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Curative effect of ganglioside sodium for adjuvant therapy on acute severe craniocerebral injury

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ABSTRACT

Objective: To study the effect of adjuvant therapy of ganglioside sodium on intracranial pressure (ICP), partial pressure of brain tissue oxygen ($P_{bt}O_2$), nerve injury molecules, nerve protection molecules and indexes of oxidative stress in patients with acute severe craniocerebral injury.

Methods: Forty-seven patients with severe craniocerebral injury treated in the emergency department of our hospital during the period time from December 2012 to October 2015 were selected for retrospective analyses. They were divided into the ganglioside group and the normal treatment group according to the usage of ganglioside sodium in the process of the emergency treatment. At days 1, 3, 5 and 7 before and after treatment, the ICP and $P_{bt}O_2$ in patients of the two groups were measured. After 7 days of treatment, the nerve injury molecules, nerve protection molecules and the indexes of oxidative stress in serum of the patients of the two groups were determined.

Results: At days 1, 3, 5 and 7 before and after treatment, the ICP in patients of the ganglioside group were all significantly lower than those of the normal treatment group, while the $P_{bt}O_2$ were all significantly higher than those of normal treatment group. After 7 days of treatment, the contents of serum methane dicarboxylic aldehyde, advanced oxidation protein products, 8-hydroxy-2'-deoxyguanosine urine, S100β, glial fibrillary acidic portein, neuron specific enolase, myelin basic protein, neuroglobin and ubiquitin carboxyl-terminal hydrolase L1 in patients of the ganglioside group were notably lower than those of the normal treatment group, while the contents of superoxidase dismutase, glutathione peroxidase, catalase, nerve growth factor and brain derived neurotrophic factor were significantly higher than those of the normal treatment group.

Conclusions: The adjuvant therapy of ganglioside sodium in patients with severe craniocerebral injury can effectively reduce ICP, improve $P_{bt}O_2$ and alleviate the injuries of neurons and glial cells caused by oxidative stress.

1. Introduction

Severe craniocerebral injury is a common emergency in the Department of Cerebral Surgery with critical condition and severe nerve function impairment, and it progresses rapidly with higher disability and death rates for patients. The local pathological and physiological changes of craniocerebral injury are complex, and there are many factors causing nerve function impairment. The compression of brain tissue caused by hematoma, increase in intracranial pressure (ICP) and the large amount of toxic metabolic products are all related to the destruction of nerve function after craniocerebral injury[1,2]. In clinical practice, hematoma clearance operation and decompressive craniectomy are the main ways in emergency treatment of craniocerebral injury assisted with mannitol to lower ICP, neurotrophic drugs and functional exercise to make positive effect in patients with mild craniocerebral injury[3,4]. However, for patients with severe craniocerebral injury, due to the severe local tissue damage and the continuous production of toxic metabolic products, conventional emergency surgery can effectively remove the hematoma and reduce ICP, but it cannot effectively block the production of toxic metabolic products. Thus, there exist poor prognosis for patients and high mortality and morbidity rates[5,6].

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The study protocol was performed according to the Helsinki declaration and approved by the ethic committee of Zigong Fourth People's Hospital. Informed written consent was obtained from patients' family members.

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Ganglioside sodium is a new medicine applied to cure cerebrovascular diseases in recent years, which can induce the growth of neurons axon and the formation of synapse and has a promoting effect on repairing the injury of central nerve system. Also, it can stabilize the structure of cell membrane and protect the nervous system from the damage of toxic metabolic products. Besides, ganglioside sodium has the effect of scavenging oxygen free radical and also alleviates nerve tissue damage caused by oxidative stress reaction. Clinical studies have reported that ganglioside sodium can improve the nerve function in patients with cerebral infarction and cerebral hemorrhage[7,8]. But, there have been few clear reports about the effect of this drug in the treatment of craniocerebral injury. In the following studies, the effect of adjuvant therapy of ganglioside sodium on ICP, partial pressure of brain tissue oxygen ($P_{bt}O_2$), nerve injury molecules, nerve protection molecules and indexes of oxidative stress in patients with acute severe craniocerebral injury were analyzed.

