Am J Transl Res 2022;14(2):1024-1033
www.ajtr.org /ISSN:1943-8141/AJTR0137963

Original Article

Effects of the triple therapy of carnosine glycoside, edaravone, and Xueshuantong in hemorrhagic cerebral infarction

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Received August 3, 2021; Accepted November 23, 2021; Epub February 15, 2022; Published February 28, 2022

Abstract: Objective: This study was designed to evaluate the effects of the triple therapy of Muscular Amino Acid and Peptides and Nucleosides (MAAPN), edaravone, and Xueshuantong on neurological function, tumor volume, and adverse reactions in patients with hemorrhagic cerebral infarction. Methods: In this retrospective study, a total of 115 patients with hemorrhagic cerebral infarction admitted to the hospital from January 2020 to January 2021 were enrolled and assigned to the observation group (n=57) or the control group (n=58) according to different treatment methods. The two groups were both treated with a conventional treatment regimen, and the observation group was additionally given carnosine, edaravone, and Xueshuantong, with a course of treatment spanning 14 days. The neurological and motor functions and changes in cerebral edema and cerebral infarct lesion size in patients were evaluated. The levels of inflammatory factors, blood lipids, neuron-specific enolase (NSE), S-100β, and matrix metalloproteinase-9 (MMP-9) of the two groups were determined and compared. The adverse effects and rebleeding of patients were recorded. The Barthel index (BI) was used to evaluate the quality of life of patients. Results: The treatment efficiency in the observation group was significantly higher than that in the control group (P<0.05). After treatment, the observation group obtained more favorable outcomes in terms of the neurological and motor functions, lesions of brain edema and cerebral infarction, and BI scores, than those of the control group (all P<0.05). In addition, after treatment, the levels of inflammatory factors, blood lipids, NSE, S-100β, MMP-9, plasma viscosity, and whole blood viscosity of the two groups of patients all decreased remarkably, with better outcomes in the observation group when compared with the control group (all P<0.05). The observation group showed a markedly lower rebleeding rate than the control group (P<0.05). Conclusion: For patients with hemorrhagic cerebral infarction, the triple therapy of carnosine glycoside, edaravone, and Xueshuantong effectively enhances the neurological and motor function, reduces cerebral edema and cerebral infarction, and improves the quality of life, with high safety.

Keywords: Hemorrhagic cerebral infarction, muscular amino acid and peptides and nucleosides, edaravone, Xueshuantong, triple therapy, neurological function, tumor volume, adverse effect

Introduction

Hemorrhagic cerebral infarction is one of the special types of cerebral infarction, accounting for 10% to 20% of all cerebral infarctions [1]. After cerebral infarction, the sudden reappearance of blood perfusion in the ischemic area causes secondary bleeding, leading to neurological and motor dysfunction in patients, which can be life-threatening in severe cases [2]. Moreover, after blood perfusion, the leakage of blood from the damaged vessel wall may give rise to secondary oozing of blood, known as hematoma. Research has confirmed hematoma enlargement as one of the important factors causing death or unfavorable prognosis of patients with hemorrhagic cerebral infarction [3]. At the current stage, clinical treatment against hemorrhagic cerebral infarction focuses on timely hemostasis, hematomas elimination, brain nerve damage mitigation, and neuroprotection to improve the prognosis of patients.

Edaravone is a brain-protective agent that can alleviate neurological damage by increasing the local cerebral blood flow around the infarct area

in the acute phase of cerebral infarction and slowing down the progression of cerebral edema and cerebral infarction [4]. Muscular Amino Acid and Peptides and Nucleosides (MAAPN) is an important drug for the treatment of cerebral dysfunction, stroke, and cerebral hypofunction triggered by insufficient blood flow to the brain because of its effectiveness in reducing vascular resistance and improving blood circulation disorders [5]. The main active ingredient of Xueshuantong is notoginseng saponins, which can dilate blood vessels and improve blood circulation, with potential efficacy in the treatment of cardiovascular and cerebrovascular diseases [6]. Previous research has demonstrated that Xueshuantong reduces the progression of acute cerebral infarction and optimizes the prognosis of cerebral infarction [7]. Edaravone is a new type of potent antioxidant, hydroxyl radical scavenger, and cerebroprotective agent with clinical characteristics of a high lipid solubility (little effect on hemodynamics), a high blood-brain barrier passage rate (up to 60%), and a strong antioxidant property, which can reduce the area of infarct lesions by inhibiting lipid peroxidation and scavenging reactive oxygen molecules in the body and cytotoxic free radicals in the brain [4]. It can effectively inhibit the peroxidation of brain cells, nerve cells, and vascular endothelial cells and postpone the death of nerve cells, thus alleviating brain edema and brain tissue damage.

