation, long time consumption and higher requirements for doctors, it is not well promoted and applied in primary hospitals. The latter, with the advantages of having simple technologies and devices, is convenient and an efficient operation with little trauma, so it can be finished in a short time, and most patients readily accept it [6]. Currently, the thrombolytic drugs commonly used in clinical practice include alteplase and urokinase. Urokinase is the first generation of thrombolytic drugs derived from streptococcus hemolyticus and it can cause the hyperfibrinolysis. Besides, its specificity is poor. Alteplase is the second generation of thrombolytic drugs and is derived from the active matter of plasminogen found in animals and bacteria. With intermediate selectivity and compatibility in fibrous proteins of thrombus, it can reduce the incidence of adverse reactions, like bleeding, etc. Besides, it will not cause hyperfibrinolysis [7]. According to clinical research, athrombus is a therapeutic drug recognized internationally, while the application of urokinase is still in dispute. There are not many studies about the influence of these two drugs on IF of ACI patients.

ACI is a multifactorial disease influenced by environmental factors, genetic factors and acquired factors. It is often complicated with an abnormal expression of IF [8]. Foreign scholars indicated [9] that ACI was characterized by a high disability rate and high recurrence rate and atherosclerosis was the basis of its pathogenesis. Furthermore, a variety of IF participate in the process of ACI onset and thus mediated the severe immune response and accelerated the occurrence of disease. So in this study, ACI patients were selected as subjects of study to discuss the application effects of alteplase and urokinase in ACI patients, with the report shown below.

Material and methods

Clinical parameters

In total, 72 patients who were diagnosed with ACI from May, 2018 to June, 2019 were selected as subjects of study and randomly divided into the UG (n=36 cases) and the AG (n=36 cases). This study was approved by Hospital Ethics Committee of The Central Hospital of Wuhan and the patients and their family members signed the Informed Consent Form. There was no statistical significance between the general data of two groups (P>0.05), as shown in **Table 1**.

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients complied with the diagnostic criteria of ACI in *China's Guidelines*

for Cerebrovascular Disease (CVD) Prevention and Treatment [10]. (2) Patients had indications of TT and were not allergic to thrombolytic drugs as alteplase and urokinase. (3) Patients, with NIHSS scores ≥4, were conscious and were able to communicate with their family members/doctors.

Exclusion criteria: This study excluded (1) patients complicated with active bleeding and coagulation disorders or with incomplete medical records; (2) those complicated with ataxia and sensory disorders or treated with heparin therapy within 48 h; (3) those complicated with intracranial aneurysm and mental disorders or treated with major surgery recently or with severe trauma; and (4) those complicated with gastrointestinal bleeding, urologic bleeding or other diseases.

Methods

(1) Preparation before treatment. After admission, routine treatment and intervention were performed in the two groups to finish relevant examinations, including neurological examination and enquiry about medication situation, to assist the CT and MRI examinations, evaluate the physical condition of patients, monitoring of blood pressure and heart rate, oxyhemoglobin saturation and routine blood work of patients. The specific time from onset to thrombolysis after admission was calculated precisely. Medication given; 180 mg ticagrelor (Guangdong Lingnan Pharmacy Co., Ltd., SFDA approval number: H20074238) was taken orally and the dose was 90 mg on the following day for twice a day [11]. (2) Treatment methods. UG: the UG was treated with urokinase through TT. The mixed solution of 125 U urokinase (Hubei Qian Jiang Pharmaceutical Co., Ltd., SFDA approval number: H42020666) and 100 mL normal saline (NS) was infused into patients through continuous intravenous drip for 30 min. AG: the AG was treated with alteplase through TT. After the mixing of 0.9 mg/kg alteplase (Boehringer Ingelheim Pharma GmbH & amp; amp; amp; Co. KG, registration number: S20160055) and 100 mL NS, 10% of the mixed solution was injected intravenously and the rest was dripped intravenously for 1 h. The maximum dose of alteplase did not exceed 90 mg. In the course of treatment, the vital signs were improved, the blood glucose assay was regularly measured and the antihypertension treatment was performed in patients with high blood pressure. Anticoagulant therapy through bayaspirin and low molecular heparin was stopped within 24 h after TT. After treatment, the patients were followed up for 3 months.

