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Effects of intravenous thrombolysis with alteplase combined with edaravone on cerebral hemodynamics and T lymphocyte level in patients with acute cerebral infarction

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Abstract

Our study aimed to investigate the effect of intravenous thrombolysis with alteplase and edaravone on cerebral hemodynamics and T lymphocyte level in patients harboring acute cerebral infarction.

There involved a total of 118 patients with acute cerebral infarction from November 2017 to May 2019 in our hospital were randomly divided into 2 groups: the observation group (59 patients were treated with intravenous thrombolysis with alteplase combined with edaravone) and the control group (59 patients were treated with intravenous thrombolysis of alteplase). The clinical effect, neurological function, cerebral hemodynamic index, T lymphocyte level, oxygen free radical scavenging level and oxidative stress index of the 2 groups were observed and compared.

Before the treatment, there were no significant differences in neurological function, cerebral hemodynamic indexes, T-lymphocyte level, oxygen free radical scavenging level and oxidative stress indexes between the 2 groups ($P > .05$). After the treatment, the neurological function, cerebral hemodynamic indexes, T-lymphocyte level, oxygen free radical scavenging level and oxidative stress indexes of the 2 groups were significantly improved. In addition, the observation group exerted greater beneficial effect in terms of the clinical effect, neurologic function, cerebral hemodynamic index, T lymphocyte level, oxygen free radical scavenging level and oxidative stress index than those of the control group ($P < .05$).

The intravenous thrombolysis with alteplase and edaravone is effective in the treatment of acute cerebral infarction, which also provides better results in terms of improving the clinical efficacy and prognosis of patients and might be an alternative option for clinical practice.

Abbreviations: AOPP = advanced oxidation protein products, CT = computed tomography, DSA = digital substraction angiography, LPO = lipid peroxidation, MDA = malonaldehyde, MRI = magnetic resonance imaging, NIHSS = national institute of health stroke scale, NO = nitric oxide, OH = hydroxyl, SOD = superoxide dismutase.

Keywords: acute cerebral infarction, cerebral hemodynamic indexes, edaravone, intravenous thrombolysis with alteplase

1. Introduction

Acute cerebral infarction is a common ischemic cerebrovascular condition in neurology, with incidence accounting for about 70% of all stroke diseases. It occurs due to a serious of factors that local brain tissue has blood supply disorder, resulting in brain tissue necrosis and develop rapidly within hours or days after the occurrence of the disease. Some of the patients will be accompanied by different degrees of consciousness disorder. If the lesions involve cerebellum, brain stem and other positions, the patients can be accompanied by serious consciousness disorder, induce brain hernia and sequelae, which have a serious impact on the quality of life and mental health of patients.[1,2] At present, drugs, arterial thrombectomy and intravenous thrombolysis are often used in clinical treatment,[3] among which drug therapy is mainly for patients who miss the window of thrombolysis treatment. Arterial thrombectomy needs to be supported by digital substraction angiography (DSA) and other equipment, which is difficult to operate and requires a long time for doctors. Intravenous thrombolysis can effectively restore cerebral blood flow perfusion of patients with thrombolysis indications and save ischemic brain tissue.[4] However, single intravenous thrombolytic drugs can not completely improve the clinical symptoms of patients, which is not conducive to the prognosis of patients. Hence, it has important clinical value and significance to choose an available and valid treatment option to improve the treatment effect of patients. The inflammatory role of T lymphocytes cells following stroke has been well documented. It plays an important role in propagating the pro-inflammatory cycle following stroke.[5] Furthermore, it has been reported that higher

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The authors declare no conflicts of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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percentages of T lymphocytes were independently associated with poorer outcomes.[6] Thus, it can be an indicator for clinical prognosis. Focus has been laid in this study with an attempt to explore the effect of intravenous thrombolysis with alteplase and edaravone on cerebral hemodynamics and T-lymphocyte level in patients harboring acute cerebral infarction.

