

Original Article

Xingnaojing injection is helpful to improve the efficacy, safety and inhibit serum inflammatory factors in the treatment of patients with acute intracerebral hemorrhage

Jie Cao^{1,2,3}, Min Li², Jie Zhang², Mingshan Hou², Weidong Huang², Wei Shi¹

¹Department of Neurosurgery, The Second Affiliated Hospital of Xi'an Jiao Tong University, Xi'an 710004, Shaanxi Province, China; ²Department of Neurosurgery, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China; ³Department of Neurosurgery, Affiliated Hospital of Xi'an Medical College, Xi'an 710068, Shaanxi Province, China

Received July 1, 2020; Accepted August 15, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: To seek the effect of Xingnaojing injection on efficacy, safety and serum inflammatory factors in patients with acute intracerebral hemorrhage (ICH). Methods: From January 2018 to June 2019, 125 patients with acute ICH admitted to our hospital were selected and separated into two groups. In the control group (CG), patients (60 cases) received routine treatments, while patients in the research group (RG) (65 cases) received Xingnaojing injection on the basis of the CG. The clinical efficacy was observed and total response rate and the incidence of adverse reactions (IAR) were calculated in both groups. The consciousness, neurologic impairment and activities of daily living (ADL) were evaluated in both groups before and after treatment. Before and after treatment, the levels of inflammatory cytokines IL-6, NSE, hs-CRP, and TNF- α were measured in both groups. Logistic regression analysis was applied to analyze the risk factors that affected the efficacy of patients. Results: After therapy, the total response rate in RG was significantly higher than that in CG ($P=0.015$), and the IAR in RG was significantly lower than that in CG ($P=0.004$). After treatment, the GCS scores in RG were obviously higher than those in CG ($P<0.001$). After treatment, the NIHSS scores in RG were obviously lower than those in CG ($P<0.001$). After treatment, the ADL scores in RG were obviously higher than those in CG ($P<0.001$). After treatment, the IL-6, NSE, hs-CRP and TNF- α levels in RG were obviously lower than those in CG ($P<0.001$). Multivariate logistic regression analysis revealed that age, blood loss, smoking history, diabetes history, hypertension history, IL-6, NSE, hs-CRP, TNF- α and treatment methods were independent risk factors that affected the efficacy of patients with acute ICH. Conclusion: Xingnaojing injection is helpful to improve the efficacy, safety and inhibit serum inflammatory factors in treating patients with acute ICH.

Keywords: Xingnaojing injection, acute intracerebral hemorrhage, safety, inflammatory factors, application effect

Introduction

Intracerebral hemorrhage (ICH) is a common clinical disease in cerebrovascular diseases, which refers to hemorrhage caused by primary and non-traumatic vascular rupture in cerebral parenchyma [1]. Epidemiological investigation shows that the incidence of ICH in stroke is about 10-30%, and the fatality rate is as high as 30-50% within 6 months after onset [2]. Acute ICH is a common critical and severe disease in neurology department. Its onset is acute and its condition progresses rapidly, which poses a severe threat to the life and

health of patients and has a high mortality and disability rate [3]. The etiology of ICH is still unclear. The main causes of ICH are hypertension, cerebral arteriosclerosis, obesity, hyperglycemia, etc [4]. For now, the pathogenesis of ICH is not completely clear, but some studies have shown that ICH is closely related to cerebrovascular arteriosclerosis and long-term hypertension [5]. Patients with ICH may have severe headache, unilateral or bilateral limb movement disorders, unilateral sensory disturbance, aphasia, cognitive disorders, loss of consciousness and other clinical manifestations, which may endanger life in severe cases

[6]. Clinically, patients are diagnosed mainly through CT or MRI examination combined with clinical manifestations [7]. At present, the treatment methods of acute ICH mainly include reducing intracranial pressure, adjusting blood pressure, protecting brain cells, supporting symptomatic treatment and surgical operation [8]. Recent studies on acute ICH have shown that there is no effective treatment to continuously improve the neurological function, but the prognosis of patients can be improved by actively managing blood pressure and reducing the progress speed of hematoma, and patients can also have more treatment options through oral anticoagulants and fibrinolytic enzymes. Recent studies have also shown that the therapeutic regimen with different mechanisms of action can synergistically increase the therapeutic effect and improve the prognosis of patients [9]. Therefore, it is of great clinical significance to explore a safe and effective therapeutic method for patients with acute ICH.

The harm of ICH is not only the damage of intracerebral hematoma to brain tissue, but also secondary brain injury. Inflammation is the most important aspect in secondary brain injury [10]. Therefore, any treatment measures that can reduce the release of inflammatory factors and inhibit inflammatory reactions can improve the clinical efficacy and prognosis of patients [11]. According to traditional Chinese medicine, ICH belongs to the category of "apoplexy". Its etiology lies in the deficiency of qi and blood in liver and kidney, and it is also affected by wind, fire, phlegm, deficiency and blood stasis, which leads to the imbalance of yin and yang in the viscera, thus causing hemorrhagic apoplexy [12]. Inducing resuscitation, herb drugs for eliminating phlegm, calming the liver to clear the wind-evil, cooling and activating blood, expelling stasis and frees meridians are the common methods of Chinese medicine in treating acute hemorrhagic stroke [13]. Xingnaojing injection is a patented Chinese medicine prepared through pharmacological research on the ancient prescription of Angong Niu Huang pill and modification based on it. Its main components include musk, gardenia, curcuma aromatica, borneol and other traditional Chinese medicines [14]. Modern pharmacological studies have shown that Xingnaojing injection can act on the central nervous system through the blood-brain barrier, and it can obviously ameliorate

the anoxia tolerance of nerve cells and improve the balance between supply and demand of cerebral oxygen, so it has been clinically used in the treatment of brain diseases [15].

