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Effects of edaravone combined with hyperbaric oxygen on cerebral vascular dynamics, oxidative stress products and inflammatory factors in patients with acute cerebral hemorrhage

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ABSTRACT

Objective: To investigate the effect of edaravone combined with hyperbaric oxygen therapy on cerebral vasculature, oxidative stress and inflammatory cytokines in patients with acute cerebral hemorrhage (ACH). **Methods:** A total of 96 patients with ACH were divided into control group (n=48) and observation group (n=48) according to the random number table. Both groups were treated routinely. On this basis, the control group was treated with edaravone injection, and the observation group was treated with edaravone injection combined with hyperbaric oxygen therapy. The change of cerebrovascular dynamics, oxidative stress products and inflammatory factors were examined in all subjects before and after treatment. **Results:** There were no significant differences in cerebrovascular function between the two groups before treatment. After treatment, the levels of Vmean and Qmean in both groups were significantly higher than those before treatment. The levels of Vmean and Qmean in the observation group were higher than those of the control group after treatment. There was no significant difference in serum oxidative stress between the two groups before treatment. After treatment, the levels of SOD in two groups were significantly higher than those before treatment. The level of SOD in the observation group was higher than that in the control group after treatment. After treatment, the levels of MDA in the two groups were significantly lower than that before treatment. The level of MDA in the observation group was lower than that of the control group after treatment. There were no significant differences in the level of serum inflammatory factors between the two groups before treatment. After treatment, the level of TNF-α and IL-1β in two groups were significantly lower than before treatment. The level of TNF-α and IL-1β in the observation group was lower than those of the control group after treatment. **Conclusion:** Edaravone combined with hyperbaric oxygen therapy can effectively improve cerebral vascular dynamics, reduce oxidative stress and inflammatory response in patients with ACH, which is beneficial to the prognosis of patients.

1. Introduction

Acute cerebral hemorrhage is common brain parenchymal internal hemorrhage in clinic, with high disability rate[1]. It was reported that secondary brain injury was main reason of bad prognosis of ACH, blood circulation disorder, oxygen free radical and massive release of inflammatory factor played critical role in this process[3,4]. At present, in clinic, edaravone is a strong free-radical scavenger, which could stabilize illness condition of ACH patients, whereas long-term therapeutic effect was not perfect[5]. In recent, hyperbaric oxygen therapy was widely applied in treatment of ACH, moreover with excellent clinical effect[6]. This paper was aimed to provide basis for ACH treatment through observing the effect of combined therapy on cerebral vascular dynamics, oxidative stress and inflammatory factor level.

2. Data and method

2.1. General data

A total of 96 cases of patients with ACH admitted in our hospital form January 2015 to June 2017 were selected and divided into two groups according to random number table method, observation

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group and control group respectively contained 48 cases. In control group, 23 males, 25 females, aged from 40-69 years old; bleeding site: 14 cases of brain lobe, 11 cases of putamen, 17 cases of thalamus, 6 cases of other sites. In observation group, 27 males, 21 females, aged from 42-71 years old; bleeding site: 13 cases of brain lobe, 12 cases of putamen, 18 cases of thalamus, 5 cases of other sites. There was no obvious difference in general data of both subjects, comparable experiment could be conducted. Patient personally and their family were informed and signed informed consent, this research was approved by ethics committee of hospital.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) subjects were conformed with standard of "Diagnosis and treatment guidance of Chinese cerebral hemorrhage" [7]. (2) subjects were diagnosed as cerebral hemorrhage through brain CT; (3) disease time of subjects within 72 h. Exclusion criteria: (1) subject with history of stroke cerebral apoplexy; (2) subjects with cerebral hemorrhage caused by trauma or tumor in brain; (3) subjects with severe heart, hepatic and renal primary disease; (4) subjects with arrhythmia, obstructive pulmonary disease, pneumothorax, not suitable for hyperbaric oxygen therapy.

2.3 Treatment method

All subjects were given conventional therapy, such as inhalation oxygen, controlling intracranial pressure, regulating bloos glucose and pressure. On this basis, control group was given edaravone injection (Nanjing Xiansheng Dongyuan Pharmaceutical Co. Ltd, approval number: H20050280), 30 mg/time, 2 times/d, finished drip within 30 min after diluting by normal saline, 14 d were a treatment course, continuously treated for 2 periods. On the base of control group, hyperbaric oxygen therapy was applied for observation group, adopted single pure oxygen cabin, pressure was approximately 0.20-0.25 Mpa, 1 time/d, 2 h each time (30 min added pressure, 60 min inhalation oxygen, 30 min reduced pressure), continuously treated for 28 d.