Observation targets

(1) Short-term curative effect: Significant effect: Symptoms and signs disappeared and the language function was restored. The descending rate of NHISS scores was 90.0%-100.00%. Better: Symptoms and signs were improved, the language function was enhanced and pseudobulbar palsy was alleviated. The descending rate of NHISS scores was 46.0%-89.00%. Invalid: The therapeutic effect was poor or the patients died [4]. (2) Coagulation function. Five mL peripheral venous blood (fasting) was collected before treatment and 3 months after treatment for centrifugation. Then, the automatic hamocyte analyzer was used to measure FIB, APTT, PT and PLT level [12]. (3) ADL. NIHSS (including 42 scores in total. The lower the scores, the better the effect) and ADL Scale (including 100 scores in total. The higher the scores, the higher the living ability) were used to evaluate the nerve defect and ADL of patients [3]. (4) IF level. The serum specimens were used to evaluate the hs-CRP level through immunoturbidimetry before treatment and 15 d after treatment. The enzyme linked immunosorbent assay was used to evaluate the levels of NT-pro-BNP, IL-6 and matrix metalloproteinase 9 (MMP-9) [13]. (5) Treatment and prognosis. After treatment, the two groups were followed up for 3 months to record the revascularization rate, complication rate, bleeding rate and death rate of patients after treatment.

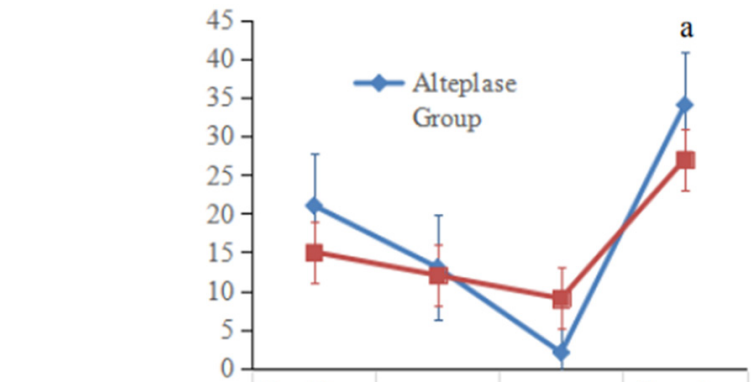
Statistical analysis

SPSS 18.0 software was used for statistical analysis. The enumeration data were represented by n (%) in χ^2 test and the measurement data were represented by ($\bar{x} \pm s$) in *t* test. $P<0.05$ meant that the difference had statistical significance.

Results

Comparison of short-term curative effect rate between the two groups

The short-term curative effect rate of the AG was 94.44% after the intervention with al-



	Significant Effect	Better	Invalid	Curative Rate
Alteplase Group	21	13	2	34
Control Group	15	12	9	27

Figure 1. Comparison of clinical effect between the two groups. Compared with the control group, [a]P<0.05.

teplase, which was higher than 75.00% of the UG (χ^2=6.391, P=0.025), as shown in **Figure 1**.

Comparison of coagulation function between the two groups

Before treatment, there was no statistical significance in CF between the two groups (P>0.05). After treatment, the PT and APTT of CF were respectively (11.58 ± 0.92) s and (28.98 ± 2.21) s in the AG, which were longer than (10.63 ± 0.83) s and (25.93 ± 2.18) s in the UG (P<0.05). The FIB level and PLT level of CF were respectively (2.34 ± 0.47) g/L and (168.24 ± 12.32)×10^9/L in the AG, which were lower than (3.34 ± 0.51) g/L and (253.94 ± 21.31)×10^9/L in the UG (P<0.05), as shown in **Table 2**.

Comparison of ADL between the two groups

The NIHSS scores of the AG and UG were respectively (13.25 ± 3.52 and 23.29 ± 3.56) after treatment, which were lower than (32.58 ± 3.41 and 32.60 ± 3.73) before treatment (P<0.05). The ADL scores of the AG and UG were respectively (87.46 ± 6.84 and 74.51 ± 5.67) after treatment, which were higher than (68.93 ± 3.59 and 68.96 ± 3.64) before treatment (P<0.05). After treatment, the NIHSS scores of the AG were (13.25 ± 3.52), which were lower than (23.29 ± 3.56) of the UG (P<0.05); and the ADL scores of the AG were (87.46 ± 6.84), which were higher than (74.51 ± 5.67) of the UG (P<0.05), as shown in **Figure 2**.