At present, there are few studies on the treatment of acute ICH with Xingnaojing injection. In this study, we explored the effect of Xingnaojing injection on clinical efficacy, safety and serum inflammatory factors in treating acute ICH, and analyzed the factors affecting the efficacy, hoping to provide clinical basis for the therapy of patients with acute ICH.

Materials and methods

Baseline data

From January 2018 to June 2019, 125 patients with acute ICH admitted to Shaanxi Provincial People's Hospital were selected and separated into CG and RG in accordance with different treatment methods, including 60 cases in CG and 65 cases in RG. In CG, patients received routine treatment, while patients in RG received Xingnaojing injection on the basis of the CG. In CG, there were 40 men and 20 women, aged 45-70 years old, with a mean age of 61.15 ± 6.52 years old. In RG, there were 44 men and 21 women, aged 42-71 years old, with a mean age of 60.87 ± 6.35 years old.

Inclusion and exclusion criteria

Inclusion criteria: (1) All patients conformed to the diagnostic criteria for acute ICH and they were diagnosed by brain CT or MRI [16]; (2) The time from onset to admission in all patients was within 24 hours. (3) All patients suffered from the disease for the first time. (4) This research was ratified by the ethics committee of our hospital. All patients and their families were informed and affixed a fully medical informed consent document.

Exclusion criteria: (1) The patient had herniation of brain via cranial CT scan; (2) The patient was complicated with cerebral vascular malformation, cerebral aneurysm rupture and hemorrhage; (3) The patient was complicated with serious organic diseases such as heart, liver, lung and kidney; (4) The patient was complicated with infectious and immune system diseases.

Effect of Xingnaojing injection on acute intracerebral hemorrhage

es; (5) Patient with end-stage chronic diseases and malignant tumors; (6) Patient with cognitive impairment, language and hearing impairment; (7) The patient was complicated with mental diseases or family history of mental illness; (8) The patient was allergic to this therapeutic drug.

Methods of treatment

In both groups, patients were given basic symptomatic and supportive treatment and were absolutely bedridden. Their blood pressure, heart rate, respiration, pulse and other vital signs were monitored, and their blood pressure was controlled within 140-160/60-90 mmHg. Respiratory secretions were removed in a timely manner, the water-electrolyte imbalance was corrected, and nutritional support was strengthened. In CG, patients were given 250 mL of mannitol injection (Shijiazhuang Siyao Co., Ltd., Shijiazhuang, China, H13023037) intravenously and intravenous drip once every 12 h. The oxiracetam injection (4.0 g) (Guangdong Shixin Pharmaceutical Co., Ltd, Jieyang, China, H20050860) was dissolved in 250 mL of 0.9% sodium chloride injection for intravenous drip once a day.

On the basis of treatment in the CG, 20 mL of Xingnaojing injection (Henan Tiandi Pharmaceutical Co., LTD., Kaifeng, China, Z41020664) was dissolved in 250 mL of 0.9% sodium chloride injection, and then the patient was injected intravenously once a day in RG. All patients were treated for 14 days.

Outcome measures

The clinical efficacy was analyzed in both groups and the total response rate was calculated. Meanwhile, the IAR was recorded during treatment.

GCS score: Glasgow coma scale (GCS) [17] was used to evaluate the consciousness state of patients in both groups before and after treatment. The total score was 0-15 points, 15 points were normal, 12-14 points were slight coma, 9-11 points were medium coma, and 0-8 points were severe coma. The higher the score, the better the consciousness state.

NIHSS score: The NIHSS [18] was applied to assess the neurologic impairment in both

groups before and after treatment. The higher the score, the more serious the neurologic impairment.

ADL score: Barthel index scoring scale was applied to assess the activities of daily living (ADL) of patients in both groups before and after treatment [19]. The scale includes 10 items: defecation, miction, making-up, going to toilet, eating, moving, action, dressing, stair activity and bath, with a full score of 100 points. <20 meant a very serious functional impairment and patients needed to be fully cared for by others; A score of 20-40 indicated that patients needed to be taken care of to a large extent; A score of 40-60 indicated that patients needed to be cared for by others; >60 points was basically self-care for patients. The higher the score, the stronger the abilities of daily living.

Inflammatory factors: Before and after treatment, 5 ml of fasting venous blood was obtained from patients in both groups and centrifuged at 2000 r/min for 10 min at room temperature, and then the upper serum was collected. The levels of serum interleukin-6 (IL-6), neuron specific enolase (NSE), high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor- α (TNF- α) were tested by enzyme-linked immunosorbent assay (ELISA). The operation was conducted strictly in accordance with the specifications of human IL-6 ELISA, human NSE ELISA, human HS-CRP ELISA, human TNF- α ELISA (Shanghai Jingkang Biological Engineering Co., LTD., Shanghai, China, JK-(a)-0023, JK-(a)-1746, JK-(a)-1617, JK-(a)-1446) kits.

Efficacy evaluation

Cure: NIHSS score was reduced by more than 90%; Markedly effective: NIHSS score was reduced between 46% and 90%; Effective: NIHSS score was reduced between 18% and 45%; Ineffective: NIHSS score was reduced by less than 18% or increased. Total response rate = (number of cured cases + number of markedly effective cases + number of effective cases)/total number of cases \times 100%.