2.4 Sample detection

Extracted 304 mL of venous blood before and after treatment of all subjects, centrifuge and obtain supertanant for detection. (1) cerebral vascular function index: cerebral vascular mean velocity (Vmean) and mean quantity of flow (Qmean), Vmean and Qmean indicated cerebral vascular dynamic parameter, value decreasing indicated that insufficient blood supply of brain; equipment was ultrasound through brain Doppler blood analyzer (Nanjing Kejin industry Co.Ltd, type: KJ-2V6). (2) Oxidative stress indexes: superoxide dismutase (SOD) and malondialdehyde (MDA); thiobarbituric acid method and xanthine oxidase method; equipment was ELIASA microplate reader (Thermo Fisher, type: MK3). (3) Inflammatory factor indexes: tumor necrosis factor-α (TNF-α) and interleukin1-β (IL-1β) measured by full automatic eletrochemiluminescence immune analyzer (Roche company, type: RocheE601). All kits were purchased from Shanghai Meilian Biological Technology Co. Ltd, operation was strictly with introduction.

2.5 Statistical analysis

Statistical Software SPSS 20.0 was used for all data processing and analyzing, measuring data were represented by Mean ± SD, t-test was adopted, $P<0.05$ indicated the difference was statistical significant.

3. Results

3.1. Comparison of cerebral vascular function index Vmean and Qmean change of both groups

Before treatment, there was no difference in cerebral vascular function of observation group and control group ($P>0.05$); after treatment, Vmean and Qmean level in observation group were (17.07±1.36) cm/s and (12.65±1.28) mL/s, in control group they were respectively (15.76±1.24) cm/s and (11.07±1.16) mL/s, which was higher than before treatment intragroup ($P<0.05$), moreover, observation group was higher than control group in same period, the difference was significant ($P<0.05$). As shown in table 1.

3.2 Comparison of serum oxidative stress level before and after treatment of both groups

Before treatment, there was no difference in serum oxidative stress level of observation group and control group ($P>0.05$); after treatment, SOD level of observation group and control group were (103.39±5.54) U/mL and (81.82±5.17) U/mL, which higher than before treatment of intragroup ($P<0.05$), observation group was higher than control group in same period, the difference was significant ($P<0.05$). After treatment, MDA level of observation group and control group were (6.34±1.21) mmol/L and (8.41±1.37) mmol/L, which was lower obviously than before treatment in same

Table 1.
Comparison of cerebral vascular function index Vmean and Qmean change of both groups.

Group	*n*	Times	Vmean (cm/s)	Qmean (mL/s)
Control group	48	Before treatment	13.54±1.32	8.53±1.05
		After treatment	15.76±1.24$^{\#}$	11.07±1.16$^{\#}$
Observation group	48	Before treatment	13.37±1.51	8.49±0.84
		After treatment	17.07±1.36$^{\#*}$	12.65±1.28$^{\#*}$

Note: Compared with before treatment, $^{\#}P<0.05$; compared with control group after treatment, $^{*}P<0.05$.

Table 2.
Comparison of serum oxidative stress level before and after treatment of both groups.

Group	*n*	Time	SOD (U/mL)	MDA (mmol/L)
Control group	48	Before treatment	74.63±5.03	9.74±2.63
		After treatment	81.82±5.17#	8.41±1.37#
Observation group	48	Before treatment	73.78±4.86	9.68±2.57
		After treatment	103.39±5.54#*	6.34±1.21#*

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

Table 3.
Comparison of serum inflammatory factor before and after treatment of both groups.

Group	*n*	Time	TNF-α (ng/L)	IL-1β (pg/mL)
Control group	48	Before treatment	90.36±17.83	273.65±32.64
		After treatment	74.32±13.72#	246.82±27.32#
Observation group	48	Before treatment	91.78±18.16	266.77±34.58
		After treatment	62.93±16.53#*	217.34±25.43#*

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

group (*P*<0.05), moreover observation group was lower than control group in same period, the difference was significant (*P*<0.05). As shown in table 2.

3.3 Comparison of serum inflammatory factor before and after treatment of both groups

Before treatment, there was no difference in serum inflammatory factor level of observation group and control group (*P*>0.05); after treatment, TNF-α and IL-1β level in observation group were respectively (62.93±16.53) ng/L and (217.34±25.43) pg/mL, TNF-α and IL-1β level in control group were (74.32±13.72) ng/L and (246.82±27.32) pg/mL, which was dramatically lower than before treatment of same group (*P*<0.05), moreover observation group was lower than control group in same period, the difference was significant (*P*<0.05). As shown in table 3.