Notoginseng saponins, the main component in Xueshuantong, has been demonstrated with marked anti-endothelin, antithrombotic, and thrombolytic effects by regulating the synthesis of nitric oxide to reduce platelet activity and inhibiting platelet aggregation [7]. The novelty of this study is that the combined treatment can effectively rescue the ischemic semidark zone and lessen the cerebral cell perfusion renal injury, which can significantly ameliorate the neurological deficits and daily living ability scores in patients. Moreover, the combination therapy barely affects blood picture, urine routine indicators, coagulation function, liver and kidney function, and electrocardiogram after treatment, which possesses a favorable safety profile. To further improve the prognosis of patients with hemorrhagic cerebral infarction and their quality of life, this study explored the effects of the triple therapy of MAAPN, edaravone, and Xueshuantong on neurological function, tumor volume, and adverse reactions in them.

Materials and methods

Clinical data

A total of 115 patients with hemorrhagic cerebral infarction admitted to The Second Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine from January 2020 to January 2021 were enrolled in this study. The inclusion criteria: (1) patients aged 18-80 years old; (2) patients who met the relevant diagnostic criteria of hemorrhagic cerebral infarction [8]; (3) patients who suffered the first onset of hemorrhagic cerebral infarction within 24 h after onset; (4) patients with cerebral hemorrhage not breaking into the ventricles; (5) all selected cases met the diagnostic criteria in the Diagnostic Points of Various Cerebrovascular Diseases [7], and the diagnosis was confirmed by clinical symptoms observation, cranial CT, or MRI examination. The exclusion criteria: (1) patients with hypertension, brain tumor, severe liver, kidney, or other vital organ dysfunction, or abnormal blood coagulation; (2) patients with cognitive or consciousness disorders or mental disorder; (3) patients with a predisposition to active bleeding; (4) patients with an allergic constitution or a history of drug allerg. The patients were divided into the observation group and the control group according to different treatment methods. The observation group consisted of 57 cases, aged 38 to 71 years old, with a bleeding volume of 8-29 mL and a course of disease between 6 and 24 h. The control group consisted of 58 cases, aged 40-78 years old, with a bleeding volume of 9-30 mL and a course of disease between 5 and 24 h. The study was approved by the hospital ethics committee (2019-12-19), and all the patients signed informed consent forms.

Treatment methods

The control group was given conventional treatment, including strict bed rest, intracranial pressure maintenance, anti-thrombotic and anti-platelet treatments against minor hemorrhage, hematoma removal or decompression by bone craniectomy against massive hemorrhage, blood pressure control, maintenance of

acid-base water and electrolyte balance, nutrition and psychological support, and prevention of complications.

The observation group was additionally treated with MAAPN, edaravone, and Xueshuantong based on the treatment protocols for the control group: 10 mL MAAPN (Shenyang Pharmaceutical Dalei Yunshang Pharmaceutical Co., Ltd., NMPA approval number: H20052546) dissolved in 500 mL 0.9% sodium chloride injection was given to the patients by intravenous drip at 2 mL/min, 1 time/day; 30 mg edaravone (Nanjing Xiansheng Dongyuan Pharmaceutical Co., Ltd., NMPA approval number: H20031342) dissolved in 100 mL 0.9% sodium chloride injection was also given to the patients by intravenous drip within 30 min, twice a day; 4 mL Xueshuantong (Guangxi Wuzhou Pharmaceutical Group Co., Ltd., NMPA approval number: Z45021770) dissolved in 100 mL 0.9% sodium chloride injection was given to the patients in the same way at 1 time/day. The course of treatment spanned 14 days.

Outcome measures

The primary outcome measures were exposure factors and patients' conditions, which are listed below.

(1) Neurological function: With a total score of 0-42 points, the National Institute of Health Stroke Scale (NIHSS) was adopted for the assessment of the neurological function of patients [8]. A higher score indicates more severe neurological impairment.