Statistical methods

SPSS20.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. GraphPad Prism 7 was applied to draw the data picture. The

Effect of Xingnaojing injection on acute intracerebral hemorrhage

Table 1. Comparison of baseline data of patients between the two groups ($\bar{x} \pm sd$)

Classification	RG (n=65)	CG (n=60)	t/ χ^2 value	P value
Gender			0.015	0.903
Male	44 (67.69)	40 (66.67)		
Female	21 (32.31)	20 (33.33)		
Age/years old	60.87 \pm 6.35	61.15 \pm 6.52	0.243	0.808
BMI (kg/m ²)	23.06 \pm 3.21	23.11 \pm 3.05	0.089	0.929
Blood loss (mL)	10.03 \pm 2.01	9.89 \pm 1.96	0.394	0.694
Bleeding site			0.996	0.910
Basal ganglia region	28 (43.08)	26 (43.33)		
Thalamus	20 (30.77)	18 (30.00)		
Cerebral lobe	10 (15.38)	12 (20.00)		
Brainstem	5 (7.69)	3 (5.00)		
Cerebellum	2 (3.08)	1 (1.67)		
Marital status			0.001	0.986
Married	51 (78.46)	47 (78.33)		
Unmarried or widowed	14 (21.54)	13 (21.67)		
Place of residence			0.026	0.870
City	24 (36.92)	23 (38.33)		
Rural	41 (63.08)	37 (61.67)		
Nation			0.002	0.960
Han	49 (75.38)	45 (75.00)		
Minority nationality	16 (24.62)	15 (25.00)		
Educational background			0.397	0.528
\geq High school	31 (47.69)	32 (53.33)		
<High school	34 (52.31)	28 (46.67)		
Smoking history			0.002	0.964
Yes	42 (64.62)	39 (65.00)		
No	23 (35.38)	21 (35.00)		
Drinking history			0.030	0.861
Yes	38 (58.46)	36 (60.00)		
No	27 (41.54)	24 (40.00)		
Diabetes history			0.067	0.795
Yes	43 (66.15)	41 (68.33)		
No	22 (33.85)	19 (31.67)		
Hypertension history			0.077	0.780
Yes	44 (67.69)	42 (70.00)		
No	21 (32.31)	18 (30.00)		

counting data were represented by [n (%)]. The Chi-square test was applied for comparison of the counting data between groups. When the theoretical frequency in Chi-square test was less than 5, the Chi-square test with continuity correction was used. The measurement data were represented by mean number \pm standard deviation ($\bar{x} \pm sd$). The comparison of measurement data between groups was performed by

independent sample t test. Paired T test was applied for comparison between groups before and after therapy. The logistics multivariate regression was applied to analyze the risk factors affecting the efficacy of patients with acute ICH. The difference was statistically significant with $P < 0.05$.

Results

Baseline data

There was no obvious difference in general clinical baseline data such as gender, age, body mass index (BMI), blood loss, bleeding site, marriage, place of residence, nationality, educational background, history of smoking, history of drinking, diabetes history and hypertension history between the two groups ($P > 0.05$) (**Table 1**).

Comparison of therapeutic effects of patients in both groups after therapy

After therapy, the total response rate of the patients in RG was 94.44% and that in CG was 82.81%. The total response rate in RG was obviously higher than that in CG ($P < 0.05$) (**Table 2**).

Comparison of incidence of adverse reaction in both groups

The IAR was 4.62% in RG and 21.66% in CG. The IAR in RG was obviously lower than that in CG ($P < 0.05$) (**Table 3**).

Comparison of GCS scores in both groups

Before treatment, there was no obvious difference in GCS scores between the two groups ($P > 0.05$). After therapy, the GCS scores in the two groups were significantly higher than those before treatment ($P < 0.05$), and the GCS scores in RG were obviously higher than those in CG ($P < 0.05$) (**Figure 1**).

Effect of Xingnaojing injection on acute intracerebral hemorrhage

Table 2. Comparison of therapeutic effects of patients in the two groups after treatment [n (%)]

Grouping	Cure	Markedly effective	Effective	Ineffective	Total response rate (%)
RG (n=65)	32 (49.23)	22 (33.85)	8 (12.31)	3 (4.61)	62 (95.39)
CG (n=60)	15 (25.00)	21 (35.00)	13 (21.67)	11 (18.33)	49 (81.67)
χ^2	-	-	-	-	5.903
P	-	-	-	-	0.015

Table 3. Comparison of incidence of adverse reaction between the two groups [n (%)]

Grouping	Rash	Rapid heartbeat	Rapid breathing	Diarrhea	Myalgia	Abnormal liver function	Total incidence
RG (n=65)	1 (1.54)	1 (1.54)	0 (0.00)	0 (0.00)	1 (1.54)	0 (0.00)	3 (4.62)
CG (n=60)	3 (5.00)	3 (5.00)	2 (3.33)	2 (3.33)	2 (3.33)	1 (1.67)	13 (21.66)
χ^2	-	-	-	-	-	-	8.127
P	-	-	-	-	-	-	0.004

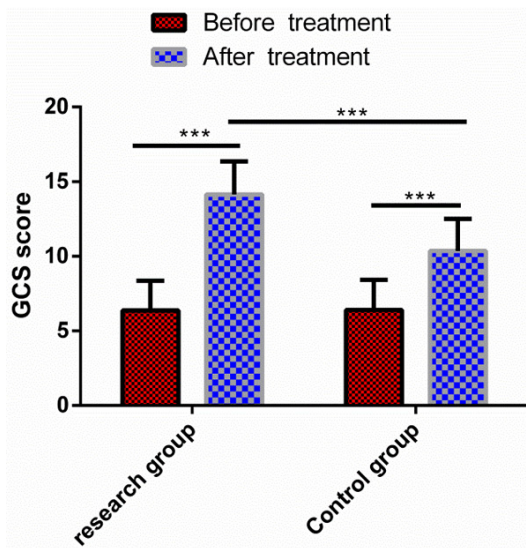


Figure 1. Comparison of GCS scores between the two groups. Before treatment, there was no significant difference in GCS scores between the two groups. After treatment, GCS scores in the two groups were significantly higher than those before treatment, and patients in RG were significantly higher than those in CG. Note: *** $P < 0.001$.

