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Curative effect of surgery combined with nerve growth factor preparation treatment of acute cerebral hemorrhage

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ABSTRACT

Objective: To study the effect of surgery combined with nerve growth factor preparation treatment of acute cerebral hemorrhage on nerve cytokines and nerve injury.

Methods: 68 patients with acute cerebral hemorrhage who received emergency minimally invasive evacuation of hematoma in Zigong No. 4 People's Hospital between August 2014 and September 2016 were selected and randomly divided into mNGF group and control group, mNGF group received postoperative mouse nerve growth factor preparation combined with conventional therapy, and control group accepted routine postoperative treatment. 10d, 20d and 30d after treatment, the serum was collected to determine the levels of nerve cytokines and nerve injury molecules.

Results: 10d, 20d and 30d after treatment, serum BDNF (5.29±0.88 vs. 3.58±0.61, 6.94±0.93 vs. 3.78±0.55, 9.28±1.13 vs. 4.57±0.62 ng/ml), NTF-α (2.94±0.52 vs. 1.35±0.18, 3.88±0.58 vs. 1.51±0.20, 5.21±0.72 vs. 2.95±0.46 ng/ml), NGF (0.89±0.11 vs. 0.62±0.08, 1.02±0.15 vs. 0.78±0.09, 1.45±0.18 vs. 0.92±0.12 ng/ml) and VEGF (147.53±19.52 vs. 110.38±14.28, 184.95±22.51 vs. 121.29±17.85, 237.49±31.28 vs. 145.38±18.31 pg/ml) levels of mNGF group were significantly higher than those of control group while S100β (1.27±0.20 vs. 2.19±0.33, 0.94±0.14 vs. 1.76±0.25, 0.71±0.09 vs. 1.32±0.17 ng/ml), GFAP (2.08±0.36 vs. 4.42±0.55, 1.65±0.25 vs. 3.57±0.51, 1.31±0.17 vs. 2.93±0.42 pg/ml), NSE (34.21±5.82 vs. 73.19±9.35, 27.58±4.12 vs. 58.76±8.28, 22.12±3.25 vs. 39.52±5.28 ng/ml), MBP (5.28±0.93 vs. 11.28±1.86, 3.89±0.51 vs. 9.12±1.14, 3.12±0.41 vs. 6.79±0.94 ng/ml), MDA (6.97±0.93 vs. 14.21±1.87, 5.02±0.78 vs. 11.75±1.76, 3.57±0.62 vs. 8.12±0.99 μmol/L), AOPP(65.19±9.68 vs. 155.62±19.63, 48.59±7.21 vs. 118.75±16.85, 37.83±5.28 vs. 82.11±10.18 μmol/L) and 8-OHdG (4.77±0.67 vs. 10.28±1.52, 3.52±0.51 vs. 9.38±1.15, 2.33±0.41 vs. 6.52±0.92 ng/ml) levels were significantly lower than those of control group.

Conclusion: Surgery combined with nerve growth factor preparation treatment of acute cerebral hemorrhage can improve neural nutritional status and reduce nerve injury degree, and it is beneficial to the recovery of neural function.

1. Introduction

Acute cerebral hemorrhage is a quite severe clinical cerebrovascular accident, and the cerebrovascular rupture and parenchymal hemorrhage can cause neurologic injury, rapid illness development, poor prognosis as well as high morbidity and mortality. After cerebral hemorrhage occurs, the local hematoma can increase intracranial pressure, oppress parenchymal hematoma and cause primary cerebral damage, and severe cases may cause cerebral hernia; space-occupying hematoma can cause local ischemia hypoxia and lead to secondary brain tissue damage through oxidative stress, cell apoptosis, inflammation and other links[1-3]. In clinical practice, the primary and secondary brain tissue damage caused by space-

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occupying hematoma after intracerebral hemorrhage can work together to cause serious neurologic damage[4-5]. Minimally invasive evacuation of hematoma is the emergency surgery to cure acute cerebral hemorrhage in recent years, it can remove the intracranial hematoma in time and reduce the primary injury and secondary damage caused by space-occupying hematoma, and it helps to improve neural function[6-7]. There have been irreversible primary and secondary damage to neural function after cerebral hemorrhage, the evacuation of hematoma can relieve the further damage of primary and secondary factors to nerve function, but it has no significant fixing value for the nerve function with irreversible damage.

In clinical practice, drug therapy, functional exercise and other means are needed to enhance the recovery and reconstruction of neural function in the convalescence of acute cerebral infarction after emergency operation. Mouse nerve growth factor is a cytokine with nerve repair function, its biological function is similar to human nerve growth factor, and it can not only promote the neuron regeneration, survival, proliferation and differentiation, but is also conducive to nerve fiber growth and nerve injury repair[8-9]. In clinical practice, mouse nerve growth factor preparation is widely used in the treatment of diabetic peripheral neuropathy, acute spinal cord injury, optic nerve injury and other neurological lesions [10-12], and it is less reported in the rehabilitation treatment after acute cerebral hemorrhage. In the following study, the effect of surgery combined with nerve growth factor preparation treatment of acute cerebral hemorrhage on nerve cytokines and nerve injury was analyzed.