(2) The treatment efficiency was divided into four levels, namely, cured, markedly effective, effective, and ineffective [9]. After treatment, if the clinical symptoms disappeared completely, and the NIHSS score was reduced by >90%, it was considered as cured. After treatment, if the clinical symptoms were relieved, and the NIHSS score was reduced by 46% to 90%, it was considered as markedly effective. After treatment, if the clinical symptoms were slightly relieved, and the NIHSS score was reduced by 18% to 45%, it was considered as effective. After treatment, if the clinical symptoms were not relieved or even exacerbated, and the NIHSS score was reduced by <18%, it was considered as ineffective. Total effective rate (%) = (the number of cured cases + the number of markedly effectively treated cases + the number of effectively treated cases)/the total number of cases ×100%.

(3) The areas of cerebral edema and cerebral infarction: Head CT scan (RS-250, US RSD) was performed, on which the cerebral edema and cerebral infarction volume were calculated according to the Tada formula [10, 11].

(4) Motor function: With a total score of 0-100 points, the Fugl-Meyer assessment (FMA) was adopted for the assessment of motor function. The FMA score is positively correlated with motor function.

(5) Self-care ability: The Barthel index (BI) was used for the evaluation of self-care ability. It has a total score of 0-100 points, and a higher score indicates better self-care skills.

(6) Adverse reactions and rebleeding: The patients' adverse reactions and rebleeding during the treatment were recorded, on which the incidence rates of them were calculated.

The secondary outcome measures were the clinical effectiveness of the intervention, which are listed below.

(1) Biochemical inspection: Venous blood was drawn from each patient before and after treatment and centrifugated at 4000 r/min to obtain the serum. Then the levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), neuron-specific enolase (NSE), matrix metalloproteinase-9 (MMP-9) were determined using corresponding kit instructions. The information of the kits is presented as follows: TNF-α ELISA Kit (YM-S0122, Shanghai Yuanmu Biotechnology Co., Ltd.); IL-6 ELISA Kit (YM-S0136, Shanghai Yuanmu Biotechnology Co., Ltd.); IL-1β ELISA Kit (YM-S0456, Shanghai Yuanmu Biotechnology Co., Ltd.); NSE Colorimetric/Fluorescent Enolase Assay Kit (ab79757, Abcam); Matrix metalloproteinase-9 ELISA Kit (BEK-2073-2P, Biosensis). A PE-6000 automatic blood cell analyzer (Shenzhen Pukang Electronics Co., Ltd.) was used to determine the serum levels of total cholesterol (TC) and triglyceride (TG).

(2) Hemorheology: Venous blood was drawn from each patient before and after treatment, and whole blood viscosity and plasma viscosity were determined using a blood viscometer (NDJ-8S, Biao Zhuo Co., Ltd.).

Table 1. Comparison of clinical baseline data between the two groups

Index	Observation group (n=57)	Control group (n=58)	X^2/t	P
Gender			1.264	0.564
Male	26	29		
Female	31	29		
Average age (years)	63.29±5.44	64.37±5.42	2.451	0.3245
Average blood loss (ml)	18.38±4.61	17.89±4.56	3.458	0.563
Average course of disease (h)	17.37±2.13	17.41±2.15	2.365	0.754

Statistical analyses

SPSS20.0 was used to process the obtained data in this research, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) to visualize the data into required graphics. The counting data were analyzed using the chi-square test and expressed by [n (%)]. The measurement data were expressed by ($\overline{x}$±s) and analyzed using two independent samples t-test for comparison between groups and paired t-test for comparison within the group. P<0.05 indicated statistically significant difference.

Results

Comparison of clinical baseline information

There was no statistically significant difference in baseline information between the two groups of patients (P>0.05). See **Table 1**.

Comparison of treatment efficacy

The treatment efficacy in the observation group was significantly higher than that in the control group (P<0.05). See **Table 2**.

Comparison of neurological function

Before treatment, no significant difference was found in NIHSS scores between the two groups of patients (P>0.05). After treatment, NIHSS scores of both groups decreased significantly, with lower results obtained in the observation group than those in the control group (P<0.05). See **Table 3** and **Figure 1**.

Comparison of brain edema and cerebral infarction lesion areas

Before treatment, there was no significant difference in the areas of brain edema and cerebral infarction between the two groups of patients (both P>0.05); Hematoma type manifests as secondary high-density shadows in the original infarct, uneven density, irregular edges, and flaky or mass; non-hematoma manifests as high-density shadow in scattered spots, patches, and stripes in the original infarct. After treatment, the areas of brain edema and cerebral infarction lesions in the two groups decreased markedly, with better outcomes observed in the observation group than those in the control group (both P<0.05). See **Table 4**.

