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Effect of edaravone combined with nimodipine on oxidative stress, inflammatory factors in patients with craniocerebral injury

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ABSTRACT

Objective: To observe the effect of edaravone combined with nimodipine on oxidative stress, inflammatory factors in patients with craniocerebral injury. **Methods:** A total of 126 patients with craniocerebral injury were randomly divided into the observation group (66 cases) and the control group (60 cases). The control group was given nimodipine based on conventional therapy, and the observation was given edaravone based on the control group. For 14 days, the changes of oxidative stress indicators (SOD, MPO, MDA) and inflammatory factors (CRP, TNF- α , IL-8) between the two groups were observed. **Results:** There was significantly difference in SOD, MPO, MDA in these two groups (F_{group}=5.483, 6.275, 6.561, P<0.05), they were all showed a rising then reducing trend over time (F_{time}=13.062, 8.172, 7.842, P<0.05), the rising amplitude of SOD in observation group was less than the control group and MPO, MDA was more than the control group ($F_{interaction}$=5.305, 4.631, 5.327, P<0.05). There was significantly difference of TNF- α , CRP, IL-8 in these two groups (F_{group}=9.308, 10.375, 11.350, P<0.05), they were all showed a rising then reducing trend over time (F_{time}=9.308, 10.375, 11.350, P<0.05), the rising amplitude in observation group was less than the control group ($F_{interaction}$ =5.071, 4.736, 6.347, P<0.05). **Conclusions:** Edaravone combined with nimodipine can inhibits oxidative stress and inflammatory reaction significantly in craniocerebral injury, and better than nimodipine alone.

1. Introduction

Craniocerebral injury is a clinical emergency, prompt and effective treatment is the key to improve the prognosis, protect the nerve cells and reduce the secondary damage[1]. Nimodipine is recognized as a brain protective agent, the application of a longer history, clinical efficacy; edaravone is a new free radical scavenger, in the application of cerebral infarction[2] shows the cerebral protective effect is outstanding, the current is gradually applied in the craniocerebral injury treatment. In recent years, edaravone combined with nimodipine on craniocerebral injury is increasing, but the relevant reports are rare, by observing the effects of combined application on oxidative stress and inflammatory factors in patients with craniocerebral injury, the effectiveness of the program was clarified.

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2.Materials and methods

2.1. General data

All cases were from the patients with craniocerebral injury in our department from February 2014 to February 2016, the choice of patients admitted to hospital after injury in 12 h included in the study. Exclusion criteria: ①patients with heart, liver, lung and kidney disease, hyperthyroidism and tumor; ② penetrating craniocerebral injury, or bilateral pupil has been equal and fixed;

③ patients with previous severe craniocerebral injury or epilepsy; ④ unstable vital signs, oxygen partial pressure <60 mmHg and (or) systolic blood pressure <90 mmHg; ⑤ with drug abuse or alcoholics; ⑥ incomplete clinical data, death or referral cases during treatment; ⑦ The legal agent has not signed the informed consent. A total of 126 cases were selected into the study, and were randomly divided into observation group and control group. The observation group (66 cases) included 41 males and 25 females; aged 35-73 (47.52±16.64) years; Glass Coma Scale (GCS) scored 4-12 (8.21±3.67) points; craniocerebral injury types: 31 cases of cerebral contusion and laceration, 18 cases of hard external hematoma, 12 cases of subdural hematoma, 5 cases of intracranial hematoma; 45 cases of conservative treatment, 21 cases of surgical treatment. The control group (60 cases) included 39 males and 21 females; aged 36-72 (48.78±17.35) years; Glass Coma Scale (GCS) scored 4-12 (8.45±3.57) points; craniocerebral injury types: 28 cases of cerebral contusion and laceration, 17 cases of hard external hematoma, 11 cases of subdural hematoma, 4 cases of intracranial hematoma; 41 cases of conservative treatment, 19 cases of surgical treatment. There was no significant difference in the comparison of general data between the two groups (P>0.05).