2. Materials and methods

2.1. Participants

A total of 118 patients with acute cerebral infarction admitted to our hospital from November 2017 to May 2019 were randomly divided into the observation group and the control group of 59 cases each. In the observation group, there were 40 males and 19 females, aged 28 to 74 years old, with an average age of (54.87 ± 7.82) years; the course of disease was 1 to 4 hours, with an average time of (2.13 ± 0.19) hours; the infarct range was (6.18 ± 1.46) cm^3. The infarct site included cerebellum in 4 cases, brain stem in 7 cases, lobes in 17 cases, basal ganglia in 31 cases. Complications: 11 cases with hyperlipidemia, 13 with type 2 diabetes, 12 with heart disease and 22 with hypertension. Control group included 41 males and 18 females, aged 27 to 73 years old, with a mean age of (54.08 ± 8.06) years old; course of disease was 1 to 4 hours, with mean time of (2.09 ± 0.21) hours; infarct range was (6.16 ± 1.51) cm^3. The infarct site included cerebellum in 3 cases, brainstem in 6 cases, lobus in 18 cases, basal ganglia in 32 cases. Complications: 10 patients with hyperlipidemia, 12 with type 2 diabetes, 12 with heart disease and 25 with hypertension. Patients should meet the following inclusion criteria:

1. all patients met the diagnostic criteria of Chinese guidelines for the diagnosis and treatment of acute ischemic stroke;
2. patients were diagnosed by computed tomography (CT) and magnetic resonance imaging (MRI);
3. patients occurred the condition with conscious for the first time, onset time ≤4.5 hours;
4. patients with normal thinking and normal language communication ability;
5. patients with national institute of health stroke scale (NIHSS) neurological deficit score ≥4 points;
6. this study was approved by the hospital theoretical Committee and agreed by the patients.

Exclusion criteria were as follows:

1. patients were allergic to the drugs used in this study;
2. patients with previous intracranial hemorrhage;
3. patients with cerebral hemorrhage and large-area imaging cerebral infarction characteristics;
4. patients with serious infection, immune system and blood system diseases;
5. patients with serious injury to other important organs;
6. patients with history of cerebral hemorrhage;
7. patients with severe coma or mental disorder;
8. patients undergoing surgical treatment within 2 weeks.

There was no significant difference in age between the 2 groups ($P > .05$).

2.2. Treatment

Routine treatment: after admission, all patients were required to have bed rest, and the vital signs such as body temperature, heart rate, respiration, and blood pressure were closely monitored. For the patients with hypertension, diabetes, hyperlipidemia and other basic diseases or other complications, the etiology should be found with following symptomatic treatment such as reducing blood pressure, correcting water and electrolyte disorders, taking antibiotics, etc.

On the basis of the above treatment, the control group was given intravenous drip of alteplase (Trade Name: alteplase for injection (aitongli); specification: 50 mg; manufacturer: Boehringer Ingelheim Pharma GmbH & Co.KG; Standard No: s20110052). 0.9 mg/kg was dissolved into 100 ml normal saline, the maximum dose was not more than 90 mg; 10.00% of the total dose was injected within 1 minutes, and the remaining 90% within 1 hour. At the same time, aspirin enteric coated tablets were given orally (Trade Name: aspirin enteric coated tablets; specification: 100 mg * 30 second; manufacturer: Shenyang ojina Pharmaceutical Co., Ltd.; Standard No.: h20065051) once a day, 100 mg/d each time. Brain CT examination was performed 24 hours after the completion of thrombolysis.

On the basis of the abovementioned treatment, the observation group was given edaravone intravenous drip (Trade Name: Edaravone; specification: 20 ml: 30 mg × 1 piece/box; manufacturer: Hebei Medical University Pharmaceutical Factory; Standard No: h20090351) 30 mg dissolved into 100 ml physiological saline, intravenous drip twice a day for 10 days.

2.3. Observation indicators

The clinical effect, neurological function, cerebral hemodynamic index, T-lymphocyte level, oxidative stress index and oxygen free radical scavenging level of the 2 groups were observed and compared.

2.3.1. Clinical efficacy. The neurological function of all patients were assessed by Stroke Scale (NIHSS) before and after treatment, and the clinical symptoms were evaluated according to the current clinical condition and the improvement of NIHSS, including the following aspects:

1. ineffective: NIHSS defect symptoms and clinical symptoms such as vertigo and headache experienced no change or aggravation;
2. effective: NIHSS defect symptom score was reduced by 18% to 45%, vertigo, headache and other clinical symptoms were slightly reduced;
3. significantly effective: NIHSS defect symptom score was reduced by 46% to 90%, vertigo, headache and other clinical symptoms were obviously relieved;
4. cured: NIHSS defect symptom score was reduced by more than 90%, vertigo, headache and other clinical symptoms basically disappeared.

Total effective rate = cure rate + significantly effective rate + effective rate.

2.3.2. Neurological function. All patients were assessed with NIHSS before and after treatment. There were 11 items in total, including neglect, consciousness level, dysarthria, facial paralysis, etc., with the full score of 42 points. The higher the score, the more serious the neurological function defect was, the less effective the treatment was.