Comparison of motor function

Before treatment, no significant difference was obtained in the FMA score between the two groups of patients (P>0.05). After treatment, FMA scores of the two groups of patients elevated remarkably, with better results in the observation group when compared with the control group (P<0.05). See **Table 5**.

Comparison of serum inflammatory factor levels

Before treatment, there was no statistically significant difference in serum TNF-α, IL-6, and IL-1β levels between the two groups of patients (all P>0.05). After treatment, significant declines were found in the serum levels of TNF-α, IL-6, and IL-1β in the two groups, with lower results observed in the observation group in comparison with the control group (P=0.032, 0.021, 0.012). See **Figure 2**.

Comparison of serum NSE, S-100β, and MMP-9 levels

Before treatment, there was no significant difference in serum levels of NSE, S-100β, and MMP-9 between the two groups of patients (all P>0.05). After treatment, the serum levels of NSE, S-100β, and MMP-9 in the two groups showed significant decreases, with lower results in the observation group than those in the control group (all P=0.026, 0.020, 0.015). See **Figure 3**.

Comparison of blood lipid levels

Before treatment, the two groups presented similar levels of TC and TG (both P>0.05). After

Table 2. Comparison of treatment efficacy between the two groups [n (%)]

Groups	n	Cured	Markedly effective	Effective	Ineffective	Total effective rate
Observation group	57	14/24.56	19/33.33	13/22.81	11/19.30	46/80.70
Control group	58	10/17.24	14/24.14	8/13.79	26/44.83	32/55.17
χ^2						19.284
P-value						0.012

Table 3. Comparison of NIHSS scores between the two groups (points, $\bar{x}\pm s$)

Groups	n	Before treatment	After treatment
Observation group	57	17.68±3.43	6.38±4.22*
Control group	58	17.45±2.47	10.21±4.25*
t		0.413	4.849
P-value		0.680	<0.01

Note: Compared with before treatment, *P<0.05.

treatment, the levels of TC and TG in the two groups declined drastically, with greater decreases in the observation group than those in the control group (P=0.002, 0.017). See **Figure 4**.

Comparison of hemorheological indicators

Results in **Table 6** show no significant difference in plasma viscosity and whole blood viscosity before treatment between the two groups (both P>0.05). What stands out in the Table is the significant declines in plasma viscosity and whole blood viscosity of the two groups after treatment, with lower results obtained in the observation group as compared to the control group (both P<0.05).

Comparison of self-care ability

Before treatment, there was no statistically significant difference in BI scores between the two groups of patients (P>0.05). After treatment, BI scores of the two groups of patients increased significantly, with higher BI scores of the observation group than those of the control group (P<0.05). See **Table 7**.

Comparison of adverse reactions and rebleeding

During the treatment, the observation group showed an incidence of adverse reactions of 5.26% (3/57), and the control group showed an incidence of adverse reactions of 3.45% (2/58). There was no significant difference in adverse reactions between the two groups (χ^2=7.382, P=0.492). In addition, after treatment, the rebleeding rate in the observation group was significantly lower than that in the control group (19.30% *vs.* 3.45%, χ^2=14.286, P<0.01). See **Table 8**.

Discussion

Hemorrhagic cerebral infarction is a common type of cerebral infarction, characterized by high morbidity, disability, and mortality rates [12], which cause poor prognosis and insufficient use of thrombolytic therapy in patients with cerebral infarction [13-15]. The pathogenesis of cerebral infarction may impact the body's immune system, inducing the secretion of neutrophil and monocyte chemokines that damage or accelerate damage to the vascular endothelium and promote an inflammatory response. Upon ischemia and hypoxia in brain tissue, the high expression of TNF-α induces the release of potent vasoactive substances, resulting in vasoconstriction, reduction of local cerebral blood flow, and an increase in capillary permeability, which facilitates the development of cerebral ischemia and edema. Currently, notwithstanding certain curative effects that have been achieved by conventional treatments, the treatment efficiency of hemorrhagic cerebral infarction remains unsatisfactory.

A study has showed that edaravone ameliorates neurological deficits and the daily living ability of patients with acute cerebral infarction, and effectively reduces the level of oxidative stress and inflammatory response [16]. Furthermore, it has also been reported that edaravone reduces the occurrence of hemorrhagic transformation after intravenous thrombolysis with recombinant tissue-type plasminogen activator in patients with acute cerebral infarction by downregulating the levels of inflammatory factors such as MMP-9 [17].