2.2. Treatment methods

All permitted cases were treated with conventional treatment, includig oxygen inhalation, control intracranial pressure, cranial nerves feeding, improve microcirculation, expand blood vessels and anti infection. Sedation and analgesia, sustain balance of water, electrolyte and acid-base. Surgical patients were given hematoma evacuation, craniotomy evacuation of hematoma or decompressive craniectomy according to the types of craniocerebral injury. The control group was given nimodipine (manufacturer: Xian Janssen Pharmaceutical Ltd, J20090130) on the basis of conventional treatment, usage: the first 5 days of intravenous infusion of 10 mg/ day, followed by oral 60 mg/ time, 3 times per day, a total of 14 days; the observation group was given edaravone (manufacturer: Fujian Tianquan Pharmaceutical Co., Ltd, H20110090) on the basis of the control group, usage: 30 mg/time, 2 times per day, a total of 14 days.

2.3. Observation indexes

Oxidative stress indexes including superoxide dismutase (SOD), malondialdehyde (MDA) and myeloperoxidase (MPO) were determined by Colorimetric method, the reagent kits were produced by Nanjing Jiancheng Bioengineering Institute; Inflammatory factor including C reactive protein (CRP), tumor necrosis factor α (TNF-α) and interleukin -8 (IL-8). TNF- and IL-6 were detected by enzyme linked immunosorbent assay (ELISA), the reagent kits were produced by Beijing Jingmei Biological Technology Co., Ltd.; CRP was detected by immunoturbidimetric assay, the reagent kits were produced by RANDOX company.

Venous blood was collected for each detection before treatment and 3, 7, 14 days after treatment.

2.4. Statistical treatment

SPSS17.0 software was adopted. Measurement data was described as mean±sd, and analyzed by repeated measure variance, with P<0.05 as statistically significant difference.

3. Results

3.1. Comparison of oxidative stress indexes between two groups

The levels of SOD, MPO, MDA between the two groups showed statistically significant differences (F_{group}=5.483, 6.275, 6.561, P<0.05), the two groups of MPO, MDA and LPO showed the trend of increasing first and then decreasing with prolonged time (F_{time}=13.062, 8.172, 7.842, P<0.05), the increasing extent of SOD in the observation group was higher than that of the control group, while the increasing extents of MDA and MPO were lower than those of the control group ($F_{interaction}$=5.305, 4.631, 5.327, P<0.05) (Table 1).

3.2. Comparison of inflammatory factors before and after treatment between two groups

The levels of TNF-α, CRP, IL-8 between the two groups showedstatistically significant differences (F_{group}=5.037, 6.285,

Table 1
Comparison of oxidative stress indexes before and after treatment between two groups.

Groups	Time	SOD (U/mL)	MDA (μmol/mL)	MPO (mg/L)
observation group (66 cases)	Before treatment	67.54±17.43	6.77±1.16	1.56±0.43
	Third day of treatment	124.35±21.45	9.79±2.84	3.41±0.87
	Seventh day of treatment	112.13±23.30	8.46±2.36	2.51±0.54
	Fourteenth day of treatment	104.17±18.23	7.35±1.83	1.92±0.38
Control group (60 cases)	Before treatment	65.84±21.33	6.69±1.35	1.52±0.39
	Third day of treatment	102.46±24.16	12.14±3.02	4.61±1.01
	Seventh day of treatment	104.13±20.72	10.19±2.26	3.25±0.74
	Fourteenth day of treatment	100.54±17.34	9.21±2.39	2.37±0.52

Table 2

Comparison of inflammatory factors before and after treatment between two groups.

Group	Time	TNF- α (ng/L)	CRP (mg/L)	IL-8 (pg/mL)
observation group (66 cases)	before treatment	24.87±8.32	35.36±17.43	225.34±47.65
	third day of treatment	35.13±11.49	47.24±14.71	265.73±54.87
	seventh day of treatment	13.34±5.01	29.54±15.10	202.82±42.90
	fourteenth day of treatment	29.96±13.95	14.46±7.47	147.40±51.69
Control group (60 cases)	before treatment	25.22±8.51	49.25±18.46	221.79±51.04
	third day of treatment	44.46±13.36	44.52±16.14	306.37±61.23
	seventh day of treatment	23.41±9.34	33.57±13.53	247.09±52.44
	fourteenth day of treatment	18.84±7.02	20.38±10.42	186.42±34.24

6.017, P<0.05), the two groups of TNF- α , CRP, IL-8 showed the trend of increasing first and then decreasing with prolonged time (F_{time}=9.308, 10.375, 11.350, P<0.05), the increasing extents of observation group was lower than those of control group ($F_{interaction}$=5.071, 4.736, 6.347, P<0.05) (Table 2).