Comparison of NIHSS scores between the two groups

Before therapy, there was no obvious difference in NIHSS scores between the two groups ($P > 0.05$). After therapy, NIHSS scores in the two groups were obviously lower than those before therapy ($P < 0.05$), and the scores of patients in RG were obviously lower than those in CG ($P < 0.05$) (Figure 2).

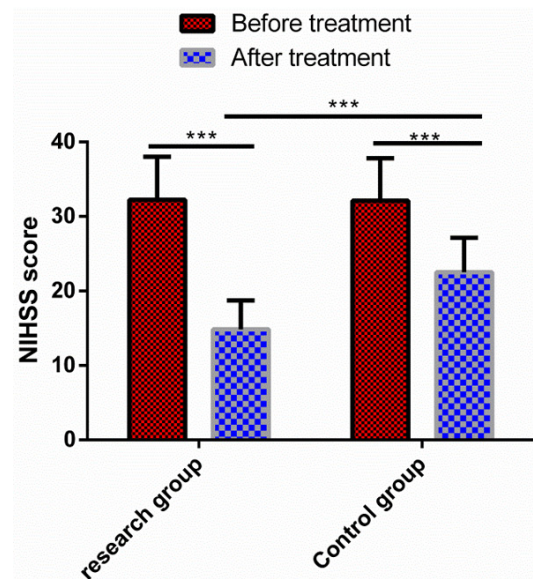


Figure 2. Comparison of NIHSS scores between the two groups. Before treatment, there was no significant difference in NIHSS scores between the two groups. After treatment, the NIHSS scores in the two groups were significantly lower than those before treatment, and the scores in RG were significantly lower than those in CG. Note: *** $P < 0.001$.

Comparison of ADL scores in both groups

Before treatment, there was no obvious difference in ADL scores between the two groups ($P > 0.05$). After therapy, the ADL scores in the two groups were significantly higher than those before treatment ($P < 0.05$), and the scores in RG were obviously higher than those in CG ($P < 0.05$) (Figure 3).

Effect of Xingnaojing injection on acute intracerebral hemorrhage

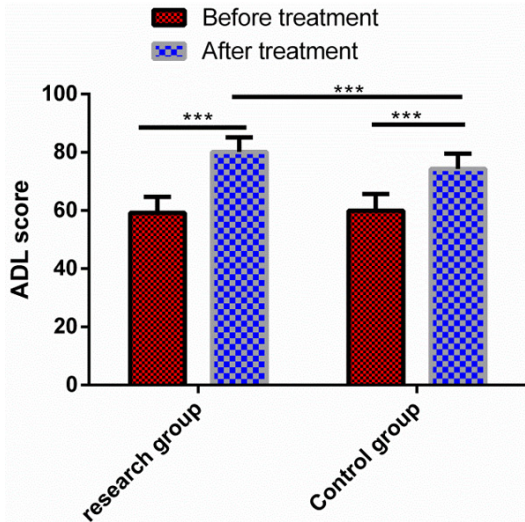


Figure 3. Comparison of ADL scores between the two groups. Before treatment, there was no significant difference in ADL scores between the two groups. After treatment, the ADL scores in the two groups were significantly higher than those before treatment, and the scores of the patients in RG were significantly higher than those in CG. Note: *** $P < 0.001$.

Comparison of inflammatory factors in both groups

Before treatment, there was no obvious difference in the levels of inflammatory factors IL-6, NSE, hs-CRP and TNF- α between the two groups ($P > 0.05$). After therapy, the levels of inflammatory factors IL-6, NSE, hs-CRP, TNF- α in both groups were significantly lower than those before therapy ($P < 0.05$), and the inflammatory factors (IL-6, NSE, hs-CRP, TNF- α) levels in RG were significantly lower than those in CG ($P < 0.05$) (Figure 4).

Analysis of single factor influencing curative effect in patients with acute ICH

The results of this research revealed that there were 111 patients with effective treatment and 14 patients with ineffective treatment. We conducted a single factor analysis of patients in the effective and ineffective groups. This results revealed that there was no obvious difference in gender, BMI, bleeding site, marriage, place of residence, nation and educational background in both groups ($P > 0.05$), while there were statistical differences in age, blood loss, smoking history, drinking history, diabetes history, hypertension history, IL-6, NSE, hs-CRP,

TNF- α and treatment methods ($P < 0.05$) (Table 4).

Analysis of multiple factors influencing curative effect in patients with acute ICH

We included the above factors with differences (age, blood loss, smoking history, drinking history, diabetes history, hypertension history, IL-6, NSE, hs-CRP, TNF- α and treatment methods) for analysis, and listed them as independent variables for assignment. The effectiveness of the treatment was used as a dependent variable for multivariate logistic regression analysis. The results revealed that age ($P = 0.013$), blood loss ($P = 0.009$), smoking history ($P = 0.034$), diabetes history ($P < 0.001$), hypertension history ($P < 0.001$), IL-6 ($P < 0.001$), NSE ($P < 0.001$), hs-CRP ($P < 0.001$), TNF- α ($P < 0.001$) and treatment methods ($P < 0.001$) were independent risk factors that affected the therapeutic effect in patients with acute ICH (Tables 5, 6).