2.3.3. Cerebral hemodynamic indexes. All patients were measured by cerebrovascular hemodynamic monitor before

Table 1

Comparison of clinical efficacy between the 2 groups (%, n).

Group	Ineffective	Effective	Significantly effective	Cured	Cure rate
Observation group (n = 59)	2 (7.25)	17 (28.81)	21 (35.59)	19 (32.20)	57 (96.61)[b]
Control group (n = 59)	9 (15.25)	22 (37.29)	18 (30.51)	10 (16.95)	50 (84.75)

Compared with the control group; ([b]$P < .05$).

Table 2

Comparison of NIHSS scores between the 2 groups ($\overline{x} \pm s$).

Group	Before treatment	After treatment
Observation group (n = 59)	14.82 ± 1.46	7.08 ± 1.01^{ab}
Control group (n = 59)	14.91 ± 1.35	10.72 ± 1.42^{b}

Before treatment, compared with the same group ([a]$P < .05$); after treatment, compared with the control group ([b]$P < .05$).

and after treatment, including mean carotid blood flow (Q_{mean}), mean blood velocity (V_{mean}), peripheral resistance level and characteristic impedance.

2.3.4. T-lymphocyte level. Before and after treatment, 3 ml of fasting venous blood was taken from patients at 6:00 in the morning. After anticoagulation treatment, the proportion of CD4 +, CD8+ and the ratio of CD4+/CD8+ in peripheral blood T-lymphocyte subsets were measured by BD flow cytometry. The levels of lipid peroxidation (LPO), nitric oxide (NO), and hydroxyl (OH) oxygen free radical were measured by free radical test box, and the contents of advanced oxidation protein products (AOPP), superoxide dismutase (SOD) and malonaldehyde (MDA) were determined by enzyme-linked immunosorbent assay.

2.4. Statistical analysis

In this study, SPSS18.0 software was used to analyze the statistics. $\overline{x} \pm s$ and t test was used to represent the measurement data of neurological function and cerebral hemodynamic indexes. The clinical efficacy and other measurement data were expressed as number and percentage, and x^2 test or Fisher accurate test was used. $P < .05$ represented the significant statistical difference.

3. Results

3.1. Comparison of clinical effects between the 2 groups

The clinical effect of the observation group was better than that of the control group (96.61% vs 84.75%) ($P < .05$). See Table 1 for details.

3.2. Comparison of neurological function between the 2 groups

Before treatment, there was no significant difference in NIHSS scores between the 2 groups ($P > .05$); after treatment, NIHSS scores were significantly improved, and the NIHSS scores in the observation group were lower than those in the control group ($P < .05$). See Table 2 for details.

3.3. Comparison of cerebral hemodynamic indexes between the 2 groups

Before treatment, there was no significant difference in Q_{mean}, V_{mean}, peripheral resistance level and characteristic impedance between the 2 groups ($P < .05$); after treatment, the Q_{mean}, V_{mean}, peripheral resistance level and characteristic impedance in the 2 groups were improved, among which the Q_{mean}, V_{mean} and peripheral resistance level of in the observation group were higher than that in the control group, and the characteristic impedance was lower than that in the control group ($P < .05$). See Table 3 for details.

3.4. Comparison of T lymphocyte levels between the 2 groups

Before treatment, there was no significant difference in CD4 +, CD8 +, CD4 +/CD8 + between the 2 groups ($P < .05$); after treatment, CD4 +, CD8 +, CD4 +/CD8 + in the 2 groups were improved, among which CD4 +, CD4 +/CD8 + in the observation group were higher than that in the control group, and CD8 + was lower than that in the control group ($P < .05$). As laid out in Table 4.

3.5. Comparison of oxygen free radical levels and oxidative stress indexes between the 2 groups

Before treatment, there was no significant difference in LPO, NO, and OH between the 2 groups ($P < .05$); after treatment, there was improvement in LPO, NO, and OH in the 2 groups, among which LPO, NO, and OH in the observation group were higher than those in the control group ($P < .05$). Before treatment, no significant difference was observed in AOPP, SOD, and MDA

Table 3

Comparison of cerebral hemodynamic indexes between the 2 groups ($\overline{x} \pm s$).