2. Methods

2.1 Included cases

68 patients with acute cerebral hemorrhage who received emergency minimally invasive evacuation of hematoma in Zigong No. 4 People's Hospital between August 2014 and September 2016 were selected, and the inclusion criteria were as follows: (1) in line with the diagnostic criteria for acute cerebral hemorrhage, diagnosed after imageological examination and with hematoma volume 20-60ml; (2) with Glasgow coma scale > 5 points and not associated with cerebral hernia; (3) admitted to hospital within 24 hours after onset, and receiving emergency minimally invasive evaluation of hematoma after admission; (4) with complete case data and serum specimen collection.

2.2 Clinical information collection

68 patients with cerebral hemorrhage who underwent emergency minimally invasive evacuation of hematoma were retrospectively analyzed and divided into mNGF group and control group according to the different therapies after evacuation of hematoma, both groups of patients received emergency minimally invasive evacuation of hematoma with YL-1 type intracranial hematoma smash puncture needle, control group received routine postoperative therapy such as reducing intracraninal pressure by dehydration, maintaining water and electrolyte balance, taking antibiotics to prevent infection, taking citicoline to nourish nerve and limb function exercise. mNGF group, on the basis of conventional treatment, received intramuscular injection of 30μg mouse nerve growth factor preparations, 1 time/day, for continuous 30 days.

2.3 Serum index collection and detection methods

10d, 20d and 30d after treatment, 5ml peripheral venous blood was collected and centrifuged to get serum, and enzyme-linked immunosorbent assay kits were used to detect BDNF, NTF-α, NGF, vascular endothelial growth factor (VEGF), S100β protein, glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), myelin basic protein (MBP), malondialdehyde (MDA), advanced oxidation protein products (AOPP) and 8-hydroxy-2-deoxyguanosine (8-OHdG) content.

2.4 Statistical methods

SPSS19.0 version software was used to input and analyze data. Measurement data was in terms of mean ± standard deviation and analyzed by t test; count data was in terms of frequency and analyzed by chi-square test. $P<0.05$ was the standard of statistical significance in differences.

3. Results

3.1 General clinical information of two groups of patients

mNGF group, a total of 32 cases, included 22 male cases and 10 female cases, they were 54.2±7.4 years old, BMI was 22.9±2.8kg/m2, 23 cases were associated with hypertension, 13 cases were associated with diabetes and 19 cases were associated with hyperlipemia; control group, a total of 36 cases, included 24 male cases and 12 female cases, they were 55.1±7.8 years old, BMI was 23.1±3.4kg/m2, 28 cases were associated with hypertension, 15 cases were associated with diabetes and 22 cases were associated with hyperlipemia. After statistical analysis, mNGF group and control group were not significantly different in gender, age, BMI as well as complication of hypertension, diabetes or hyperlipemia

(P>0.05).

3.2 Serum nerve cytokine levels of two groups of patients

10d, 20d and 30d after treatment, analysis of serum nerve cytokines BDNF, NTF-α, NGF and VEGF levels between two groups of patients was as follows: 10d, 20d and 30d after treatment, serum BDNF (5.29±0.88 vs. 3.58±0.61, 6.94±0.93 vs. 3.78±0.55, 9.28±1.13 vs. 4.57±0.62 ng/ml), NTF-α (2.94±0.52 vs. 1.35±0.18, 3.88±0.58 vs. 1.51±0.20, 5.21±0.72 vs. 2.95±0.46 ng/ml), NGF (0.89±0.11 vs. 0.62±0.08, 1.02±0.15 vs. 0.78±0.09, 1.45±0.18 vs. 0.92±0.12 ng/ml) and VEGF (147.53±19.52 vs. 110.38±14.28, 184.95±22.51 vs. 121.29±17.85, 237.49±31.28 vs. 145.38±18.31 pg/ml) levels of mNGF group were significantly higher than those of control group. Differences in serum BDNF, NTF-α, NGF and VEGF levels were statistically significant between two groups of patients 10d, 20d and 30d after treatment (P<0.05).