Discussion

Acute ICH is a cerebrovascular disease that seriously endangers people's life and health. It can make the body lose part of its functions, which may cause severe disability to patients and even directly lead to death [20]. With the aging population, the incidence of the disease is on the rise year by year. But in recent years, it has been found that patients with ICH tend to be younger, which may be related to people's lifestyle and social pressure [21]. However, there is no ideal treatment for ICH now. The treatment cost is high, the treatment is not timely, and the early brain protection measures are insufficient, which lead to long-term disability and increases in psychological and economic pressure to the society and patients [22]. Therefore, it is the focus of clinical research to explore a safe and effective treatment for acute ICH in early stage. In recent years, with the development of traditional Chinese medicine (TCM), many studies have found that the application of Chinese medicine preparation can significantly improve the clinical efficacy in treating cerebrovascular diseases, such as salvia injection and Xuesaitong injection in the treatment of cerebral infarction [23, 24]. In this research, we used Xingnaojing injection to treat patients with acute ICH and explored its clinical value.

Effect of Xingnaojing injection on acute intracerebral hemorrhage

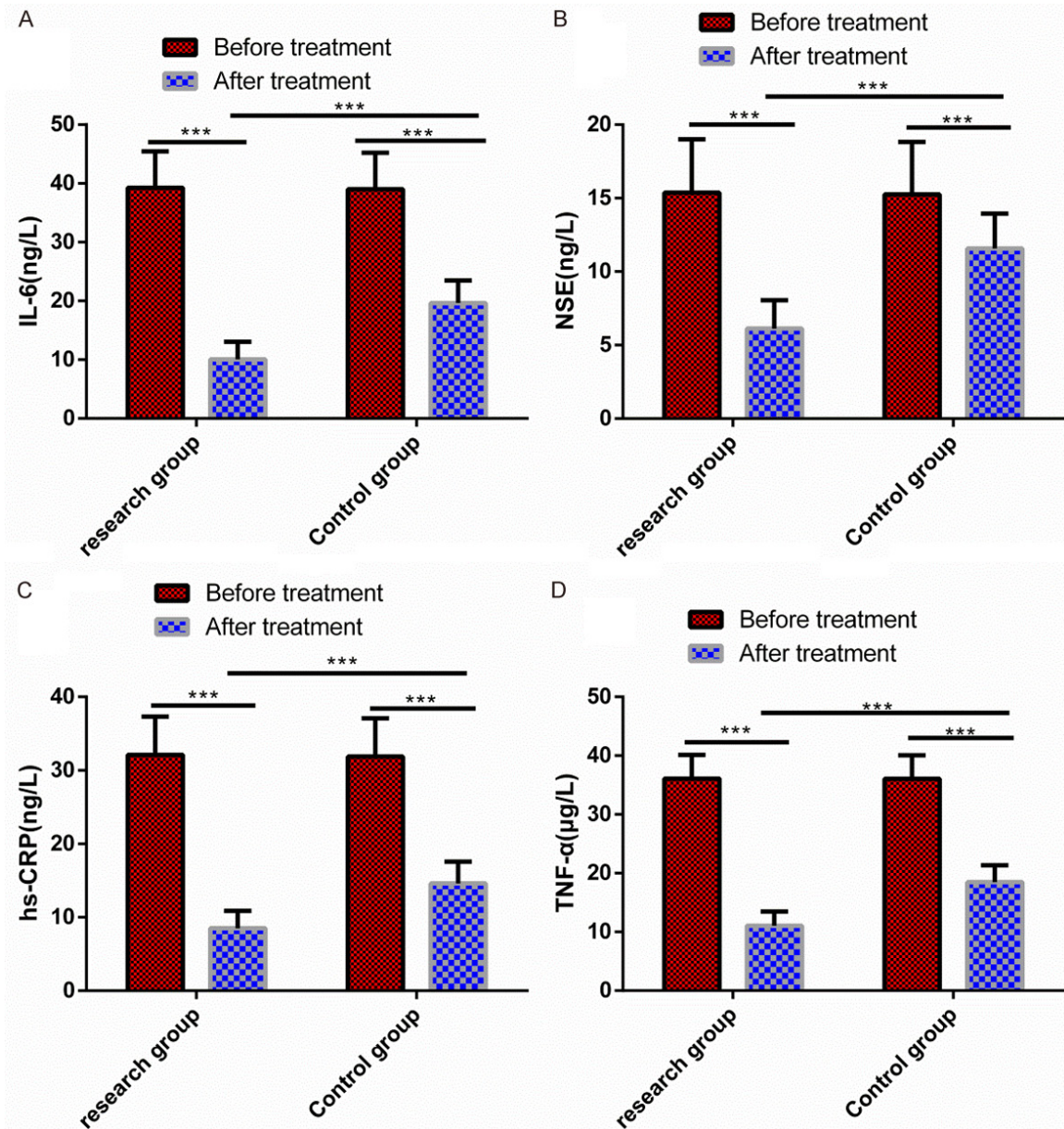


Figure 4. Comparison of inflammatory factors between the two groups. Before treatment, the levels of IL-6 (A), NSE (B), hs-CRP (C), TNF- α (D) had no significant difference in the two groups. After treatment, the levels of IL-6 (A), NSE (B), hs-CRP (C), TNF- α (D) in the two groups were significantly lower than those before treatment, and the levels of IL-6 (A), NSE (B), hs-CRP (C), TNF- α (D) in RG were significantly lower than those in CG. Note: *** $P < 0.001$.