2. Materials and methods

2.1. Research objects

Forty-seven cases with severe craniocerebral injury treated in the Emergency Department of our hospital during the period time from December 2012 to October 2015 were selected for the study. The inclusion criteria were described as follows: I. patients with determinate history of trauma and sent for emergency treatment within 6 h after injury; II. patients with Glasgow coma score < 8 on admission; III. patients diagnosed with craniocerebral injury by brain CT scan or magnetic resonance imaging; IV. patients given decompressive craniectomy for emergency treatment; V. patients with complete medical records. Those patients combined with heart, liver and kidney and other important organ injuries or with shock were excluded. The causes of injuries in enrolled patients were as follows: 32 cases of traffic injury, 11 cases of falling injury and 4 cases of striking injury. The medical records of the patients were analyzed retrospectively and the patients were divided into the ganglioside group and normal treatment group according to the usage of ganglioside sodium in the process of emergency treatment. There were 26 patients in the ganglioside group including 18 males and 8 females with ages of (39.5 ± 5.2) years, and there were 21 patients in the normal treatment group including 14 males and 7 females with ages of (38.6 ± 4.9) years.

2.2. Research methods

2.2.1. Therapeutic methods

Patients in the ganglioside group and normal treatment group were treated with dehydration, hemostasis, anti-inflammation and other routine treatments immediately after they were hospitalized in the Emergency Department. They were treated with 5 mL/kg of 20% mannitol by intravenous drip which should be finished in 30 min, and 0.4 mg/kg of furosemide, 8 mg of naloxone and 1 000 IU of thrombin for injection were added into 20 mL of Xingnaojing injection for intravenous injection. At the same time, surgeries were prepared. Decompressive craniectomy was operated after the examinations and preparations. Patients of the ganglioside group were treated with ganglioside sodium additionally. They were treated with 100 mg of ganglioside sodium injection by intravenous drip with once a day for two weeks and after that 40 mg of ganglioside sodium injection by intravenous drip once a day for six weeks sequentially.

2.2.2. Measuring methods of ICP and $P_{bt}O_2$

At days 1, 3, 5 and 7 before and after treatment, Intellivue Mp30 system was adopted (Philip, Amsterdam, Netherlands). ICP was monitored by the brain hydraulic conductivity method and $P_{bt}O_2$ was measured by a cerebral oxygen and brain temperature detector.

2.2.3. Collection of serum specimen and index detection method

After 7 days of treatment, 5 mL of peripheral venous blood was collected. After the serum was acquired by centrifugation, the contents of S100β, glial fibrillary acidic portein (GFAP), neuron specific enolase (NSE), myelin basic protein (MBP), neuroglobin (NGB), ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) were measured by ELISA kit. The contents of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), methane dicarboxylic aldehyde (MDA), advanced oxidation protein products (AOPP) and 8-hydroxy-2'-deoxyguanosine urine (8-OHdG) were measured by radioimmunoassay kits.

2.3. Statistical method

The data was input and analyzed by SPSS 19.0 software. Measurement data were expressed by mean ± SD and analyzed by *t*-test. Enumeration data were presented by frequencies and analyzed by *Chi*-square test. Differences were statistically significant when $P < 0.05$.

3. Results

3.1. ICP and $P_{bt}O_2$

Before treatment, the ICP [(29.14 ± 3.26) *vs.* (29.32 ± 3.78)