4. Discussion

Craniocerebral injury occurs primary brain injury and secondary brain injury, when the latter is not well controlled, the adverse effects on the body can be even more than the former[3], become the major risk factor for poor prognosis. The pathological and physiological process of secondary brain injury is complex, oxidative stress and inflammatory reaction are important links[4], other factors, such as cerebral ischemia and hypoxia, cerebral edema, cerebral metabolic disturbance, ischemia reperfusion injury, are closely related to them. Oxidative stress and inflammatory reaction can directly damage nerve cells[5], and also cause cerebral vasospasm, blood coagulation, microcirculation disturbance and so on to make the cerebral ischemia and hypoxia increased and continue to damage the nerve cells, and if they activate the blood platelets resulting in thrombosis induced cerebral infarction[6,7], the consequences are more serious. In addition, severe oxidative stress and inflammatory response can lead to insufficient blood supply of vital organs, causing lung and kidney damage[8]; or to inhibit the immune function and increase the risk of intracranial infection and systemic infection[9,10]. Visible the importance of controlling oxidative stress and inflammatory reaction in craniocerebral injury, the inflammatory reaction can aggravate oxidative stress, and the oxidative stress can stimulate the release of inflammatory mediators and cause the inflammatory cascade[12]. In this study, the oxidative stress indexes for SOD, MPO, MDA, SOD were antioxidant substances, excessive consumption after craniocerebral injury due to against mass generation of free radicals, so the activity was lower than normal population[13]; MPO is an oxidizing substance, which can stimulate free radical production, and MDA is an oxidative metabolite. These two kinds of serum levels rise rapidly after craniocerebral injury[14]. Inflammatory factors TNF- α , CRP and IL-8 are commonly used to detect indicators, and all belong to pro-inflammatory cytokines, these indicators also rise rapidly after craniocerebral injury.

Nimodipine is a calcium antagonist, can inhibit the influx of calcium ions and reduce the apoptosis of the cells, at the same time, it can improve erythrocyte deformation capacity, improve blood flow and reduce blood brain barrier permeability to increase blood and oxygen supply of brain tissue, through these functions, it can protect the function of nerve cells[16]. At the same time, the inhibition of platelet aggregation, improve ischemia and anoxia can help to inhibit oxidative stress and inflammatory response to further reduce the nerve cell damage, long-term application in the treatment of craniocerebral injury fully confirmed its effectiveness[17,18]. Edaravone is a potent free radical scavenger and antioxidant, it can scavenge a large number of free radicals, inhibit lipid oxidation and cerebral edema, reduce vascular endothelial injury and ischemic penumbra size, a large number of applications in cerebral infarction confirmed the effectiveness of the drug, a large number of applications in the treatment of cerebral infarction confirmed its effectiveness[2,19]. The pathological and physiological basis of cerebral infarction and craniocerebral injury is very similar[20], this is also the theoretical basis for increasing application in latter in recent years, and gradually visible reports also have certified assessment[21]. The analysis showed that the cerebral protection mechanism of edaravone and nimodipine is different, combined use of the two should have synergistic effect.

The results of this study showed that the level of SOD after treatment in the observation group was significantly higher and the levels of MPO and MDA were significantly lower than those of the control group, indicated that edaravone combined with nimodipine can effectively increase the antioxidant capacity and inhibit the expression of oxidative capacity, better than the single use of nimodipine; the levels of TNF- α , CRP and IL-8 after treatment in the observation group were significantly lower than those of the control group, indicated that inhibitory effects of combination on inflammatory response of the body was better than the single use of nimodipine. The control of oxidative stress and inflammatory reaction in the observation group was better than the control group, meant that patients of this group can benefit from the combined use

of edaravone and nimodipine, it can be expected that the program will be more useful.

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