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Mechanism of edaravone combined with urinary kallidinogenase for acute cerebral infarction patients

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ABSTRACT

Objective: To observe the effects of edaravone combined with urinary kallidinogenase on serum ox-LDL, PCT, hs-CRP, TNF-α and T cell subsets in patients with acute cerebral infarction, so as to explore the mechanisms of combination therapy on patients with acute cerebral infarction. **Methods:** 86 cases of patients with acute cerebral infarction in our hospital from March 2014 to May 2016 were randomly divided into two groups: control group and observation group, 43 cases in each group. All patients were given general treatment according to their own specific conditions, including hypoglycemic, pressure adjustment, prevention and treatment of complications, symptomatic support therapy, etc. The control group were given 30 mg Edaravone Injection on this basis with once per day for 14 d; The observation group was treated with 0. 15 PNA urinary kallidinogenase intravenous drip with once per day for 14 d on the basis of the control group. The levels of serum x-LDL, PCT, hs-CRP, TNF-α and $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ were detected and compared between the two groups. **Results:** (1) Before treatment, there was no significant difference between the two groups on the levels of serum ox-LDL, PCT, hs-CRP, and TNF-α; after treatment, the serum levels of ox-LDL, PCT, hs-CRP and TNF-α in the two groups were significantly lower than that before treatment, and the difference was significant (P<0.05); (2) Before treatment, there was no significant difference between the two groups on the levels of serum $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$; after treatment, the serum levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were significantly increased in the two groups, and the level of $CD8^+$ was significantly decreased compared with the same group before treatment, and the difference was significant (P<0.05); and the levels of serum $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ in the observation group were significantly better than those in the control group, and the difference was significant (P<0.05). **Conclusions:** The treatment of combined application of urinary kallidinogenase and edaravone in patients with acute cerebral infarction, can significantly improve the serum levels of ox-LDL, PCT, hs-CRP, TNF-α and T cell subsets, further illustrates the synergistic effect of the combination, also shows that the two drugs for acute cerebral infarction can inhibit thrombosis to expand, reduce inflammation, relieve cerebral tissue damage, and improve neurological function.

1. Introduction

Acute cerebral infarction is a common clinical disease, and brain blood supply in patients with sudden interruption will result in brain tissue necrosis. The cause of most patients is cerebral blood supply artery atherosclerosis or thrombosis, resulting in luminal stenosis or occlusion caused by focal cerebral ischemia and morbidity, and few patientsare due to foreign bodies, including solid, gas into the cerebralartery or carotid artery, resulting in disruption of the blood supply or blood flow to the brain, then damaging the corresponding region of the brain. Acute cerebral infarction has the characteristics of high mortality and disability rate, which is a serious threat to the quality of life of patients[1,2]. In the clinical treatment, the disease is mainly to thrombolysis, against platelet aggregation, improve blood circulation and protect, and repair the nerve. Edaravone and urinary kallidinogenase are a new type of drugs listed in recent years, and

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they have the function of scavenging free radicals, expanding the cerebral blood vessels and so on, which areused for the clinical treatment of acute cerebral infarction[3]. This study was to observe the effects of edaravone combined with urinary kallidinogenase on serum ox-LDL, PCT, hs-CRP, TNF-α and T cell subsets in patients with acute cerebral infarction.

2. Materials and methods

2.1. General information

86 cases of patients with acute cerebral infarction in our hospital from March 2014 to May 2016 were randomly divided into two groups: control group and observation group, 43 cases in each group. In the control group, 22 cases were male, 21 were female, the age was 49–79 years old; Infarction site: 18 cases of thalamus, 9 cases of unilateral frontotemporal, 3 cases of brain stem, 4 cases of unilateral temporal parietal lobe, 9 cases of internal capsule; NIHSS score was (23.4±5.1). In the observation group, 24 cases were male, 19 cases were female, the age was 52–80 years old. Infarction site: 20 cases of thalamus, 7 cases of unilateral frontotemporal, 4 cases of brain stem, 3 cases of unilateral temporal parietal lobe, 9 cases of internal capsule; NIHSS score was (24.2±6.3). The general data of the two groups were analyzed by statistical comparison method, and the results showed no significant difference (P>0.05).

2.2. Inclusion criteria

(1) criteria for the diagnosis of acute myocardial infarction by clinical examination with all patients, and the incidence was in 72 h; (2) the drug was well tolerated and no contraindication of the drugs; (3) agree with this treatment method and intent and signed the informed consent form.

2.3. Exclusion criteria

(1) Patients with heart, liver, kidney and other important organs of severe functional damage; (2) complicated with myocardial infarction, diabetes, severe infection, autoimmune diseases, tumor and other diseases; (3) recently taking other drugs that may affect the results of the treatment process; (4) Patients which replace or add drug by themselves during treatment.

