

Original Research Article

Effect of Angong Niu Huang pill combined with mild therapeutic hypothermia on acute cerebral hemorrhage in patients

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Abstract

Purpose: To investigate the effect of Angong Niu Huang pill combined with mild therapeutic hypothermia on acute cerebral hemorrhage.

Methods: From July 2017 to December 2020, 118 patients with acute cerebral hemorrhage treated in Dongying Honggang Hospital were recruited and assigned randomly to receive either routine treatment (control group, n = 59) or Angong Niu Huang Pill plus mild therapeutic hypothermia (study group, n = 59).

Results: The study group showed a higher treatment efficacy (98.31 %) than the control group (82.78 %, $p < 0.001$). After treatment, patients in the study group achieved significantly higher Glasgow Coma Scale (GCS) scores (13.01 ± 2.31) and a lower intracranial pressure (14.25 ± 3.12) versus those in the control group (10.18 ± 2.05 , 18.15 ± 3.05 , respectively, $p < 0.001$). The study group displayed lower blood glucose and blood pressure levels than the control group ($p < 0.001$).

Conclusion: Combined Angong Niu Huang Pill and mild therapeutic hypothermia therapy in patients with acute cerebral hemorrhage significantly improves treatment efficacy, as well as reduces intracranial pressure, blood sugar, blood pressure, and tumor marker levels in the patients. It also improves the ability of daily living of the patients and lowers the incidence of adverse reactions.

Keywords: Angong Niu Huang pill, Mild therapeutic hypothermia, Acute cerebral hemorrhage

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INTRODUCTION

Intracerebral hemorrhage (ICH) refers to hemorrhage caused by primary non-traumatic intracranial parenchymal vascular rupture [1] with a high mortality and disability rate, accounting for 20 - 30 % of all cerebral apoplexy. The pathogenesis of ICH is closely related to hyperlipidemia, diabetes, and hypertension [2].

The mortality rate of ICH reaches up to 30%-40% in the acute phase of the disease [3].

The onset of acute cerebral hemorrhage is mostly associated with significantly increased blood pressure and intracranial pressure, and patients usually present with varying degrees of impaired consciousness, headache, vomiting, and in severe cases, even convulsions, heart rate changes, and death. Most survivors also

experience sequelae such as cognitive impairment, motor impairment, and speech and swallowing disorders [4].

The current treatment methods for acute ICH include surgical treatment and conservative medication. Nonetheless, the mortality of ICH remains high despite surgical interventions with curative intent, and currently, no specific drugs are available for conservative treatment [5]. *Angong Niuhuang* pill is a traditional Chinese medicine (TCM) preparation that clears heat, detoxifies the body, and relieves convulsions. Prior research has shown a higher treatment efficiency of *Angong Niuhuang* Pill for acute ICH versus conventional treatment [6], indicating that *Angong Niuhuang* Pill has benefits for the neurological function improvement of patients.

Therapeutic hypothermia offsets neuroexcitation in brain cells through the stabilization of calcium and glutamate release, thereby reducing cell death [7]. A previous study found that a 2 - 3 °C drop in brain temperature is protective against ischemic brain injury [8]. In recent years, mild therapeutic hypothermia (with a temperature of 30 - 35 °C) has been adopted for cerebral ischemia, cerebral hypoxia, and cerebral hemorrhage with favorable outcomes [9,10]. In this study, the effects of *Angong Niuhuang* pill /mild therapeutic hypothermia for acute ICH were investigated.

METHODS

General patient information

A total of 118 patients with acute ICH who were hospitalized in Dongying Honggang Hospital between July 2017 and December 2020 were included and assigned to a control group (n = 59) and a study group (n = 59). In the control group, there were 30 males and 29 females, and the patients were aged 49.68 ± 8.19 years, with a mean course of disease of 11.13 ± 2.03 h. In the study group, there were 33 males and 26 females, and the patients were aged 50.23 ± 7.86 years, with a mean course of disease of 11.07 ± 1.63 h. The patient characteristics of the

two groups were comparable ($p > 0.05$), as shown in Table 1.

Ethical approval

The ethics committee of Dongying Honggang Hospital has ratified this study (2017 - 6 - 30). This study was conducted in strict accordance with the guidelines of Helsinki Declaration [11].

Inclusion and exclusion criteria

Inclusion criteria

Patients who met the diagnostic criteria for acute ICH and provided written informed consent were included.

Exclusion criteria

Patients who had a history of allergy to the drug used in the study, with serious side effects, and with hospital referrals were excluded from this study.

