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Original Research Article

Assessment of mild hypothermia combined with edaravone for the treatment of severe craniocerebral injury

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Abstract

Purpose: *To study the clinical effect of combining mild hypothermia with edaravone in the treatment of severe craniocerebral injury.*
Methods: *One hundred and twenty (120) patients with severe craniocerebral injury who were admitted to Tianjin Medical University General Hospital were assigned to control and study groups, respectively. Patients in the control group were given conventional treatment while those in the study group received combined treatment of mild hypothermia and edaravone, in addition to the conventional treatment received by control group. Clinical efficacy and prognosis were compared between the two groups.*
Results: *The intracranial pressure (ICP) of both groups decreased after admission, but the decrease in ICP was more pronounced in the study group at various time points ($p < 0.05$). Blood lactic acid levels decreased in both groups after admission, while brain-derived neurotrophic factor (BDNF) levels increased. Improvement in blood lactic acid and BDNF was greater in the study group than in control group ($p < 0.05$). The treatment resulted in significant decrease in residual hematoma volume and edema range in the study group, relative to control ($p < 0.05$). There was a decrease in National Institutes of Health Stroke Scale (NIHSS) scores, and increase in Glasgow outcome scale (GOS) scores in both groups. However, improvement in NIHSS and GOS scores in the study group was superior to those in control group ($p < 0.05$).*
Conclusion: *Mild hypothermia in combination with edaravone exerts a beneficial clinical effect in severe craniocerebral injury. The combined treatment rapidly reduces ICP and range of encephaledema, improves cerebral blood supply, promotes absorption of intracranial hematoma, and relieves nervous dysfunction.*

Keywords: *Mild hypothermia, Edaravone, Severe craniocerebral injury, Intracranial pressure, Neurotrophic factor*

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INTRODUCTION

Severe craniocerebral injury, the most common neurosurgical disease, is a major cause of dysneuria worldwide [1,2]. According to relevant statistical data, craniocerebral injury ranks second among all traumas, but it is always associated with the highest death and disability rates [3]. It has been estimated that approximately 600,000 Chinese

people have craniocerebral injury every year, 16 - 18 % of which result in death [4]. With rapid development of transportation and construction industries in recent years, the incidence of severe craniocerebral injury has risen. Therefore, it is very important to develop appropriate and effective methods for treating patients with severe craniocerebral injury.

In traditional clinical treatment, decompressive craniectomy and removal of intracranial hematoma are usually combined to relieve intracranial pressure and improve cerebral blood supply. However, a large proportion of the affected patients still have nervous dysfunction which can severely affect their quality of life and bring large burden to their families and the society [5,6]. Recent studies found that mild hypothermia could protect the brain by reducing energy supply and cerebral oxygen consumption, inhibiting lipid peroxidation, and relieving cerebral perfusion [7,8]. Clinically, the temperature of mild hypothermia is usually between 32 and 36 °C. As a measure which protects the function of the central nervous system, mild hypothermia technology has continued to attract attention in recent years [9,10]. Patients with severe craniocerebral injury who receive mild hypothermia treatment have good prognosis, and the operation is simple [11]. Early mild hypothermia significantly improves the prognosis of patients with acute severe brain injury [12].

Edaravone is a free-radical scavenger which has been widely applied in clinics; it also relieves secondary cerebral injury and coordinates with mild hypothermia [13]. In this study, 120 patients with severe craniocerebral injury were selected for randomized controlled trial. The study was aimed at investigating the clinical effect of edaravone in combination with mild hypothermia in the treatment of severe craniocerebral injury.

EXPERIMENTAL

General patient profile

In this study, 120 patients with severe craniocerebral injury who were admitted to the hospital between June 2015 and June 2017 were selected as trial subjects. The inclusive criteria were: admission to the hospital within 24 h after craniocerebral injury, cases that conformed with the indications for emergency operation; acute epidural hematoma of more than 30 mL, temporal hematoma of more than 20 mL, unilateral or bilateral pupil dilation, and uncontrollable intracranial hypertension. The exclusive criteria were: presence of organ failure or injury, hypotension-induced shock, and intracranial infection.