mmHg] and $P_{bt}O_2$ [(12.52 ± 1.94) *vs.* (13.03 ± 1.18) mmHg] in patients of the two groups had no significant differences ($P > 0.05$). At days 1, 3, 5 and 7 after treatment, the ICP [(21.35 ± 2.79) *vs.* (25.28 ± 3.23) mmHg], [(17.98 ± 2.27) *vs.* (23.09 ± 2.61) mmHg], [(13.71 ± 2.13) *vs.* (20.26 ± 2.38) mmHg] and [(10.93 ± 1.58) *vs.* (15.73 ± 1.96) mmHg] in patients of the ganglioside group were significantly lower than those of the normal treatment group; while the $P_{bt}O_2$ [(15.65 ± 1.78) *vs.* (13.55 ± 1.56) mmHg], [(18.14 ± 2.31) *vs.* (15.48 ± 1.77) mmHg], [(22.13 ± 3.28) *vs.* (16.03 ± 1.93) mmHg] and [(24.19 ± 4.57) *vs.* (16.58 ± 2.35) mmHg] were all significantly higher than those of the normal treatment group. The levels of ICP and $P_{bt}O_2$ in patients of the two groups at days 1, 3, 5 and 7 after treatment were statistically significant ($P < 0.05$) (Table 1).

Table 1
Comparison of ICP and $P_{bt}O_2$ in patients of the two groups (mmHg).

Parameters		Ganglioside group (n = 26)	Normal treatment group (n = 21)	P
ICP	Before treatment	29.14 ± 3.26	29.32 ± 3.78	> 0.05
	1 day after treatment	21.35 ± 2.79	25.28 ± 3.23	< 0.05
	3 days after treatment	17.98 ± 2.27	23.09 ± 2.61	< 0.05
	5 days after treatment	13.71 ± 2.13	20.26 ± 2.38	< 0.05
	7 days after treatment	10.93 ± 1.58	15.73 ± 1.96	< 0.05
$P_{bt}O_2$	Before treatment	12.52 ± 1.94	13.03 ± 1.18	> 0.05
	1 day after treatment	15.65 ± 1.78	13.55 ± 1.56	< 0.05
	3 days after treatment	18.14 ± 2.31	15.48 ± 1.77	< 0.05
	5 days after treatment	22.13 ± 3.28	16.03 ± 1.93	< 0.05
	7 days after treatment	24.19 ± 4.57	16.58 ± 2.35	< 0.05

3.2. Indexes of serum oxidative stress damage

After 7 days of treatment, the contents of serum MDA [(6.14 ± 0.89) *vs.* (10.24 ± 1.45) μmol/L], AOPP [(56.51 ± 7.22) *vs.* (102.14 ± 13.47) μmol/L] and 8-OHdG [(4.38 ± 0.57) *vs.* (7.94 ± 0.89) ng/mL] in patients of the ganglioside group were significantly lower than those of the normal treatment group. The contents of SOD [(153.36 ± 19.34) *vs.* (94.26 ± 10.24) IU/mL], GSH-Px [(196.34 ± 24.24) *vs.* (108.15 ± 13.78) IU/mL] and CAT [(69.35 ± 9.18) *vs.* (42.26 ± 5.97) IU/mL] were significantly higher than those of the normal treatment group. The contents of serum SOD, GSH-Px, CAT, MDA, AOPP and 8-OHdG in patients of the two groups after treating for 7 days were statistically significant ($P < 0.05$) (Table 2).

Table 2
Comparison of the oxidative stress indexes of the two groups.

Indexes	Ganglioside group (n = 26)	Normal treatment group (n = 21)	P
MDA (μmol/L)	6.14 ± 0.89	10.24 ± 1.45	< 0.05
AOPP (μmol/L)	56.51 ± 7.22	102.14 ± 13.47	< 0.05
8-OHdG (ng/mL)	4.38 ± 0.57	7.94 ± 0.89	< 0.05
SOD (IU/mL)	153.36 ± 19.34	94.26 ± 10.24	< 0.05
GSH-Px (IU/mL)	196.34 ± 24.24	108.15 ± 13.78	< 0.05
CAT (IU/mL)	69.35 ± 9.18	42.26 ± 5.97	< 0.05