Treatments

The patients in the control group were given conventional therapy for acute ICH, including dehydration therapy to lower the intracranial pressure, as well as to control cerebral edema, nutritional therapy, maintenance of water and electrolyte balance, clearance of free radicals. Antibiotics were used to prevent pulmonary and other infections, enhance brain cell metabolism, and prevent complications.

The study group was given a combined treatment of *Angong Niuhuang* Pill and mild therapeutic hypothermia. (1) The patients received one *Angong Niuhuang* Pill daily, which was decocted or dissolved in warm water for administration. If the patient was in a coma, it was administered by nasogastric feeding, and the duration of treatment was 7 days. (2) T1B type mild therapeutic hypothermia treatment instrument was used. The patients were given ice packs on their heads, and a temperature control blanket was used to maintain the patient's body temperature at 33 - 35 °C. The treatment time varied from 2 to 14 days.

Table 1: Comparison of general patient information between the two groups ((mean \pm SD, n = 59)

Group	Male (N)	Female (N)	Age (years)	Course of disease (h)
Control	30	29	49.68 ± 8.19	11.13 ± 2.03
Study	33	26	50.23 ± 7.86	11.07 ± 1.63
T	-	-	0.372	0.177
P-value	-	-	0.711	0.860

During the treatment, the body temperature, pulse, blood pressure, and response to hypothermia of the patients were closely monitored.

Evaluation of parameters/indicators

Clinical treatment efficacy

Based on the degree of neurological deficit of patients, the treatment efficacy was divided into cured, markedly effective, effective, ineffective or aggravated, with the neurological deficits improvement of 91 - 100 % for cured, 46-90 % for markedly effective, 18 - 45 % for effective, and less than 18 % for ineffective or aggravated.

GCS and intracranial pressure level

Glasgow Coma Scale (GCS) was used to evaluate the degree of coma in patients with a total score of 15 points. The score was proportional to the severity of coma.

Tumor markers

Serum levels of neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), and myelin basic protein (MBP) were determined using enzyme-linked immunosorbent assay, the serum level of C-reactive protein (CRP) was determined using an automatic biochemical analyzer, while serum level of lactate dehydrogenase was determined using lactate dehydrogenase analyzer.

Plasma BNP level

Before and after treatment, about 2 - 3 mL of peripheral venous blood was obtained from patients and centrifuged for 15 min to obtain the serum. The plasma brain natriuretic peptide (BNP) levels were determined using the Roche BNP diagnostic kit and supporting reagents in strict accordance with the kit instructions.

Blood glucose and blood pressure

Approximately 2 - 3ml of fasting venous blood was obtained from the patients, and blood glucose and blood pressure (BP) were measured

by the glucose oxidase method. Blood glucose of ≥ 6.1 mmol/L was considered high blood glucose, and BP was measured three times and averaged.

Activities of daily living score

The score of activities of daily living (ADL) was evaluated via the modified Barthel Index (BI). The scale totaled 100 points, and a low score indicates a poor ADL.

Incidence of adverse reactions

The adverse reactions included constipation, lung infection, gastrointestinal bleeding, and renal function damage.

Data analysis

GraphPad Prism 8 software was used to process images while SPSS 22.0 software was used to process the data. Count data (n (%)) and measurement data (mean \pm SD) were subjected to chi-square and t-tests, respectively, and statistical significance was defined as $p < 0.05$.

RESULTS

Clinical efficacy

The study group had more cases with efficacy of cured (37.29 %) and markedly effective (45.76 %) and fewer cases with efficacy of ineffective or aggravated (1.69 %) versus the control group (18.64, 25.42, and 18.64 %, $p < 0.05$). Angong Niu Huang pill/mild therapeutic hypothermia for the study group resulted in higher treatment efficacy (98.31 %) when compared with conventional therapy (82.78 %, $p < 0.05$). (Table 2).

GCS and intracranial pressure levels

After treatment, Angong Niu Huang pill / mild therapeutic hypothermia used in the study group was associated with a higher GCS score and intracranial pressure versus conventional therapy ($p < 0.05$, Table 3).