The patients were divided into control group and study group using random number table, with 60 patients in each group. In the control group, there were 34 males and 26 females aged 26 - 56 years (mean age = 40.5 ± 5.6 years). They comprised 17 cases of epidural hematoma, 11 cases of traumatic intracerebral hematoma, 32 cases of subdural hematoma, 30 cases of cerebral contusion and laceration, and 2 cases of primary brain-stem injury. With respect to clinical manifestations, there were 10 cases of unilateral pupil dilation, 7 cases of bilateral pupil dilation, and 36 cases of breathing changes.

Ten (10) patients were injured by crashing objects, 36 patients were involved in traffic accidents, while 14 patients were injured in falls. In the study group, there were 35 males and 25 females aged 24 - 54 years (mean age = 40.8 ± 5.9 years). There were 18 cases of epidural hematoma, 11 cases of traumatic intracerebral hematoma, 31 cases of subdural hematoma, 28 cases of cerebral contusion and laceration, and 4 cases of primary brain-stem injury. With respect to clinical manifestations, there were 12 cases of unilateral pupil dilation, 5 cases of bilateral pupil dilation, and 40 cases of breathing changes. Eight (8) patients were injured by crashing objects, 37 patients sustained injuries from traffic accidents, while 15 patients were injured through falls. There were no statistically significant differences in baseline data between the two groups ($p > 0.05$). The study was approved by Medical Ethics Committee of Binzhou People's Hospital (approval no. GYK20161208), and was carried out in line with the guidelines of the Declaration of Helsinki [14].

Treatments

Both groups were admitted to neuroscience intensive care unit. Breathing, heart rate, pulse and oxygen saturation, and changes in consciousness and pupil were monitored.

Emergency treatment was carried out according to the patient's condition. Imaging data were used to actively control intracranial pressure and strengthen the application of dehydration drugs. Patients who needed craniotomy received same immediately. Breathing was kept smooth, and hypoxemia was positively corrected. Some patients were given tracheal intubation, while some were given tracheotomy. All patients were given conventional treatments such as oxygen inhalation, electrocardiograph monitoring, intracranial pressure reduction, hemostasis,

expectoration, prevention of infection, brain cell nourishment, prevention of epilepsy, acid suppression and stomach protection, systemic nutrition support, blood gas analysis and symptomatic treatment.

In the study group, combined treatment with edaravone and mild hypothermia was given, in addition to the above treatment regimen. Mild hypothermia refers to cooling the whole body using semiconductor cooling blanket. The patients' heads were cooled using ice cap, while hibernation mixture was intravenously injected. During this period, the temperature of the tympanic membrane and anal temperature were monitored. The temperature was gradually regulated between 32 and 35 ^{o}C within 5 h. After one week, the patients' heads were naturally re-warmed to normal state. Moreover, 30 mg of edaravone was mixed with 100 mL 0.9 % sodium chloride injection, and the mixture was administered intravenously twice daily for 2 weeks.

Study indices

Levels of ICP, blood lactic acid and BDNF of patients were determined and recorded on admission, and at the 24th, 48th, 72nd and 96th h after admission. The levels of blood lactic acid and BDNF were determined with a fully automatic biochemical analyzer, using 4 mL of blood collected from each patient.

Encephaledema in the two groups was observed and recorded, including the residual hematoma volume and edema range.

Before treatment, and six months after treatment, neurological function and prognosis were evaluated using NIHSS [15] and GOS [16]. The evaluation indices of NIHSS include level of consciousness, staring, field of view, movement of upper and lower limbs, sensation, language and limbs ataxia. Higher scores indicated severer neurologic impairment. The GOS scores are usually based on five grades: good (5 points), moderately disabled (4 points), severely disabled (3 points), vegetative status (2 points), and death (1 point). Lower scores indicated poorer prognosis.