4. Discussion

Acute cerebral hemorrhage (ACH) is common cerebral vascular complication in clinic, severely affected health of human[8]. Temporary or continuous hemorrhage of brain both formed intracranial hematoma, formation of hematoma was main pathogenesis and lethal reason of patients with ACH. ACH occupation would press periphery cerebral tissue, and cause cerebral vascular hemodynamics disorder; whereas reduction of vascular blood flow can activate xanthine reaction system generate massive free radical, aggregate intracranial edema formation, result in general inflammatory reaction. Moreover, severe inflammatory cascade reaction would further stimulate development of intracranial edema[9,10]. Therefore, improved cerebral vascular function, reduced oxidative and inflammatory reaction, prevent secondary brain injury in time was effective means that rescued life of patients. Edaravone and hyperbaric oxygen therapy were common method in clinic for treating ACH, whereas how to enhance efficacy was the difficulty and hot of clinical medical dispute. This research was aimed to provide basis for ACH treatment through observing the effect of combined therapy on cerebral vascular dynamics, oxidative stress and inflammatory factor level.

Researches have demonstrated that blood of ACH patients presented sticky, thick, cohesive, severely affected blood microcirculation of brain tissue, viscosity increased; in the meanwhile, fat stacked in blood, easy to cause intravascular stenosis and sclerosis, reduce blood velocity, aggregate formation of intracranial hematoma[9]. This research showed that after treatment both therapies could effectively increase cerebral vascular Vmean and Qmean; moreover, efficacy of observation group was superior to control group. The reason may be edaravone with high lipid solubility, it could effectively eliminate free radical, reduce brain tissue vascular injury, promote blood circulation[11]. Hyperbaric oxygen therapy could enhance partial pressure of blood oxygen and capillaries oxygen tension, reduce brain tissue local anoxia and intracranial hematoma resulted from vasospasm and promote capillaries blood circulation[12]. Edaravone combined with hyperbaric oxygen therapy could improve brain blood circulation and enhance cerebral vascular mean velocity and flow.

Oxidative stress was closely related to intracranial hematoma in patients with cerebral hemorrhage. Drastic oxidative stress reaction could release a quantity of free radical in patients with ACH, broke xidation-antioxidation balance, excessive oxygen free radical attacked unsaturated fatty acid double bond on cellular membrane of cerebral tissue, caused permeability increase and aggregated intracranial hematoma[13]. When oxidative injury appeared in patients with ACH, MDA promoted oxidative metabolism of amine, reduced monoamines and led to nervous injury. SOD was a main enzyme that eliminated free radical generated in metabolism, avoiding free radical damage. Hence, detected MDA nad SOD level could reflect degree of oxidative stress and ability of anti-oxidation. This research found that after treatment both treatment could reduce serum MDA concentration and increase SOD level, moreover, efficacy of observation group was better than control group. The reason was that edaravone was a free radical scavenger with small molecule weight, could pass blood brain barrier, eliminate OH- that was high cellular toxicity in brain of ACH patients, downregulated expression of caspase-3 and other apoptosis-promoting genes, inhibit MDA activity, thereby deferred oxidative injury of brain tussue, relieved brain tissue injury and hematoma[14]. Hyperbaric oxygen could increase blood oxygen concentration of ACH patients, promote periphery tissue blood circulation of hemotoma, enhance

blood supply of anxia tissue, relieve vascular dysfunction, thereby promote hematoma absorb, decrease ox, idative stress and reduce symptom of hematoma[15,16]. Therefore edaravone combined with hyperbaric oxygen therapy could effectively eliminate excessive free radical, inhibit formation of hematoma, enhance efficacy of clinical treatment.

In addition, inflammatory factors also played critical role in process of intracranial hematoma in patients with ACH[17]. Inflammatory factors was a kind of peptide with biological activity and regulated cellular reaction. Some research reported that inflammatory factors could gather white blood cell to obstruct blood vessel, cause pro-coagulation of local cerebral tissue, aggregate neuron apoptosis, thereby induced genesis of intracranial hematoma[17,18]. This paper found that after treatment both therapies could decrease serum TNF-α and IL-1β level, effect of observation group was better than control group. This was due to TNF-α not only broke permeability of blood brain barrier then caused genesis of hematoma, but induced inflammatory cascade reaction, destroyed intracranial hematoma and endothelium of periphery vascular[19]. IL-1β could activate white blood cells and endothelial cells, upregulated cellular adhesion molecule, increase adhesiveness of white blood cells, meanwhile induced white blood cells secrete massive inflammatory factors, aggregate intracranial hematoma[20]. Edaravone could inhibit activity of (hypo-) xanthine oxidase, thereby down-regulate leukotrienes, cut off the cascade inflammatory reaction, reduce intracranial hematoma of ACH[21,22]. Hyperbaric oxygen therapy could inhibit secretion of inflammatory factors, prevent cascade inflammatory reaction in intracranial hematoma, control the vicious cycle of cerebral hematoma-hypertension-anxia[23]. Therefore, edaravone combined with hyperbaric oxygen therapy could effectively control serum inflammatory factors level in patients with ACH.

In conclusion, edaravone combined with hyperbaric oxygen therapy were able to improve cerebral vascular hemodynamics, reduce oxidative stress and inflammatory reaction, have certain reference for clinical treatment of ACH, however, there still need a lot of researches and testes to normalize the combined application.

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