MAAPN, mainly composed of polypeptides, amino acids, and nucleotides, is frequently used in the adjuvant treatment of cardiovascular and cerebrovascular diseases. Previous research has applied MAAPN to the early reha-

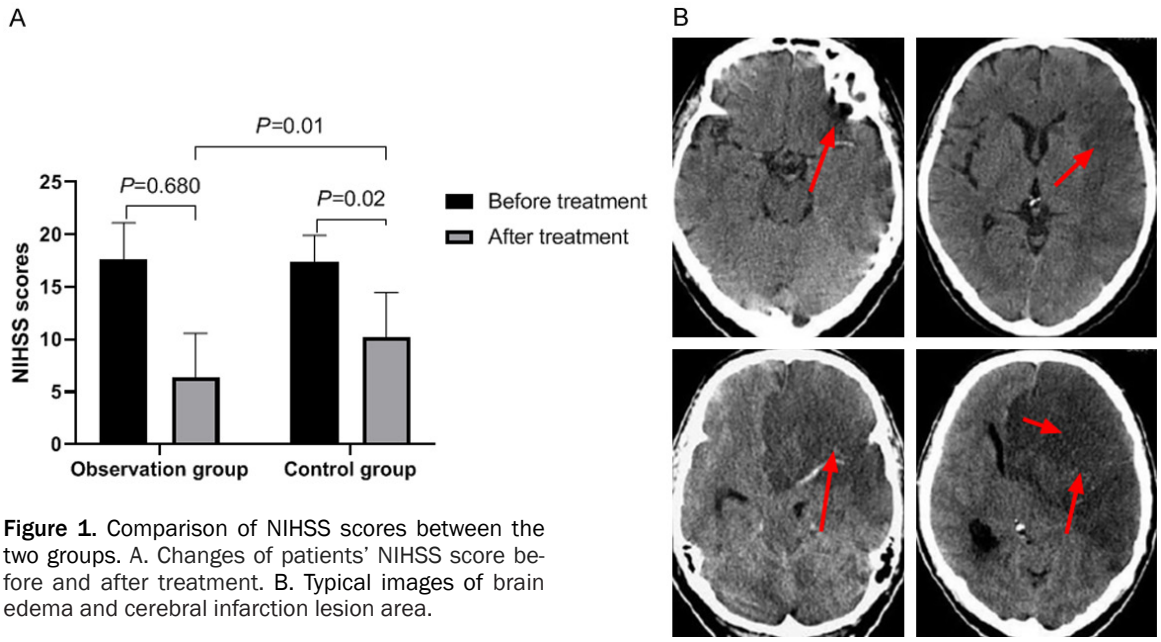

Figure 1. Comparison of NIHSS scores between the two groups. A. Changes of patients' NIHSS score before and after treatment. B. Typical images of brain edema and cerebral infarction lesion area.

Table 4. Comparison of brain edema and cerebral infarction lesion area between the two groups (cm^3, $\bar{x}\pm s$)

Groups	n	Time points	Brain edema	Cerebral infarction
Observation group	57	Before treatment	6.34±1.35	6.34±1.17
		After treatment	4.45±1.22#	2.51±1.14#
		t	7.842	17.701
		P	<0.01	<0.01
Control group	58	Before treatment	6.28±1.31	6.29±1.15
		After treatment	5.68±1.24	4.76±1.12
		t	2.533	7.259
		P	0.013	<0.01

Note: Compared with the control group after treatment, #P<0.05.

Table 5. Comparison of FMA scores between the two groups (points, $\bar{x}\pm s$)

Groups	n	Before treatment	After treatment
Observation group	57	55.34±3.28	79.37±5.43*
Control group	58	55.38±3.26	63.29±5.39*
t		0.066	15.937
P-value		0.948	<0.01

Note: Compared with the control group after treatment, *P<0.05.