Statistical analysis

Data were processed with SPSS version 20.0. Numeric data are presented as mean ± standard deviation (SD), and were statistically analyzed using t-test. Categorical data are expressed as percentage, and were analyzed using Chi-square test. Values of $p < 0.05$ were taken as indicative of statistically significant differences.

RESULTS

Intracranial pressure (ICP)

The ICP of the two groups did not show statistically significant difference on admission ($p > 0.05$). However, there were significant decreases in ICP of both groups at the 24th, 48th, 72nd and 96th h after admission, but the ICP of the study group was significantly lower than that of the control group at each time points ($p < 0.05$; Table 1).

Table 1: ICP of the subjects at different time points

Period/time after admission	Study group	Control group
On admission	28.73±4.51	28.71±4.52
24th h	23.51±2.63$^{*\#}$	25.21±2.43*
48th h	19.53±3.73$^{*\#}$	23.22±2.17*
72nd h	17.49±3.21$^{*\#}$	20.22±3.42*
96th h	16.23±3.26$^{*\#}$	18.33±2.41*

*Values are presented as mean ± SD. The unit is mmHg. $^{*}p < 0.05$, compared to ICP on the day *of admission*; $^{\#}p < 0.05$, compared to control group

Blood lactic acid and BDNF levels

The levels of blood lactic acid and BDNF in the two groups showed no significant differences on admission ($p > 0.05$). However, blood lactic acid levels of patients in both groups decreased at the 24th, 48th, 72nd and 96th h after admission, but the levels of BDNF increased. The Study group patients had lower levels of blood lactic acid and higher levels of BDNF than the control group at the different time points after admission ($p < 0.05$; Table 2).

Effect of treatment on encephaledema

There was no significant difference in residual hematoma volume and edema range between the two groups before treatment ($p > 0.05$). However, after treatment, the residual hematoma volume and edema range in the study group were significantly lower than those in the control group ($p < 0.05$, Table 3).

Effect of treatments on NIHSS and GOS scores

There were no significant differences in NIHSS and GOS scores between the two groups on the day of admission ($p > 0.05$). However, NIHSS scores decreased in both groups, while GOS scores increased at the postoperative 6th month. The study group had significantly lower NIHSS

Table 2: Blood lactic acid and BDNF of the subjects (mean ± SD)

Group	Time point (on or after admission)	Blood lactic acid (mmol/L)	BDNF (ng/mL)
Study	On admission	6.13±3.02	1.53±0.47
	24 h	2.59±1.93*#	3.42±0.27*#
	48 h	1.67±0.85*#	4.66±0.41*#
	72 h	0.85±0.42*#	5.53±0.37*#
	96 h	0.65±0.13*#	5.90±0.23*#
Control	On admission	6.14±3.04	1.55±0.47
	24 h	5.23±2.42*	2.57±0.32*
	48 h	4.40±2.83*	3.27±0.23*
	72 h	3.95±2.10*	4.42±0.35*
	96 h	2.66±1.42*	4.88±0.42*

Results are presented as mean ± SD; *$p < 0.05$, compared to ICP on the day of admission; #$p < 0.05$, compared to control group

Table 3: Residual hematoma volume and edema range

Group	Time point	Volume of hematoma (cm^2)	Hematoma and edema volume (cm^2)
Study	Before treatment	20.29±8.05	36.53±6.95
	After treatment	5.01±2.51*#	9.21±5.21*#
Control	Before treatment	20.23±7.86	37.52±7.18
	After treatment	7.29±2.14*	14.55±5.62*

Results are presented as mean ± SD. *$p < 0.05$, compared to residual hematoma volume or edema range on the day of admission; #$p < 0.05$, compared to the control group

Table 4: NIHSS and GOS scores

Group	Time point	NIHSS	GOS
Study	Before treatment	47.68±5.25	2.25±0.42
	6 months after treatment	19.24±6.72*#	4.33±0.35*#
Control	Before treatment	47.66±5.27	2.26±0.41
	6 months after treatment	26.41±5.76*	3.68±0.21*

Results are presented as mean ± SD; *$p < 0.05$, compared to NIHSS or GOS scores on the day of *admission*; #$p < 0.05$, compared to the control group

score and higher GOS score than the control group at the postoperative 6th month, ($p < 0.05$; Table 4).