2.4. Treatment methods

All patients were given general treatment according to their own specific conditions, including hypoglycemic, pressure adjustment, prevention and treatment of complications, symptomatic support therapy, etc. The control group were given 30 mg Edaravone Injection on this basis with once per day for 14 d; The observation group was treated with 0. 15 PNA urinary kallidinogenase intravenous drip with once per day for 14 d on the basis of the control group.

2.5. Observation index

The change of serum levels of ox-LDL, PCT, hs-CRP, TNF-α and T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$) were detected and compared between the two groups before and after treatment.

2.6. Statistical analysis

We used SPSS17. 0 software package to process the test result data, mean ± standard deviation ($\bar{x}\pm s$) represents measurement data, the use of t test was to compare the difference between groups, and χ^2 test analysis the groups' count data, with P<0.05 as a statistically significant.

3. Results

3.1. Serum levels of ox-LDL, PCT, hs-CRP, and TNF-α

Before treatment, the levels of serum ox-LDL, PCT, hs-CRP, and TNF-α were not significantly different between the two groups (P>0.05). After treatment, the levels of serum ox-LDL, PCT, hs-CRP, and TNF-α in the control group and observation group changed significantly, compared with that before treatment in the same group (P<0.05), and the levels of serum ox-LDL, PCT, hs-CRP, and TNF-α in the observation group were significantly better than those in the control group (P<0.05) (Table 1).

3.2. The level of serum T cell subsets

Before treatment, the levels of serum $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ were not significant different between the two groups (P>0.05). After treatment, the levels of serum $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ in the control group and observation group changed significantly, compared with the same group before treatment (P<0.05), and the levels of serum $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ in the observation group were significantly better than those in

Table 1

Comparison of serum ox-LDL, PCT, hs-CRP, and TNF-α levels before and after treatment in two groups (n=50, $\bar{x}\pm s$).

Group	Time	ox-LDL (μg/L)	PCT (ng/mL)	hs-CRP (mg/L)	TNF-α (μg/L)
Control group	Before treatment	139.55±28.62	1.04±0.18	29.22±13.77	18.34±7.43
	After treatment	114.96±88.71*	0.77±0.15*	16.27±2.64*	11.31±3.58*
Observation group	Before treatment	141.23±26.84	1.10±0.19	28.92±14.10	17.92±6.74
group	After treatment	99.17±62.53$^{*\#}$	0.56±0.13$^{*\#}$	9.56±2.11$^{*\#}$	7.95±2.63$^{*\#}$

Compared with before treatment, $^*P$<0.05; compared with the control group after treatment, $^\#P$<0.05.

the control group (P<0.05) (Table 2).

4. Discussion

After the occurrence of acute cerebral infarction, infarction area blood and oxygen supply is seriously insufficient, resulting in metabolic acidosis, and produce oxygen, hydroxyl and superoxide anion free radicals, induce neuronal cell death, damage the normal function of the brain organ. Modern studies suggest that the stenosis or occlusion of the vascular lumen caused by thrombosis in patients with cerebral infarction is the main cause of cerebral infarction. Therefore, in the course of treatment, the first consideration should be given to the infarct area to improve blood circulation and nerve function recovery, thereby blocking the ischemic brain injury, restoring tissue perfusion, reducing ischemia-reperfusion injury and protecting the ischemic penumbra[4,5].

Urinary kallidinogenase is a proteolytic enzyme, extracted from human urine and refined, and it has the function of transforming the stimulating peptide into the action of stimulating peptide and blood vessel. It can also selectively dilate blood vessel, improve blood perfusion and promote blood vessel regeneration. Research shows that urinary kallidinogenase also can inhibit platelet aggregation in diastolic artery at the same time, and also has the function of cell deformation strengthening effect. In addition, after urinary kallidinogenase intravenous injection, the body can increase blood flow to the brain, reduce infarct expansion, improve brain tissue for glucose and oxygen uptake capacity and glucose metabolism, and the spontaneous cortical EEG abnormalities also have improved effect, thus promoting nerve repair[6-8]. Edaravone is free radical scavenger, with hydroxyl radical scavenging and antioxidant effect, and for patients with cerebral infarction, timely and effectively remove free radicals can significantly reduce brain damage. Edaravone can significantly inhibit xanthine oxidase and xanthine oxidase activity, can also generate hormone induced prostacyclin, reduce inflammatory mediators, eliminate or reduce the concentration of free radicals, prevent damage to vascular endothelial cells, inhibit ischemic brain edema and improve neurological function[9,10].

Ox-LDL is a low density lipoprotein oxidation, when the base content is too high, the accumulation of its own cholesterol will in the artery wall, long time will cause atherosclerosis, while atherosclerosis is the main cause of acute cerebral infarction. Studies have shown that ox-LDL causes the body's inflammatory response by transforming monocytes into macrophages, and has inhibitory effect on macrophage free, make it accumulate in area of arteriosclerosis, allows the endothelial cells to release TNF-α, interleukin, and other cytokines under the effect of ox-LDL, then resulting in vascular plaque rupture, and even leading to vascular spasm, accelerating the development of the disease[11-13]. In addition, ox-LDL can also accelerate platelet adhesion, aggregation, thrombosis. In this study, the difference was significant when compared with the control group by using the method of edaravone combined with urinary kallidinogenase in treatment of acute cerebral infarction (P<0.05), which confirmed that it has the effect of anti-oxidative stress reaction in acute stage of cerebral infarction.