3.3. Contents of serum nerve injury molecules and protective molecules

After 7 days of treatment, the contents of serum S100β [(0.85 ± 0.11) *vs.* (1.52 ± 0.18) ng/mL], GFAP [(1.59 ± 0.22) *vs.* (3.32 ± 0.43) pg/mL], NSE [(29.42 ± 3.40) *vs.* (45.48 ± 6.48) ng/mL], MBP [(3.28 ± 0.43) *vs.* (6.39 ± 0.73) ng/mL], NGB [(1.52 ± 0.18) *vs.* (2.96 ± 0.38) μg/mL] and UCH-L1 [(2.38 ± 0.37) *vs.* (4.52 ± 0.64) ng/mL] in patients of the ganglioside group were significantly lower than those of the normal treatment group; while the contents of NGF [(7.94 ± 0.93) *vs.* (3.57 ± 0.41) ng/mL] and BDNF [(15.42 ± 1.89) *vs.* (8.14 ± 0.98) ng/mL] were significantly higher than those of the normal treatment group. The contents of serum S100β, GFAP, NSE, MBP, NGB, UCH-L1, NGF and BDNF in patients of the two groups after 7 days of treatment were statistically significant ($P < 0.05$) (Table 3).

Table 3
Comparison of nerve injury molecules and protective molecules of patients in the two groups.

Parameters		Ganglioside group (n = 26)	Normal treatment group (n = 21)	P
Nerve injury molecules	S100β (ng/mL)	0.85 ± 0.11	1.52 ± 0.18	< 0.05
	GFAP (pg/mL)	1.59 ± 0.22	3.32 ± 0.43	< 0.05
	NSE (ng/mL)	29.42 ± 3.40	45.48 ± 6.48	< 0.05
	MBP (ng/mL)	3.28 ± 0.43	6.39 ± 0.73	< 0.05
	NGB (μg/mL)	1.52 ± 0.18	2.96 ± 0.38	< 0.05
	UCH-L1 (ng/mL)	2.38 ± 0.37	4.52 ± 0.64	< 0.05
Nerve protective molecules	NGF (ng/mL)	7.94 ± 0.93	3.57 ± 0.41	< 0.05
	BDNF (ng/mL)	15.42 ± 1.89	8.14 ± 0.98	< 0.05

4. Discussion

Severe craniocerebral injury is a difficulty in the treatment of the Department of Cerebral Surgery with poor prognosis, higher mortality and morbidity rates. The increase of ICP is an important link of nerve function damage caused by severe craniocerebral injury. Intracranial hematoma caused by external trauma will directly cause the increase of ICP. Local toxic and metabolic products stimulating the nerve cells can cause brain edema and indirectly lead to the increase of ICP[9,10]. Under the effect of continuous intracranial hypertension, patients with severe craniocerebral injury will have high local tissue metabolism and low perfusion, which causes local tissue hypoxia, decrease of oxygen partial pressure, further accumulation of toxic byproduct and strengthening oxidative stress reaction, thus aggravates the nerve function impairment[11,12]. In clinic, hematoma clearance operation and decompressive craniectomy are the conventional ways to treat craniocerebral injury, assisted with mannitol and neurotrophic drugs to lower ICP and alleviate nerve function impairment[13,14]. However, toxic and metabolic products

produced continuously in the local brain tissue in patients with severe craniocerebral injury will do harm to nerve function. Conventional treatments are not sufficient to block the continual production of toxic and metabolic products, thus the overall effect is not satisfying[4,15]. Ganglioside sodium is a newly developed nerve function protective drug, which can promote the growth of the axon, the formation of synapse and eliminate the toxic and metabolic products. In order to determine the value of the usage of ganglioside sodium in the treatment of severe craniocerebral injury, the level of ICP and $P_{bt}O_2$ were determined. The results revealed that after the treatment at days 1, 3, 5 and 7 after treatment, the levels of ICP in patients of the ganglioside group were significantly lower than those of the normal treatment group, while the levels of $P_{bt}O_2$ were significantly higher than those of the normal treatment group, which indicated that adjuvant therapy of ganglioside sodium can effectively reduce ICP, improve the metabolic state of brain tissue and increase the oxygen content for patients with severe craniocerebral injury.