DISCUSSION

Patients with severe craniocerebral injury often suffer from severe secondary brain injury induced by a series of pathophysiological changes such as cerebral contusion and laceration, intracranial hematoma-associated hypertension, secondary cerebral ischemia, hypoxia, brain edema, altered brain tissue metabolism, microcirculation disturbance, and neuronal apoptosis [17]. It is a major cause of high disability and mortality in patients with severe head injury. Thus, there is need for neurosurgeons and scholars to carry out in-depth studies on the mechanism of secondary brain injuries and the mechanism of brain protection so as to block or reduce the occurrence and development of secondary brain damage [18].

Edaravone is the only new free radical scavenger that has passed phase III clinical trials. It directly scavenges oxygen free radicals, inhibits lipid peroxidation, alleviates brain edema caused by arachidonic acid, removes highly cytotoxic hydroxyl groups in the brain, stimulates the production of prostacyclin, reduces the production of inflammatory mediator leukotrienes, and reduces the concentration of hydroxyl radicals. Moreover, it reduces the area of brain edema, blocks cascade reactions of ischemia, alleviates reperfusion injury, and enhances the tolerance of nerve cells to ischemia [19]. In addition, edaravone effectively inhibits oxygen free radical-mediated irreversible damage to proteins and nucleic acids, and effectively inhibits neuronal death [20].

Mild hypothermia therapy focuses on cooling the head as a basis of cooling the patient's whole body. It significantly reduces the excitability of the brain, inhibits the body's stress responses, reduces the oxygen consumption of brain tissue and the accumulation of lactic acid, relieves encephaledema, and improves perfusion pressure of cerebral tissues [21]. Therefore, in addition to the conventional treatment, patients in

the study group were also treated with edaravone combined with mild hypothermia.

The results showed that the decrease in ICP in the study group was more significant than that in the control group at all time points after admission. This is similar to the findings of Peng *et al* [22], indicating that mild hypothermia combined with edaravone could significantly reduce ICP in patients.

Patients with severe craniocerebral injury often suffer high hyperlactacidemia at the acute stage of injury, due to elevated blood lactic acid level. In this study, blood lactic acid was at a high level before treatment in the two groups. But the decrease in blood lactic acid level in the study group was superior to that in the control group at the different time points after treatment. This indicates that the combined therapy produced significant mitigation of the inflammatory state of patients. Brain-derived neurotrophic factor, an important neurotrophic factor synthesized in the brain, is distributed in the central nervous system. It promotes the formation, differentiation and survival of neurons, and inhibits impairment of function of nerve cells [23].

Increase in ICP after the occurrence of severe craniocerebral injury lead to decreased secretion of BDNF, calcium influx and accelerated apoptosis of nerve cells, which can damage neurons and aggravate hypoxia and ischemia of cerebral tissues. The BDNF level of the patients increased significantly after mild hypothermia, and the improvement was significantly better than that of the control group, suggesting that mild hypothermia therapy protects nerves.

This study also found that the volume of residual hematoma and edema range of the study group were significantly lower than those of the control group. The NIHSS score of the patients in the study group was significantly reduced, and the GOS score increased significantly, indicating that mild hypothermia in combination with edaravone can relieve encephaledema, reduce ICP, and improve the neurological function and prognosis of patients. These results are consistent with findings in a previous work [24,25].

Limitations of the study

This study has some shortcomings. The sample number was small and the cases came from a single center. Therefore, there is need for further studies involving more samples and multiple centers to provide a reliable reference for the clinics.

CONCLUSION

Edaravone, when combined with mild hypothermia, has significant protective effect on cerebral tissues in the treatment of severe craniocerebral injury. It significantly reduces ICP and blood lactic acid levels, and enhances neurological function and prognosis.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Yi-Kuan Gao and Wen-Qiang Xin contributed equally to this work.

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