Comparison of IF and MMP-9 levels between the two groups

Before treatment, there was no statistical significance in IF and MMP-9 levels between two groups (P>0.05). The hs-CRP level, NT-pro-BNP level and IL-6 level of IF in two groups were respectively (60.32 ± 4.59 and 89.41 ± 5.77) ng/L, (155.32 ± 15.31 and 325.19 ± 17.84) umol/L and (132.49 ± 7.83 and 194.35 ± 8.91) pg/mL after treatment; which were lower than those before treatment (P<0.05). After treatment, MMP-9 levels were (146.43 ± 12.19) pg/mL in the AG and (114.39 ± 8.54) pg/mL in the UG, which were higher than those of (80.49 ± 5.71) pg/mL and (81.53 ± 5.78) pg/mL respectively before treatment. After treatment, the hs-CRP level, NT-pro-BNP level and IL-6 level of IF were respectively (60.32 ± 4.59) ng/L, (155.32 ± 15.31) umol/L and (132.49 ± 7.83) pg/mL in the AG, which were lower than (89.41 ± 5.77) ng/L, (325.19 ± 17.84) umol/L and (194.35 ± 8.91) pg/mL in the UG (P<0.05); After treatment, MMP-9 lever in the AG was (146.43 ± 12.19) pg/mL, higher than that of (114.39 ± 8.54) pg/mL in the UG (P<0.05), as shown in **Table 3**.

Comparison of treatment & prognosis between the two groups

The two groups were followed up for 3 months. The revascularization rate of the AG was higher than that of the UG after treatment (P<0.05); and the complication rate, bleeding rate and death rate of the AG were lower than those of the UG 3 months after treatment (P<0.05), as shown in **Figure 3**.

Discussion

ACI, is a common CVD found in clinical practice, and it tends to occur in the elderly. With the increasing aging of the population in China, the incidence of diseases is on the rise, which affects peoples quality of life [2]. According to clinical research, ACI is mainly caused by cholesterol precipitation and fatty degeneration in the deep layers of endarterium, which leads to

Table 2. Comparison of coagulation function between the two groups ($\bar{x} \pm s$)

Group		PT (s)	APTT (s)	FIB (g/L)	PLT (×10^9/L)
AG (n=36)	Before treatment	9.61 ± 0.83	24.31 ± 0.36	3.41 ± 0.53	323.41 ± 23.51
	After treatment	11.58 ± 0.92[a,b]	28.98 ± 2.21[a,b]	2.34 ± 0.47[a,b]	168.24 ± 12.32[a,b]
UG (n=36)	Before treatment	9.60 ± 0.82	24.03 ± 2.11	3.42 ± 0.72	323.44 ± 23.56
	After treatment	10.63 ± 0.83[b]	25.93 ± 2.18[b]	3.34 ± 0.51[b]	253.94 ± 21.31[b]

[a]*P*<0.05 refers to the comparison with UG; and [b]*P*<0.05 refers to the comparison with that before treatment.

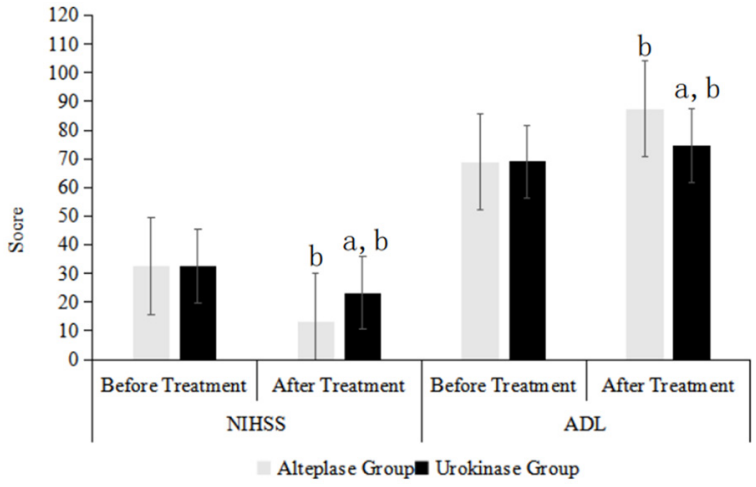


Figure 2. Comparison of ADL between the two groups. Compared with control group, [a]*P*<0.05; compared with before treatment, [b]*P*<0.05.

atherosclerotic plaque in the arteries and thus causes the proliferation of fibrous tissues. The rupture of an atherosclerotic plaque will cause platelet aggregation and thus lead to the stenosis and occlusion of the artery and blood vessels and the occurrence of cerebral infarction (CI). At the same time, the continuous stress response (CSR) after CI will lead to hypoxia and ischemic necrosis of the infarct sites and thus increase the clinical death rate [7]. Currently, the clinical treatment of CI mainly aims to stabilize the disease state and delay the progression of disease so as to reduce the clinical death rate and improve the prognosis as much as possible. Foreign scholars indicated that the oral administration of bayaspirin and other antiplatelet drugs could reduce the incidence of CVD, but the drug effect was poor and the clinical death rate was high [14].