Table 1
General clinical information of two groups of patients

	mNGF group (n=32)	Control group (n=36)	P
Gender (male/female)	22/10	24/12	>0.05
Age (years old)	54.2±7.4	55.1±7.8	>0.05
BMI (kg/m2)	22.9±2.8	23.1±3.4	>0.05
Hypertension	23(71.88%)	28(77.78%)	>0.05
Diabetes	13(40.63%)	15(41.67%)	>0.05
Hyperlipemia	19(59.38%)	22(61.11%)	>0.05

Table 2
Comparison of serum nerve cytokine levels between two groups of patients

Parameters	mNGF group	Control group	P
10d after treatment			
BDNF(ng/ml)	5.29±0.88	3.58±0.61	<0.05
NTF-α(ng/ml)	2.94±0.52	1.35±0.18	<0.05
NGF(ng/ml)	0.89±0.11	0.62±0.08	<0.05
VEGF(pg/ml)	147.53±19.52	110.38±14.28	<0.05
20d after treatment			
BDNF	6.94±0.93	3.78±0.55	<0.05
NTF-α	3.88±0.58	1.51±0.20	<0.05
NGF	1.02±0.15	0.78±0.09	<0.05
VEGF	184.95±22.51	121.29±17.85	<0.05
30d after treatment			
BDNF	9.28±1.13	4.57±0.62	<0.05
NTF-α	5.21±0.72	2.95±0.46	<0.05
NGF	1.45±0.18	0.92±0.12	<0.05
VEGF	237.49±31.28	145.38±18.31	<0.05

3.3 Serum nerve injury molecule levels of two groups of patients

10d, 20d and 30d after treatment, analysis of serum nerve injury molecules S100β, GFAP, NSE, MBP, MDA, AOPP and 8-OHdG levels between two groups of patients was as follows: 10d, 20d and 30d after treatment, serum S100β (1.27±0.20 vs. 2.19±0.33, 0.94±0.14 vs. 1.76±0.25, 0.71±0.09 vs. 1.32±0.17 ng/ml), GFAP (2.08±0.36 vs. 4.42±0.55, 1.65±0.25 vs. 3.57±0.51, 1.31±0.17 vs. 2.93±0.42 pg/ml), NSE (34.21±5.82 vs. 73.19±9.35, 27.58±4.12 vs. 58.76±8.28, 22.12±3.25 vs. 39.52±5.28 ng/ml), MBP (5.28±0.93 vs. 11.28±1.86, 3.89±0.51 vs. 9.12±1.14, 3.12±0.41 vs. 6.79±0.94 ng/ml), MDA (6.97±0.93 vs. 14.21±1.87, 5.02±0.78 vs. 11.75±1.76, 3.57±0.62 vs. 8.12±0.99 μmol/L), AOPP (65.19±9.68 vs. 155.62±19.63, 48.59±7.21 vs. 118.75±16.85, 37.83±5.28 vs. 82.11±10.18 μmol/L) and 8-OHdG (4.77±0.67 vs. 10.28±1.52, 3.52±0.51 vs. 9.38±1.15, 2.33±0.41 vs. 6.52±0.92 ng/ml) levels of mNGF group were significantly lower than those of control group. Differences in serum BDNF, NTF-α, NGF and VEGF levels were statistically significant between two groups of patients 10d, 20d and 30d after treatment (P<0.05).

Table 3
Comparison of serum nerve injury molecule levels between two groups of patients

Parameters	mNGF group	Control group	P
10d after treatment			
S100β(ng/ml)	1.27±0.20	2.19±0.33	<0.05
GFAP(pg/ml)	2.08±0.36	4.42±0.55	<0.05
NSE(ng/ml)	34.21±5.82	73.19±9.35	<0.05
MBP(ng/ml)	5.28±0.93	11.28±1.86	<0.05
MDA(μmol/L)	6.97±0.93	14.21±1.87	<0.05
AOPP(μmol/L)	65.19±9.68	155.62±19.63	<0.05
8-OHdG(ng/ml)	4.77±0.67	10.28±1.52	<0.05
20d after treatment			
S100β(ng/ml)	0.94±0.14	1.76±0.25	<0.05
GFAP(pg/ml)	1.65±0.25	3.57±0.51	<0.05
NSE(ng/ml)	27.58±4.12	58.76±8.28	<0.05
MBP(ng/ml)	3.89±0.51	9.12±1.14	<0.05
MDA(μmol/L)	5.02±0.78	11.75±1.76	<0.05
AOPP(μmol/L)	48.59±7.21	118.75±16.85	<0.05
8-OHdG(ng/ml)	3.52±0.51	9.38±1.15	<0.05
30d after treatment			
S100β(ng/ml)	0.71±0.09	1.32±0.17	<0.05
GFAP(pg/ml)	1.31±0.17	2.93±0.42	<0.05
NSE(ng/ml)	22.12±3.25	39.52±5.28	<0.05
MBP(ng/ml)	3.12±0.41	6.79±0.94	<0.05
MDA(μmol/L)	3.57±0.62	8.12±0.99	<0.05
AOPP(μmol/L)	37.83±5.28	82.11±10.18	<0.05
8-OHdG(ng/ml)	2.33±0.41	6.52±0.92	<0.05