TCM believes that treating acute ICH should focus on removing blood stasis and restoring consciousness, inducing resuscitation and promoting qi circulation, relaxing collaterals and eliminating phlegm. Xingnaojing injection is a water extract preparation of Angong Niu Huang Pills, which has the effects of restoring consciousness, promoting blood circulation, calming wind, inducing resuscitation, detoxifying, eliminating phlegm, clearing heat and activat-

ing blood. Studies by Ma et al. [25] have reported that Xingnaojing injection can obviously improve the curative effect of patients with cerebral infarction, and reduce brain tissue loss, inflammatory reaction and adverse reactions, so its application effect is definite. In this study, our results showed that the clinical efficacy of the patients in RG was obviously higher than that in CG, and the adverse reactions were obviously lower than those in CG, suggesting

Effect of Xingnaojing injection on acute intracerebral hemorrhage

Table 4. Univariate analysis of poor prognosis in patients with acute ICH [n (%), $\bar{x} \pm sd$]

Factors	n	Effective group (n=111)	Ineffective group (n=14)	t/ χ^2 value	P value
Gender				0.924	0.336
Male	84	73 (65.77)	11 (78.57)		
Female	41	38 (34.23)	3 (21.43)		
Age/years old				5.102	0.023
≥ 60	72	60 (54.05)	12 (85.71)		
< 60	53	51 (45.95)	2 (14.29)		
BMI (kg/m ²)	125	22.74 \pm 3.01	23.04 \pm 3.12		
Blood loss (mL)	125	8.31 \pm 1.94	12.87 \pm 2.14		
Bleeding site				3.412	0.491
Basal ganglia region	54	45 (40.54)	9 (64.29)		
Thalamus	38	35 (31.53)	3 (21.43)		
Cerebral lobe	22	21 (18.92)	1 (7.14)		
Brainstem	8	7 (6.31)	1 (7.14)		
Cerebellum	3	3 (2.70)	0 (0.00)		
Marital status				0.452	0.501
Married	98	88 (79.28)	10 (71.43)		
Unmarried or widowed	27	23 (20.72)	4 (28.57)		
Place of residence				0.185	0.666
City	47	41 (36.94)	6 (42.86)		
Rural	78	70 (63.06)	8 (57.14)		
Nation				1.007	0.315
Han	94	85 (76.58)	9 (64.29)		
Minority nationality	31	26 (23.42)	5 (35.71)		
Educational background				0.358	0.549
\geq High school	63	57 (51.35)	6 (42.86)		
$<$ High school	62	54 (48.65)	8 (57.14)		
Smoking history				5.441	0.019
Yes	81	70 (63.06)	13 (92.86)		
No	44	41 (36.94)	1 (7.14)		
Drinking history				4.589	0.032
Yes	74	62 (55.86)	12 (85.71)		
No	51	49 (44.14)	2 (14.29)		
Diabetes history				4.709	0.030
Yes	84	71 (63.96)	13 (92.86)		
No	41	40 (36.04)	1 (7.14)		
Hypertension history				4.251	0.039
Yes	86	73 (65.77)	13 (92.86)		
No	39	38 (34.23)	1 (7.14)		
IL-6 (ng/L)	125	9.87 \pm 2.16	25.75 \pm 4.37	22.500	< 0.001
NSE (ng/L)	125	5.67 \pm 2.04	14.38 \pm 3.19	14.020	< 0.001
hs-CRP (ng/L)	125	7.63 \pm 2.17	21.51 \pm 4.86	18.900	< 0.001
TNF- α (μ g/L)	125	10.26 \pm 2.14	22.43 \pm 3.57	18.390	< 0.001
Methods of treatment				5.903	0.015
Conventional treatment	60	49 (44.14)	11 (78.57)		
Xingnaojing therapy	65	62 (55.86)	3 (21.43)		

Effect of Xingnaojing injection on acute intracerebral hemorrhage

Table 5. Logistic multivariate regression analysis assignment

Factors	Variables	Assignment
Age	X1	<60=0, ≥60=1
Diabetes history	X2	No=0, Yes=1
Hypertension history	X3	No=0, Yes=1
Smoking history	X4	No=0, Yes=1
Drinking history	X5	No=0, Yes=1
Blood loss (ml)	X6	Data was a continuous variable and it was analyzed by using original data.
IL-6 (ng/L)	X7	Data was a continuous variable and it was analyzed by using original data.
NSE (ng/L)	X8	Data was a continuous variable and it was analyzed by using original data.
hs-CRP (ng/L)	X9	Data was a continuous variable and it was analyzed by using original data.
TNF-α (μg/L)	X10	Data was a continuous variable and it was analyzed by using original data.
Methods of treatment	X11	Routine treatment=0, Xingnaojing treatment=1

Table 6. Logistic regression analysis of multiple factors influencing curative effect in patients with acute ICH

Variables	B	S.E	Wals	P	OR	95% CI
Age	0.171	0.072	6.238	0.013	1.141	1.041~2.022
Diabetes history	2.298	0.501	19.482	<0.001	6.652	2.452~17.763
Hypertension history	1.886	0.539	12.381	<0.001	8.742	2.144~21.534
Smoking history	0.895	0.420	4.380	0.034	1.424	1.215~2.342
Drinking history	0.340	0.109	2.435	0.118	0.534	0.372~1.115
Blood loss (ml)	1.231	0.472	6.755	0.009	3.413	1.764~8.665
IL-6 (ng/L)	1.876	0.537	12.233	<0.001	6.594	2.687~10.628
NSE (ng/L)	1.928	0.508	13.105	<0.001	7.012	3.615~18.430
hs-CRP (ng/L)	2.061	0.497	21.168	<0.001	8.415	4.031~18.672
TNF-α (μg/L)	2.087	0.486	22.043	<0.001	8.234	4.017~18.588
Methods of treatment	2.525	0.458	28.548	<0.001	9.513	5.017~22.524