bilitation of patients with acute cerebral infarction and revealed that its ability to substantially improve the neurological function of patients and deliver high treatment efficacy, with high safety [18]. Yang HM et al. [19] stated that the combined use of edaravone with Shuxuening in the treatment of hemorrhagic cerebral infarction contributes to the recovery of neurological function and the improvement of daily living ability and decreases the levels of inflammatory factors. Zhang et al. [20] combined MAAPN and ginkgo damol injection in the treatment of acute cerebral infarction and confirmed that it could effectively enhance the patient's blood rheology and neurological function and drive down their blood lipids and inflammatory factor levels. In traditional Chinese medicine (TCM), hemorrhagic cerebral infarction is categorized as stroke, which is mostly interwoven with cerebral arterial obstruction and disorder of Qi and blood. Therefore, the treatment in TCM centers on the clearance of the collaterals and removal of blood stasis to promote blood and Qi circulation and refresh the brain [21]. The results of this study revealed that compared with patients with conventional treatment, those treated with the triple therapy of MAAPN, edaravone, and Xueshuantong obtained lower NIHSS scores, indicating that the triple therapy used in this study is effective in alleviating the clinical symptoms and improving the patients' neurological function, which may lead to a better prognosis of patients, as Xuehuantong potentiates the effi-

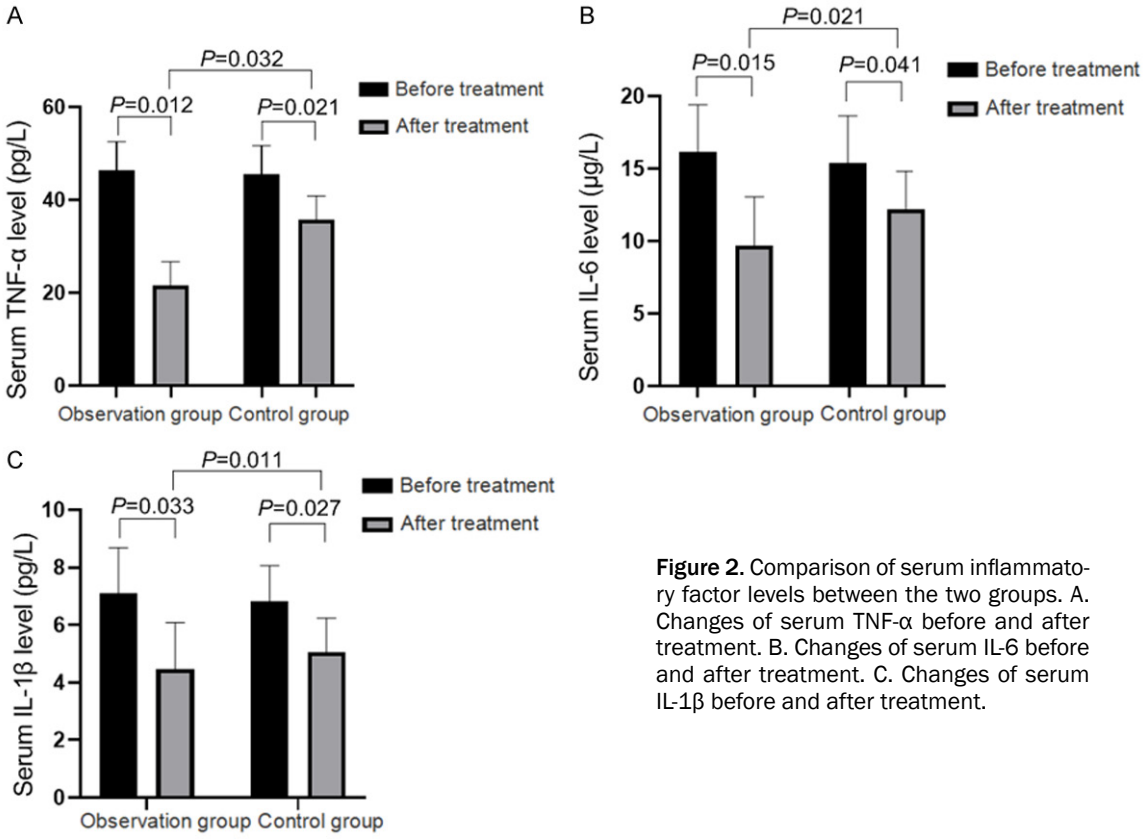

Figure 2. Comparison of serum inflammatory factor levels between the two groups. A. Changes of serum TNF-α before and after treatment. B. Changes of serum IL-6 before and after treatment. C. Changes of serum IL-1β before and after treatment.