Group	Time	Q_{mean} (cm^3/s)	V_{mean} (cm/s)	Peripheral resistance level (KPa·s)/m	Characteristic impedance (KPa·s)/m
Observation group (n = 59)	Before treatment	6.86 ± 1.23	12.58 ± 1.97	95.81 ± 3.08	16.51 ± 3.08
	After treatment	9.89 ± 2.07^{ab}	18.73 ± 2.63^{ab}	94.83 ± 4.16^{ab}	12.11 ± 3.78^{ab}
Control group (n = 59)	Before treatment	6.91 ± 1.17	12.72 ± 2.04	74.21 ± 3.93	16.47 ± 2.78
	After treatment	7.32 ± 1.22^{b}	15.26 ± 2.43^{b}	79.08 ± 4.73^{b}	14.83 ± 3.72^{b}

Before treatment, compared with the same group ([a]$P < .05$); after treatment, compared with the control group ([b]$P < .05$).

Table 4

Comparison of T lymphocyte levels between the 2 groups ($\bar{x} \pm s$).

Group	Time	CD4+ (%)	CD8+ (%)	CD4+/CD8+
Observation group (n = 59)	Before treatment	36.65 ± 2.71	23.58 ± 2.97	2.05 ± 0.38
	After treatment	40.89 ± 4.09[ab]	22.73 ± 3.03[ab]	2.31 ± 0.16[ab]
Control group (n = 59)	Before treatment	35.91 ± 1.17	24.02 ± 2.12	1.98 ± 0.41
	After treatment	37.32 ± 1.22[b]	23.65 ± 3.32[b]	2.16 ± 0.28[b]

Before treatment, compared with the same group ([a]$P < .05$); after treatment, compared with the control group ([b]$P < .05$).

between the 2 groups ($P < .05$); after treatment, AOPP, SOD, and MDA in the 2 groups were improved, among which AOPP, SOD, and MDA in the observation group were lower than those in the control group ($P < .05$). As shown in Table 5.

4. Discussion

In the present study, we found that patients with combined treatment of alteplase and edaravone showed better in clinical effect, neurologic function, cerebral hemodynamic index, T lymphocyte level, oxygen free radical scavenging level and oxidative stress index than those only with alteplase treatment. The intravenous thrombolysis with alteplase and edaravone is effective in the treatment of acute cerebral infarction.

Acute cerebral infarction is a life-threatening condition with high incidence, disability and mortality. Its main clinical manifestations are vertigo and hemiplegia. If early and effective intervention is not taken, the rapid progress of the disease will damage brain cells and nerve cells, resulting in the loss of part of the patients function and serious impact on the normal life of the patient.[7,8] Currently, there is no specific prevention and approach for acute cerebral infarction. According to Nito et al,[9] some patients with acute cerebral infarction will damage brain cells in the ischemic area due to long-term cerebral ischemia and hypoxia, resulting in the formation of a semi dark band, in serious cases, the brain cells will occur irreversible necrosis. The basic pathological basis of acute cerebral infarction is atherosclerosis.[10,11] The change of deep fat in the artery intima, sinking of cholesterol and formation of atherosclerotic plaques lead to cerebral ischemia and release of a large number of oxygen free radicals, and eventually apoptosis of neurons. However, early recovery of blood perfusion in the ischemic brain tissue area is conducive to the recovery of blood flow in the penumbra, so as to save or alleviate some reversible ischemic brain tissue. Therefore, the most important part in terms of the treatment of acute cerebral infarction is to dredge and block the blood vessels in time and effectively.

According to the aggregated results of the current study, after treatment, the NIHSS score, cerebral hemodynamic index and T-lymphocyte level of the 2 groups were improved, but the clinical efficacy, NIHSS score, cerebral hemodynamic index and T-lymphocyte level of the observation group elicited greater effect than those of the control group ($P < .05$), which was consistent with the results of Liu et al[12] and Lin et al.[13] They suggested that the patients with acute stroke who were treated with the intravenous thrombolysis with alteplase and edaravone gained significant effect, which effectively improved the neurological function of patients, help patients recover the indexes of cerebral hemodynamics, and restore the level of T-lymphocytes to normal. The following factors might contribute to the abovementioned results:

1. the advantages of intravenous thrombolysis in the treatment of acute stroke include simple and convenient operation with short time, little trauma and good treatment effect;
2. alteplase is a powerful thrombolytic agent, which is also the first gene recombinant thrombolytic drug, characterized by high specificity and long half-life. It can select and dissolve fibrin in thrombus to prevent systemic fibrinolysis and improve the blood circulation of the brain, accelerate the blood supply of the ischemic penumbra, reduce the area of the brain tissue in the ischemic area, and help the nerve cells and brain tissue to return to normal, but the effect of the drug alone on expanding the blood vessels in the brain is weak, and it is easy to appear insufficient vasodilation, so it needs to be combined with other drugs;
3. edaravone is a new type of oxygen free radical scavenger, which can protect the brain tissue and reduce the damage and prognosis and improve the perfusion pressure of the brain tissue.