that Xingnaojing injection could improve the clinical efficacy and reduce adverse reactions, with higher safety, which was similar to the research findings of Ma et al. In this study, GCS score, NIHSS score and ADL score were used to evaluate the patients' consciousness state, nerve function damage degree and ability of daily activity respectively. In the studies by Ma et al. [26], the application of Xingnaojing injection in patients with acute ICH can increase GCS score and ADL score and reduce NIHSS score compared with conventional treatment, which has shown that Xingnaojing plays a more significant role in ameliorating efficacy, improving patients' consciousness state, reducing neurological function damage, brain protection, enhancing ability of daily activity and other aspects, so it is more conducive to the prognosis of patients with acute ICH. The findings of this research revealed that the GCS scores and ADL scores of patients in RG after treatment

were obviously higher than those in CG, and NIHSS scores were obviously lower than those in CG, suggesting that Xingnaojing injection could significantly improve the patients' consciousness and ability of daily activity, reduce the damage of nerve function and protect brain tissue, which was similar to the research results of Ma et al. This might be related to the fact that Xingnaojing injection could improve the microcirculation of the patient's brain and maintain the balance of oxygen supply and demand in the brain. The research results of Peng et al. [27] have shown that the serum inflammatory factors TNF-α and hs-CRP levels in patients with ICH are obviously increased, and the brain tissue around hematoma is obviously infiltrated with inflammatory factors, which are significantly reduced after treatment with Xingnaojing injection, and the degree of reduction is greater than that of conventional treatment schemes. The findings of this rese-

Effect of Xingnaojing injection on acute intracerebral hemorrhage

arch showed that the inflammatory factors IL-6, NSE, hs-CRP and TNF- α levels in RG were significantly lower than those in CG after treatment, indicating that Xingnaojing injection could significantly inhibit the release of inflammatory factors and alleviate the inflammatory reaction in brain tissue, which was similar to the results of Peng and other studies. This might be related to the fact that Xingnaojing injection could relieve the anoxic state of the body and decrease the release of free radicals. In the studies of Huang et al. [28], Xingnaojing injection combined with minimally invasive percutaneous drainage can obviously reduce the brain edema of acute ICH and promote the recovery of nerve function, which can be used as a treatment plan for patients with moderate hypertensive basal ganglia hemorrhage. In this study, the total effective rate and recovery of neurological function of patients receiving Xingnaojing injection treatment were significantly better than those of conventional treatment, indicating that Xingnaojing injection could improve the prognosis of patients by promoting neurological function and inflammatory reaction, which was similar to the research results of Huang et al. Studies by An et al. [29] have shown that diabetes history, hypertension history and smoking history are risk factors for ICH. In the end, we also analyzed the risk factors that affected the poor prognosis of patients with acute ICH. The results showed that age, blood loss, smoking history, diabetes history, hypertension history, IL-6, NSE, hs-CRP, TNF- α levels and treatment methods were independent risk factors that affected the efficacy of patients with acute ICH.

Although we have revealed that Xingnaojing injection can bring greater benefits and clinical effects in treating patients with acute ICH, there is still room for improvement in this study. For example, we can supplement the basic experiment of the therapeutic mechanism of Xingnaojing injection to explore the risk factors affecting the efficacy of patients at the molecular level. Furthermore, we can also evaluate the compliance of patients with ICH. In the future, we will gradually improve the research from the above perspective.

To sum up, Xingnaojing injection is helpful to improve the efficacy, safety and consciousness, reduce the damage of nerve function, improve the ability of daily activities and inhibit

serum inflammatory factors in treating patients with acute ICH.

Acknowledgements

This study is financially supported by the technical system of comprehensive surgical treatment of stroke, Supported by the 11th Five Year Plan of the People's Republic of China.

Disclosure of conflict of interest

None.

Address correspondence to: Wei Shi, Department of Neurosurgery, The Second Affiliated Hospital of Xi'an Jiao Tong University, No. 157, Xiwu Road, Xincheng District, Xi'an 710004, Shaanxi Province, China. Tel: +86-18092895019; E-mail: weishixjtu@163.com

References

- [1] Zhang Z, Zhang Z, Lu H, Yang Q, Wu H and Wang J. Microglial polarization and inflammatory mediators after intracerebral hemorrhage. *Mol Neurobiol* 2017; 54: 1874-1886.
- [2] Kim JY and Bae HJ. Spontaneous intracerebral hemorrhage: management. *J Stroke* 2017; 19: 28-39.
- [3] Dang G, Yang Y, Wu G, Hua Y, Keep RF and Xi G. Early erytholysis in the hematoma after experimental intracerebral hemorrhage. *Transl Stroke Res* 2017; 8: 174-182.
- [4] Chen S, Zhao L, Sherchan P, Ding Y, Yu J, Nowrangi D, Tang J, Xia Y and Zhang JH. Activation of melanocortin receptor 4 with RO27-3225 attenuates neuroinflammation through AMPK/JNK/p38 MAPK pathway after intracerebral hemorrhage in mice. *J Neuroinflammation* 2018; 15: 106.
- [5] Wilkinson DA, Pandey AS, Thompson BG, Keep RF, Hua Y and Xi G. Injury mechanisms in acute intracerebral hemorrhage. *Neuropharmacology* 2018; 134: 240-248.
- [6] Keep RF, Andjelkovic AV, Xiang J, Stamatovic SM, Antonetti DA, Hua Y and Xi G. Brain endothelial cell junctions after cerebral hemorrhage: changes, mechanisms and therapeutic targets. *J Cereb Blood Flow Metab* 2018; 38: 1255-1275.
- [7] Fotakopoulos G, Makris D, Kotlia P, Kapsalaki E, Papanikolaou J, Georgiadis I, Zakyntinos E and Fountas K. The value of computed tomography perfusion & transcranial Doppler in early diagnosis of cerebral vasospasm in aneurysmal & traumatic subarachnoid hemorrhage. *Future Sci OA* 2018; 4: FS0313.