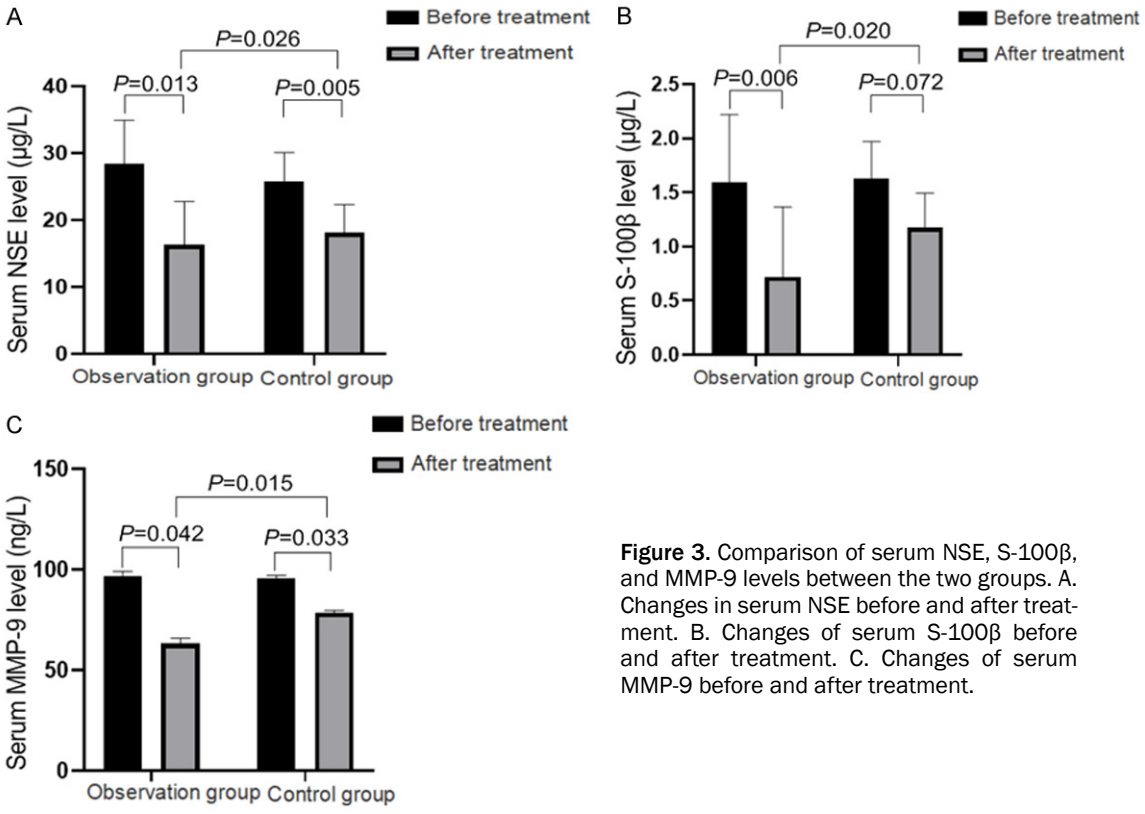

Figure 3. Comparison of serum NSE, S-100β, and MMP-9 levels between the two groups. A. Changes in serum NSE before and after treatment. B. Changes of serum S-100β before and after treatment. C. Changes of serum MMP-9 before and after treatment.

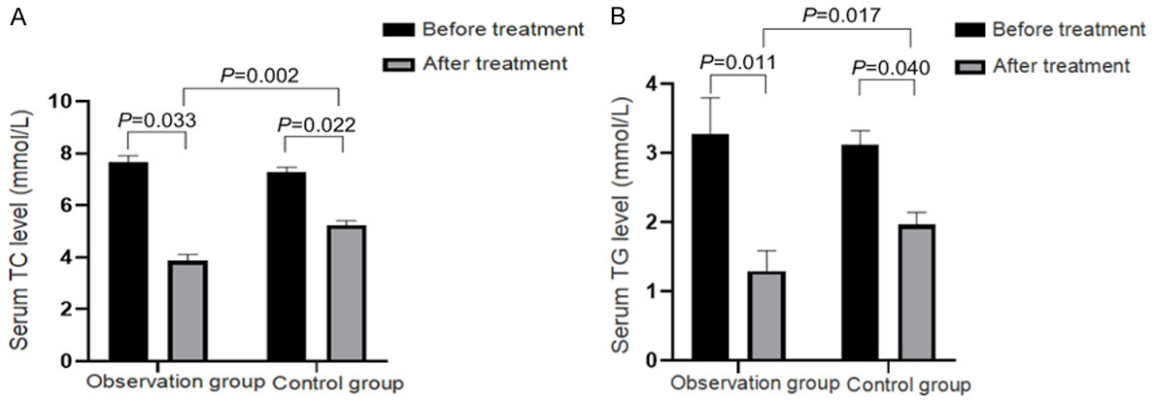

Figure 4. Comparison of blood lipid levels between the two groups. A. Changes in serum TC before and after treatment. B. Changes of serum TG before and after treatment.