PCT is a reactive protein, when the body's own immune system appears pathological changes or virus infection, its level often had no change; But when it is subjected to more severe bacterial and fungal infections, severe shock, systemic inflammatory response syndrome or significant organ dysfunction or disorder, its level was significantly increased, So detecting the level of PCT can reflect the inflammation degree, which can be used to monitor clinical infection in critically ill patients that need special care or greater risk (detection of infected cells or systemic effects of septic complications)[14-16]. hs-CRP is a common clinical index, the inflammatory reaction of the body has a certain monitoring value, after acute cerebral infarction, a large amount of hs-CRP was synthesized, and through the classical pathway of complement activation and consumption after the release of inflammatory mediators, expression of adhesion molecules induced by vascular endothelial cells, inflammatory reaction occurs, the occurrence and development process in the patients with acute cerebral infarction[17]. TNF-α is an alpha produced by macrophages and monocyte proinflammatory cytokines, it is involved in normal human inflammatory reaction and immune response. When the human body is in the pathological state of sepsis, malignant tumor, heart failure, chronic inflammatory disease, its level is obviously increased. The study found that, after the occurrence of cerebral infarction, it can be involved in a variety of ways to participate in brain injury. The level of serum TNF-α is increased, which will produce oxygen free radicals, which can cause neurotoxicity and aggravate oxidative damage; And the increase of TNF-α can induce inflammatory cells to the nerve tissue migration, resulting in acute inflammatory response, but also contributed to the coagulation and blood vessels, thereby increasing the risk of cerebral infarction and ischemic brain damage[18,19]. In this study, the serum PCT, hs-CRP, and TNF-α levels have reduced more obviously when compared with the control group after treated by edaravone combined with urinary kallidinogenase, and the difference was significant (P<0.05). This suggests that combined medication can optimize the level of serum PCT, hs-CRP and TNF-α in the patients, and reduce the level of the cascade reaction, and researches show that there is a certain degree of correlation between inflammatory factor and cerebral

Table 2

Comparison of serum T cell subsets before and after treatment in two groups (n=50, $\bar{x}\pm s$).

Group	Time	$CD3^+$ (%)	$CD4^+$ (%)	$CD8^+$ (%)	$CD4^+/CD8^+$
Control group	Before treatment	51.97±8.68	29.01±3.12	37.95±2.97	0.76±0.14
	After treatment	55.71±6.14*	33.12±3.44*	34.21±3.02*	0.98±0.18*
Observation group	Before treatment	51.86±7.92	28.92±2.75	37.73±2.65	0.76±0.15
group	After treatment	58.23±5.17*#	36.25±4.89*#	31.17±4.25*#	1.17±0.26*#

Compared with before treatment, *P<0.05; compared with the control group after treatment, #P<0.05.

infarction, Therefore, the effective reduction of those levels can optimize the inflammatory environment after the nerve cell damage, and it also has certain promotion effect on clinical rehabilitation.

T cells in the body's blood are the important components of the immune system, participate in the immune response, and are also the factors regulating humoral immune response. $CD3^+$ is a common sign of all T cells, $CD4^+$ and $CD8^+$ are two different function of peripheral T lymphocyte subsets and regulatory role in the immune response, mutual induction, mutual restriction, which plays an important role in regulating and maintaining immune cell network stability, to avoid reactions on the body caused by injury[20]. When the number of T lymphocyte subsets is abnormal, the immune disorder often occurs, which causes the disease. In recent years, the study found that after the occurrence of acute cerebral infarction, brain tissue and blood brain barrier damage will lead to immune system disorders. The presence of $CD4^+$ in atherosclerotic plaques can induce the production of antibodies, While $CD8^+$ has cytotoxicity in the early stage of atherosclerosis, with injury, complement activation, and may do damage to vascular endothelial cells and increase its permeability, and can activate the complement components for fixed factor arteriosclerosis. Therefore, $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ abnormalities reflect the immune status of the body, timely and effective regulation of immune status can reduce the incidence of cerebral infarction complicated with symptoms[21–23]. In this study, the scrum $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ levels of acute cerebral infarction patients has a better improvement after the application of edaravone combined with urinary kallidinogenase.

In conclusion, the treatment of combined application of urinary kallidinogenase and edaravone in patients with acute cerebral infarction, can significantly improve the serum levels of ox-LDL, PCT, hs-CRP, TNF-α and T cell subsets, further illustrates the synergistic effect of the combination, also shows that the two drugs for acute cerebral infarction can inhibit thrombosis to expand, reduce inflammation, relieve cerebral tissue damage, improve neurological function.

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