Effect of Xingnaojing injection on acute intracerebral hemorrhage

- [8] Chang Z, Mao G, Sun L, Ao Q, Gu Y and Liu Y. Cell therapy for cerebral hemorrhage: five year follow-up report. *Exp Ther Med* 2016; 12: 3535-3540.
- [9] Sembill JA and Kuramatsu JB. Acute treatment of intracerebral hemorrhage. *Med Klin Intensivmed Notfmed* 2019; 114: 613-619.
- [10] Ye L, Gao L and Cheng H. Inflammatory profiles of the interleukin family and network in cerebral hemorrhage. *Cell Mol Neurobiol* 2018; 38: 1321-1333.
- [11] Zou Y, Zhang W, Huang C and Zhu Y. Clinical significance of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in acute cerebral hemorrhage with gastrointestinal hemorrhage, and logistic regression analysis of risk factors. *Exp Ther Med* 2019; 18: 1533-1538.
- [12] Chen CC, Chen X, Li TC, Lin HL, Chu YT, Lee HC, Cheng YK, Chen DC, Tsai SC, Cho DY and Hsieh CL. PG2 for patients with acute spontaneous intracerebral hemorrhage: a double-blind, randomized, placebo-controlled study. *Sci Rep* 2017; 7: 45628.
- [13] Xu S, Pang Q, Lin Z and Zhang N. Effect of integrated traditional Chinese and Western medicine therapy for acute hypertensive intracerebral hemorrhage: a meta-analysis. *Artif Cells Nanomed Biotechnol* 2017; 45: 1-6.
- [14] Zhang YM, Qu XY, Zhai JH, Tao LN, Gao H, Song YQ and Zhang SX. Xingnaojing injection protects against cerebral ischemia reperfusion injury via PI3K/Akt-mediated eNOS phosphorylation. *Evid Based Complement Alternat Med* 2018; 2018: 2361046.
- [15] Zhang YM, Qu XY, Tao LN, Zhai JH, Gao H, Song YQ and Zhang SX. XingNaoJing injection ameliorates cerebral ischaemia/reperfusion injury via SIRT1-mediated inflammatory response inhibition. *Pharm Biol* 2020; 58: 16-24.
- [16] Cordonnier C, Demchuk A, Ziai W and Anderson CS. Intracerebral haemorrhage: current approaches to acute management. *Lancet* 2018; 392: 1257-1268.
- [17] Reith FC, Van den Brande R, Synnot A, Gruen R and Maas AI. The reliability of the glasgow coma scale: a systematic review. *Intensive Care Med* 2016; 42: 3-15.
- [18] Zollner JP, Misselwitz B, Kaps M, Stein M, Konczalla J, Roth C, Krakow K, Steinmetz H, Rosenow F and Strzelczyk A. National Institutes of Health Stroke Scale (NIHSS) on admission predicts acute symptomatic seizure risk in ischemic stroke: a population-based study involving 135,117 cases. *Sci Rep* 2020; 10: 3779.
- [19] Ohura T, Hase K, Nakajima Y and Nakayama T. Validity and reliability of a performance evaluation tool based on the modified Barthel Index for stroke patients. *BMC Med Res Methodol* 2017; 17: 131.
- [20] Lattanzi S, Cagnetti C, Provinciali L and Silvestrini M. Neutrophil-to-lymphocyte ratio and neurological deterioration following acute cerebral hemorrhage. *Oncotarget* 2017; 8: 57489-57494.
- [21] Lattanzi S and Silvestrini M. Blood pressure in acute intra-cerebral hemorrhage. *Ann Transl Med* 2016; 4: 320.
- [22] Charidimou A, Morotti A and Boulouis G. Cumulative meta-analysis of intensive blood-pressure lowering in acute cerebral hemorrhage: Quo vadis? *J Neurol Sci* 2017; 375: 179-180.
- [23] Wang K, Zhang D, Wu J, Liu S, Zhang X and Zhang B. A comparative study of Danhong injection and *Salvia miltiorrhiza* injection in the treatment of cerebral infarction: a systematic review and meta-analysis. *Medicine (Baltimore)* 2017; 96: e7079.
- [24] Duan X, Zhang D, Wang K, Wu J, Zhang X, Zhang B and Gao X. Comparative study of xuesaitong injection and compound *salvia miltiorrhizae* injection in the treatment of acute cerebral infarction: a meta-analysis. *J Int Med Res* 2019; 47: 5375-5388.
- [25] Ma X, Yang YX, Chen N, Xie Q, Wang T, He X and Wang J. Meta-analysis for clinical evaluation of xingnaojing injection for the treatment of cerebral infarction. *Front Pharmacol* 2017; 8: 485.
- [26] Ma X, Wang T, Wen J, Wang J, Zeng N, Zou W and Yang Y. Role of Xingnaojing Injection in treating acute cerebral hemorrhage: a systematic review and meta-analysis. *Medicine (Baltimore)* 2020; 99: e19648.
- [27] Peng W, Yang J, Wang Y, Wang W, Xu J, Wang L and Xing Z. Systematic review and meta-analysis of randomized controlled trials of Xingnaojing treatment for stroke. *Evid Based Complement Alternat Med* 2014; 2014: 210851.
- [28] Huang YJ. Effect of Xingnaojing injection combined with minimally invasive percutaneous drainage in treating brain edema and content of serum AQP4 in patients with moderate hypertensive basal ganglia hemorrhage. *Zhongguo Zhong Yao Za Zhi* 2014; 39: 2564-2568.
- [29] An SJ, Kim TJ and Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. *J Stroke* 2017; 19: 3-10.