4. Discussion

Neuron regeneration and repair ability are poor, the primary and secondary neural injury recovery caused by acute cerebral hemorrhage is extremely slow, and most patients will develop severe nerve dysfunction. It is conducive to the reconstruction of the nerve function to use effective drugs to promote the neuron regeneration and repair after minimally invasive evacuation of hematoma. mNGF is the preparation that promotes the neuron repair and the nerve fiber growth. In the study, in order to define

the value of mNGF for rehabilitation therapy after acute cerebral hemorrhage, serum contents of nerve cytokines were analyzed at first. BDNF, NTF-α and NGF are the nerve cytokines that directly promote the neuron growth, differentiation and regeneration, they are conducive to the growth of axons, the formation of synaptic structure and the maintenance of neural function, and they have played a crucial role in the recovery of neural function damage[13-14]. VEGF is a cytokine that promotes endothelial cell growth and increases angiogenesis, and in the restoration of nerve function, it can increase microvascular density to increase blood perfusion to the nerve tissue, which is helpful to the regeneration of the neurons[15]. In the study, comparison of serum levels of these nerve cytokines between two groups of patients showed that 10d, 20d and 30d after treatment, serum BDNF, NTF-α, NGF and VEGF levels of mNGF group were significantly higher than those of control group. This means that mNGF therapy can improve neural nutritional status, increase the levels of a variety of nerve cytokines and create a favorable local environment for the recovery of neural function.

The nerve injury in patients with acute cerebral hemorrhage is associated with the primary damage caused by hematoma compression as well as the oxidative stress, apoptosis, inflammation and other secondary injuries caused by hematoma metabolites. In the primary and secondary damage process of neural function, neurons and glial cells within the nervous tissue will rupture and cause the release of many marker molecules from the cytoplasm into outside of the cells, which cross through the damaged blood brain barrier and enter into the blood circulation[15-16]. S100β and NSE are the marker molecules positioning in neurons, the former is a kind of calcium-binding protein, and it is closely related to the regulation of Ca2+ homeostasis within neurons and the regulation of cytoskeleton elements; the latter is the key enzyme of glycolysis function way in neurons, and it is of great significance to the neuron ATP production and function[17]. GFAP and MBP are the marker molecules positioning in the glial cells, and they are mainly involved in the regulation of glial cell structure stability and skeleton structure formation[18-20]. In order to define the recovery of neurological function in convalescence after acute cerebral hemorrhage, serum nerve injury-related molecule levels were analyzed in the study to reflect the degree of nerve damage, and then assess the recovery of neurological function. Comparison of serum nerve injury molecule levels between two groups of patients showed that 10d, 20d and 30d after treatment, serum S100β, GFAP, NSE and MBP levels of mNGF were significantly lower than those of control group. This means that adjuvant mNGF therapy after minimally invasive evacuation of hematoma can reduce the damage rate of the neurons and glial cells, and it is beneficial to the recovery of neural function.

Oxidative stress reaction activation is an important pathogenic factor of secondary neural damage in patients with cerebral hemorrhage. Bleeding lesion oppression on brain tissue will cause local hypoxia and lead to oxidation respiratory chain coupling obstacles and massive generation of oxygen free radicals, and the oxygen free radicals have oxidizing reaction with the local tissue structure and then cause corresponding oxidative stress damage. After emergency operation to remove the hematoma, the oxidative stress reaction of local tissue will not be immediately eliminated, and the continuously produced oxygen free radicals will continue to cause oxidative stress damage to nerve function and are not conducive to the recovery of neural function. In tissue injury process caused by oxidative stress, the lipid, protein and nucleic acid in cellular structure can react with oxygen free radicals, and these oxidized cell components will further cause cell dysfunction [21-22]. MDA, AOPP and 8-OHdG are the oxidation reaction products of lipid, protein and nucleic acid respectively, and can be used to evaluate the extent of the oxidative stress reaction after released into the blood circulation[23]. In the study, serum levels of these oxidative stress products were analyzed to further reflect the degree of nerve injury, and then assess the recovery of neurological function. Analysis of serum oxidative stress product contents between two groups of patients showed that 10d, 20d and 30d after treatment, serum MDA, AOPP and 8-OHdG levels of mNGF group were significantly lower than those of control group. This means that adjuvant mNGF therapy after minimally invasive evacuation of hematoma can relieve secondary neural damage caused by oxidative stress, and it is beneficial to the recovery of neural function.

To sum up, the mouse nerve growth factor preparation therapy after emergency minimally invasive evacuation of hematoma can increase nerve cytokines to improve the nerve nutrition status and reduce the nerve injury in patients with acute cerebral hemorrhage, and it is beneficial to the recovery of neural function.

Conflict of interest statement

The authors report no conflict of interest.

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