TT is the most effective method for treatment of ACI. With the continuous development of medical technologies, intravenous thrombolysis, and arterial thrombolysis, drugs combined with ultrasonic thrombolysis and mechanical thrombectomy have been formed, but all of these methods are developing slowly [15]. Urokinase, as a traditional thrombolytic drug, is extracted from urine and kidney tissues. It has a good thrombolytic effect and can affect the fibrinolytic system of human body. Foreign scholars indicated that the application of urokinase to ACI patients played a good role in newly formed thrombus. It could enhance the ADP activity of blood vessels, inhibit the platelet aggregation mediated by ADP and prevent thrombogenesis [16]. However, there is a high incidence of side effects in clinical application of urokinase, which can easily increase the incidence of such complications as intracranial bleeding and reocclusion after thrombolysis. So there is a controversy about its clinical application. In recent years, TT with alteplase has been used in ACI patients and achieved an ideal effect. In this study, the short-term curative effect rate of the AG was 94.44% after intervention with alteplase, which was higher than 75.00% of the UG (χ^2=6.391, P=0.025), which implied that TT with alteplase could achieve a good short-term curative effect and is conducive to the recovery of patients. Alteplase, is the second generation of thrombolytic drugs, and is mainly composed of glycoprotein, including 526 amino acids in total. It has been widely used in acute myocardial infarction, acute ischemic stroke and other vascular diseases. According to modern pharmacological results [17], alteplase can combine with fibrous protein through lysine residues, activate the plasminogen combined with fibrous protein to become plasmin and activate the plasminogen selectively. Besides, the drug does not lead to bleeding complications that are usually

Table 3. Comparison of IF level between the two groups ($\bar{x} \pm s$)

Group		hs-CRP (ng/L)	NT-pro-BNP (umol/L)	IL-6 (pg/mL)	MMP-9
AG (n=36)	Before treatment	103.29 ± 6.71	425.84 ± 23.19	216.98 ± 10.29	80.49 ± 5.71
	15 d after treatment	60.32 ± 4.59[a,b]	155.32 ± 15.31[a,b]	132.49 ± 7.83[a,b]	146.43 ± 12.19[a,b]
UG (n=36)	Before treatment	102.31 ± 6.70	423.41 ± 22.85	215.62 ± 10.16	81.53 ± 5.78
	15 d after treatment	89.41 ± 5.77[b]	325.19 ± 17.84[b]	194.35 ± 8.91[b]	114.39 ± 8.54[b]

[a]*P*<0.05 refers to the comparison with UG; and [b]*P*<0.05 refers to the comparison with that before treatment.

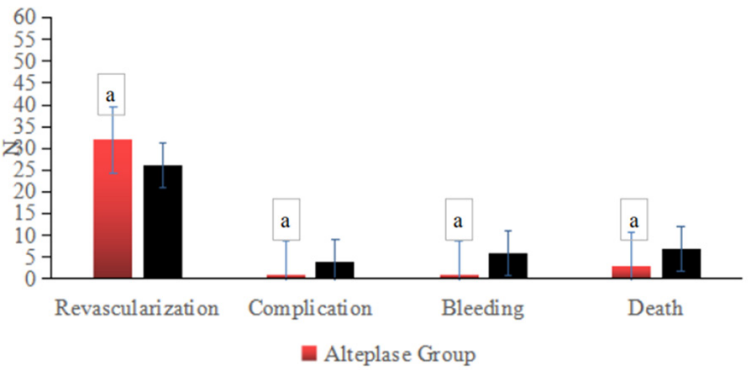


Figure 3. Comparison of treatment and prognosis between the two groups. Compared with the control group, [a]P<0.05.

caused by urokinase and thus plays a role in revascularization in ACI. As shown in kinetic studies [18], alteplase can be eliminated in the blood after intravenous injection. Half of the drug will be eliminated in the blood 5 min after medication and only 20.0% of the drug will be left 10 min after medication administration. Through liver metabolism, the drug can achieve a good therapeutic effect. In this study, PT and APTT of CF in the AG were longer than those in the UG after treatment (P<0.05); PIB level and PLT level of CF in the AG were lower than those in the UG after treatment (P<0.05); the NIHSS scores after treatment were lower than those before treatment in two groups (P<0.05); the ADL scores after treatment were higher than those before treatment in two groups (P<0.05); the NIHSS scores of the AG were lower than those of the UG after treatment (P<0.05); and the ADL scores of the AG were higher than those of the UG after treatment (P<0.05). This implied that the application of alteplase to ACI patients could improve the coagulation function, relieve the nerve defects and enhance the patients living ability.