Table 6. Comparison of hemorheology between the two groups ($\bar{x}\pm s$)

Groups	n	Time points	Plasma viscosity (mPa·s)	Whole blood viscosity (mPa·s)
Observation group	57	Before treatment	12.39±0.32	7.38±0.56
		After treatment	8.53±0.25#	5.11±0.27#
		t	71.765	27.567
		P	<0.01	<0.01
Control group	58	Before treatment	12.42±0.34	7.43±0.53
		After treatment	10.97±0.23	6.48±0.21
		t	26.902	12.691
		P	<0.01	<0.01

Note: Compared with the control group after treatment, #P<0.05.

Table 7. Comparison of BI scores between the two groups (points, $\bar{x}\pm s$)

Groups	n	Before treatment	After treatment
Observation group	57	54.23±5.16	82.67±4.59*
Control group	58	54.28±5.13	69.34±4.64*
t		0.052	15.486
P-value		0.959	<0.01

Note: Compared with Before treatment, *P<0.05.

cacy of MAAPN and edaravone, by unblocking the meridian and channels of the brain to reinforce the patients' neurological functions. Moreover, the FMA scores of the two groups of patients elevated remarkably, with better results in the observation group when compared with the control group, suggesting a more marked improvement in the motor function of patients receiving the triple therapy, which revealed a harmonious interact of the three drugs in enhancing the patients' motor functions. After treatment, the areas of brain edema and cerebral infarction lesions in the two groups decreased markedly, with better outcomes observed in the observation group than those in the control group, indicating the promising efficacy of the triple therapy in this study in the mitigation of edema and infarction. A previous study has pointed out that Xueshuantong injection prominently promotes the absorption of hematoma during the remission phase of cerebral hemorrhage and cerebral infarction and thus improves the blood rheology indicators [22].

To our best knowledge, TNF-α, IL-6, and IL-1β are important inflammatory factors that mediate the inflammatory response [16]. MMP-9 is a pro-inflammatory protease that is released in response to cytokine stimulation during neuroinflammation, increases blood-brain barrier (BBB) permeability, and may be involved in secondary damage after cerebral ischemia [17]. NSE is usually located in neurons and neuroendocrine cells, and it has been confirmed that the determination of serum NSE concentration serves as a pathological marker protein and a quantitative indicator of the degree of CNS damage [18]. Similar to previous research results [15], blood analysis in this study unveiled significant declines in the serum levels of TNF-α, IL-6, IL-1β, blood lipids, the levels of NSE, S-100β, and MMP-9 in the two groups, with

Table 8. Comparison of adverse reactions and rebleeding

Group	Gastrointestinal reaction	Fatigue	Skin rash	Incidence of adverse reactions	Rebleeding rate
Observation group (n=57)	1	1	1	3 (5.26)	11 (19.30)
Control group (n=58)	2	0	0	2 (3.45)	2 (3.45)
X^2				7.382	14.286
P				0.492	<0.01

lower levels observed in the observation group in comparison with the control group, suggesting that the triple therapy optimizes the alleviation of inflammation response and boosts their lipid metabolism, blood viscosity, and recovery of neurological function, avoids further exacerbation of the disease secondary to excessive inflammatory response, and drives down the risk of atherosclerosis with a lower blood lipid level. Furthermore, analysis results of adverse reactions and rebleeding revealed that the triple therapy did not give rise to an increase of the incidence of adverse reactions, which indicates a safety profile of the triple therapy. The limitation of this study lies in the absence of further multifactorial analysis after multi-indicator determination to obtain clinical risk factors, which may serve for early clinical intervention to improve the prognosis of patients.

In conclusion, for patients with hemorrhagic cerebral infarction, the triple therapy of carnosine glycoside, edaravone, and Xueshuantong effectively enhances the neurological and motor function, reduces cerebral edema and cerebral infarction, and improves the quality of life, with high safety.

Acknowledgements

This study was supported by Natural Science Foundation of Heilongjiang Province (LH2019-H103).

Disclosure of conflict of interest

None.

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