In addition, it can prevent the recurrence of infarction in the low perfusion area, improve the survival rate of nerve cells in the ischemic area of the brain, reduce the injury area of the cerebral infarction, and strive for time for the recovery of blood supply of the injured brain tissue.

Table 5

Comparison of oxygen free radical levels and oxidative stress indexes between the 2 groups ($\bar{x} \pm s$).

	Observation group (n = 59)		Control group (n = 59)	
Group	Before treatment	After treatment	Before treatment	After treatment
Oxygen free radical levels				
PLO (%)	50.81 ± 3.47	5.32 ± 0.47[ab]	49.89 ± 4.08	15.32 ± 2.08[b]
NO (%)	38.98 ± 3.72	12.61 ± 2.07[ab]	37.68 ± 3.65	23.07 ± 3.12[b]
OH (nmol/ml))	112.95 ± 12.38	34.31 ± 4.16[ab]	111.98 ± 11.41	62.16 ± 9.28[b]
Oxidative stress indexes				
AOPP (u/ml)	113.87 ± 17.83	71.32 ± 8.72[ab]	112.87 ± 18.08	99.32 ± 9.08[b]
SOD (umol/ml)	178.98 ± 23.72	112.45 ± 16.74[ab]	177.68 ± 24.08	152.63 ± 18.92[b]
MDA (umol/ml)	9.56 ± 1.83	5.53 ± 0.82[ab]	9.48 ± 1.23	7.21 ± 0.92[b]

Before treatment, compared with the same group ([a]$P < .05$); after treatment, compared with the control group ([b]$P < .05$).

The common active oxygen free radicals in the body include OH, NO, and LPO, etc. These active oxygen free radicals will gradually increase with the degree of brain damage. When cerebral ischemia-reperfusion occurs during thrombolytic therapy, it is easy to lead to oxidative stress reaction, and excessive oxygen free radicals in the body will lead to lipid peroxidation. According to a recent study,[14] in the pathological process such as shock, NO reacts with superoxide free radicals, which causes nitrite to play an adverse role on human body, so it is an important means to remove excessive NO in the treatment of shock and other huge trauma. The results of this study showed that the level of oxygen free radicals in the observation group was lower than that in the control group ($P < .05$), indicating the level of oxygen free radicals in the observation group could be reduced by the treatment of acute cerebral infarction with intravenous thrombolysis of alteplase combined with edaravone.

AOPP is the product of serum albumin oxidized by free radicals, which belongs to protein crosslink containing double tyrosine. Its content is positively correlated with oxidative stress and oxygen free radical damage. Sod is a kind of antioxidant enzyme, which is able to scavenge oxygen free radicals in vivo and indirectly reflects the ability of scavenging oxygen free radicals. The ultimate product of LPO is MDA, whose content can directly reflect the production of oxygen free radicals in the body, and the loss is consistent with that of oxygen free radicals.[15] A study by Kikuchi et al.[16] has confirmed that the level of AOPP and other oxides changes with the oxidative stress response, and when the level increases, the oxidative stress response also increases. According to the study supported by Li et al,[17] the combination of edaravone and thrombolysis could reduce the oxidative stress response in patients with acute cerebral infarction. The results of this study showed that the oxidative stress response of the observation group was lower than that of the control group ($P < .05$), which was consistent with the results of previous studies. It indicated that the combination of intravenous thrombolysis with alteplase and edaravone could effectively reduce the oxidative stress response in the treatment of acute cerebral infarction, which was highly associated with the effect of edaravone in terms of scavenging of oxygen free radicals and the inhibition of lipid oxidative stress. However, considering the limited sample size and short observation time, we recommend further comprehensive multi-center studies with larger sample size and longer follow-ups are needed to explore the safety and long-term effect of the drug.

In conclusion, the combination of intravenous thrombolysis with alteplase and edaravone elicited great therapeutic effect in terms of treating patients with acute cerebral infarction. It is able to effectively restore the neurological function and beneficial to the rehabilitation of patients, which might be a valid and alternative option for clinical practice.

Author contributions

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