Oxygen free radical is one of the most important toxic byproducts in the local brain tissue of patients with craniocerebral injury. The conditions of high metabolism and low perfusion in local tissues have significant promoting effects on the formation of oxygen free radical. Excessive accumulation of oxygen free radical can cause nerve function impairment by enhancing the oxidative stress reaction[16,17]. Under the effect of oxygen free radical, neuronal cells and glial cells in the brain tissue will show oxidative damage causing nerve function impairment directly. Vascular endothelial cells showing oxidative damage caused by oxygen free radical will lead to local thrombosis, microcirculation disturbance and then further increase the pathological state of the low perfusion and cause nerve function impairment[18,19]. Various components of neuronal cells, glial cells and vascular endothelial cells will be attacked by oxygen free radical. The product produced by the interaction of the lipid in cytomembrane and organelle membrane of cytoplasm and oxygen free radical is MDA. The product made from the interaction of the protein in cytomembrane and cytoplasm and oxygen free radical is AOPP. 8-OHdG is produced by the interaction of the nucleic acid in cell nucleus and oxygen free radical[20-22]. By analyzing the contents of the oxidative stress reactions above, it can be known that the contents of serum MDA, AOPP and 8-OHdG in patients of the ganglioside group were significantly lower than those of the normal treatment group. This showed that ganglioside sodium could effectively remove oxygen free radical reduce the nerve function impairment of oxidative stress response for patients with craniocerebral injury. When oxygen free radical reacted with lipids, proteins and nucleic acids, a large number of antioxidant substances in local tissues would be comsumed. SOD, GSH-Px and CAT are important antioxidant enzymes in the body, which can eliminate the oxygen free radicals generated during oxidative stress by catalyzing redox reaction and keep the local tissue in the redox state. The continuous production of oxygen free radicals in patients with severe craniocerebral injury can result in a large amount of consumptions of the above antioxidant enzymes. By analyzing the contents of the antioxidant enzymes above, it was found that the contents of serum SOD, GSH-Px and CAT in patients of the ganglioside group were significantly higher than those of the normal treatment group.

The nerve cells and glial cells in the brain tissue will be ruptured by the continuing damage of oxygen free radicals. Then, S100β, GFAP, NSE, MBP, NGB, UCH-L1 and other moleculars in endochylema would release into cerebrospinal fluid and get into the blood circulation through the impaired blood brain barrier. Thus, the contents of serum S100β, GFAP, NSE, MBP, NGB and UCH-L1 are measured to reflect the degree of nerve injury. S100β protein is a kind of acid calcium-binding protein, which participates in the regulation of calcium homeostasis, protein phosphorylation, enzyme activation, dynamic changes of cytoskeleton components and other calcium-dependent processes. GFAP is a kind of intermediate filament protein participating in the formation of glial cytoskeleton. NSE and UCH-L1 are both localized in neurons and participate in the regulation of energy metabolism in cells[23,24]. MBP is a kind of strong alkaline membrane protein of oligodendrocyte cell and scabbard film cells on the surface regulating and maintaining the cellular structure and stability of function[25]. NGB is a kind of globin located in the neurone delivering oxygen to brain tissue specifically[26,27]. By analyzing the marker molecules of nerve damage above, it can be known that the contents of serum S100β, GFAP, NSE, MBP, NGB and UCH-L1 in patients of the ganglioside group were significantly lower than those of the normal treatment group. This revealed that the adjuvant therapy of ganglioside sodium can alleviate the injury of neurons and glial cells. By further analyzing the contents of NGF and BDNF possessing neuroprotective effect in the body of patients with craniocerebral injury, it can be known that the contents of serum NGF and BDNF in patients of the ganglioside group were significantly higher than those of the normal treatment group.

In conclusion, the adjuvant therapy of ganglioside sodium in patients with severe craniocerebral injury can effectively reduce ICP, improve $P_{bt}O_2$ and alleviate the injuries of neurons and glial cells caused by oxidative stress.

Conflict of interest statement

The author reports no conflict of interest.

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