Foreign research showed [19] that atherosclerosis was the main pathological basis of CI. With the deeper understanding of CI in clinical practice, it is thought that the immunological inflammatory response mediated by IF is the major factor of atherosclerosis, which can cause injury to the vascular endothelial cells, form foam cells, lead to the migration and infiltration of monocytes, macrophagocytes and other inflammatory cells, and thus release more IF and cause a cascade reaction. Clinical research showed [20] that IF participated in the formation, stabilization and ulceration of atherosclerotic plaque. hs-CRP is an acute-phase protein synthesized by hepatocytes when the body is invaded by a microorganism or suffers from tissue damage and other inflammatory stimuli. Besides, the CRP level will be increased within several hours after inflammation and reach the peak value within 48 h. It was found in clinical research that hs-CRP was a key factor to mediate the inflammatory response (IR) of ACI and with its non-specificity it can be used as a predictive index for treatment and prognosis. Foreign scholars found [21] that hs-CRP, as an independent risk factor, had a high expression in ACI patients. The increase of its expression level was positively correlative with the incidence of ischemic stroke and its expression level not only predicted the formation of CVD, but also reflected the treatment and prognosis of patients. hs-CRP, as a marker of IR, can reflect the intensity of IR. The intensification of its expression level measurement can evaluate the prognosis of patients and provide guidance for clinical treatment. NT-pro-BNP is a precursor protein secreted by the left atrium. The reduction of cardiac function can cause congestion in the left atrium and an increase of pressure, which will stimulate and promote the levels of NT-pro-BNP in the blood and thus

increase the level of NT-pro-BNP in serum [22]. NT-pro-BNP has a low expression in the healthy human body, but the CSR in ACI patients will increase the expression level of NT-pro-BNP and thus aggravate the occurrence and development of disease. IL-6 is a cytokine mainly generated by fibroblast, monocytes/macrophagocytes, T lymphocyte and epithelial cells, etc. It can stimulate and participate in the immune response and enhance its functions of proliferation and differentiation [23]. As found in foreign research [24], IL-6 could react with IL-1 to play a synergistic role and promote the T cell proliferation. In addition, it could also react with IL-3 to stimulate and synergize multipotential myeloid stem cells, promote B cell differentiation and take the effect of IR. hs-CRP, NT-pro-BNP and IL-6 will have a low expression level or will be in a dynamic balancing state in the healthy individual, but the CSR in ACI patients will increase the expression level of them and thus aggravate the occurrence and development of disease. Clinical studies have shown that the blood-brain barrier plays an important role in the secondary injury process after acute cerebral infarction. Damage of the vascular barrier can increase the inflammatory response of nerves, leading to brain edema. Studies by foreign scholars showed that abnormal MMP-9 level was accompanied by blood brain barrier damage. To a large extent, MMP-9 belongs to a member of matrix metalloproteinase families, with a dynamic balance of degradation and remodeling of the extracellular matrix. At the same time, MMP-9 can decompose the structural complexes in the respiratory tract and lung, directly participate in the reconstruction of the respiratory tract and lung, regulate the activity of other proteases and cytokines, protect the elasticity of neutrophils, and enhance the activity of collagen cells in collagen colloid, thus regulating the decomposition of MMP-9 from interleukin-8. MMP-9 is in a state of dynamic balance in the normal human body, but in patients with ACI, it will decrease, exacerbating the occurrence and development of the disease. Clinically, the IF level can be reduced and MMP-9 can be increased if ACI patients are treated with alteplase through TT, which will control the progression of disease and achieve a favorable treatment and prognosis [25]. In this study, the levels of hs-CRP, NT-pro-BNP and IL-6 in the AG were lower than those in the UG after treatment ($P<0.05$); the level of MMP-9 in the AG was higher than that in the UG after treatment ($P<0.05$); the revascularization rate of the AG was higher than that of the UG after treatment ($P<0.05$); and the complication rate, bleeding rate and death rate of the AG were lower than those of the UG 3 months after treatment ($P<0.05$). This implied that alteplase could reduce the IF level of ACI patients and achieve a favorable treatment and prognosis. According to foreign studies [26], the pathogenesis of ACI is very complicated and the change of disease state is rapid, so relevant examinations are performed to evaluate the physical condition of patients before they are treated with alteplase. In the course of treatment, the monitoring of vital signs are important, the anticoagulant and antithrombotic therapies are performed for the intervention in underlying disease to achieve better treatment.

In conclusion, the application of alteplase to ACI patients can achieve a better short-term curative effect, which is conducive to improving coagulation function, enhancing ADL, reducing IF level and obtaining favorable treatment and prognosis, so it is worthy of promotion and application.

Disclosure of conflict of interest

None.

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