Table 2: Comparison of clinical efficacy between the two groups (% , n = 59)

Group	Cured	Markedly effective	Effective	Ineffective or aggravated	Total effective rate
Control	11 (18.64)	15 (25.42)	22 (37.29)	11 (18.64)	48 (82.78)
Study	22 (37.29)	27 (45.76)	9 (15.26)	1 (1.69)	58 (98.31)
χ^2			9.277		
P-value			0.002		

Table 3: Comparison of GCS and intracranial pressure levels between the two groups after treatment (mean ± SD, n = 59)

Group	GCS (score)	Intracranial pressure (mmHg)
Control	10.18 ± 2.05	18.15 ± 3.05
Study	13.01 ± 2.31	14.25 ± 3.12
t	7.038	6.866
P-value	<0.001	<0.001

Table 4: Comparison of tumor markers between the two groups after treatment (mean ± SD, n = 59)

Group	NSE (µg/L)	S100B (µg/L)	MBP (mg/L)	CRP (mg/L)	Lactic acid (mmol/L)
Control	33.18 ± 4.24	0.96 ± 0.23	13.28 ± 4.19	203.54 ± 42.24	2.67 ± 0.78
Study	20.76 ± 3.67	0.51 ± 0.14	7.66 ± 2.72	88.46 ± 25.31	1.93 ± 0.49
t	17.012	12.837	8.641	17.951	6.171
P-value	<0.001	<0.001	<0.001	<0.001	<0.001

Table 5: Comparison of blood glucose and blood pressure values before and after treatment in the two groups (mean ± SD, n = 59)

Group	Blood glucose (mmol/L)		Blood pressure (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment
Control	6.45 ± 1.23	5.89 ± 1.56	168.51 ± 23.22	142.16 ± 20.09
Study	6.58 ± 1.09	5.16 ± 0.89	167.36 ± 24.31	130.85 ± 19.32
T	0.608	3.122	0.263	3.117
P-value	0.544	0.002	0.793	0.002

Tumor markers

After treatment, the study group showed significantly lower serum levels of NSE, S100B, MBP, CRP, and lactate dehydrogenase than the control group ($p < 0.001$). (Table 4).

Plasma BNP levels

After treatment, the BNP levels of all patients were reduced, with higher results in the study group than in the control group ($p < 0.05$, Figure 1).

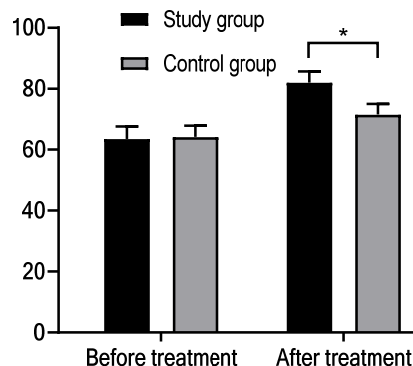


Figure 1: Comparison of plasma BNP levels between the two groups. **Note:** *significant difference between the two groups ($p < 0.05$)

Blood glucose and blood pressure

The blood glucose and BP levels in both groups were significantly decreased after treatment, with lower levels of blood glucose and BP in the study group ($p < 0.05$, Table 5).

ADL score

The ADL scores of the patients in both groups were markedly increased after treatment, with higher results in the study group ($p < 0.05$, Figure 2).

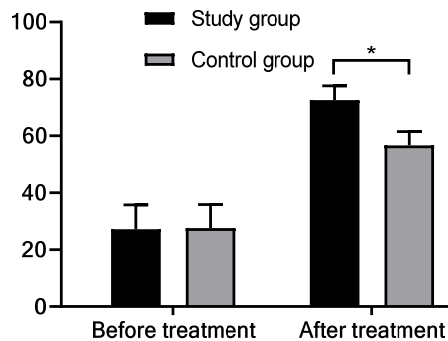


Figure 2: Comparison of ADL scores between the two groups. **Note:** *significant difference between the two groups ($p < 0.05$)

Incidence of adverse events

The incidence of adverse events in the study group (11.86 %) was lower than that in the control group (40.67 %, $p < 0.05$, Table 6).

Table 6: Comparison of adverse reactions between the two groups (%)

Group	Constipation	Pulmonary infection	Gastrointestinal bleeding	Renal function damage	Total incidence
Control	2 (3.39)	5 (8.47)	11 (18.64)	6 (10.16)	24 (40.67)
Study	0 (0.00)	2 (3.39)	4 (6.77)	1 (1.69)	7 (11.86)
χ^2			12.644		
P-value			< 0.001		

DISCUSSION

ICH has high mortality and morbidity, accounting for 20 to 30 % of all strokes [12]. After acute ICH, the occupying lesion of the hematoma is prone to complications such as cerebral edema, cerebral nerve cell necrosis, and aggravation of primary injury [13].

At present, the principles of clinical treatment for acute ICH are to reduce intracranial pressure and edema, improve vasospasm, inhibit apoptosis, and aggressively protect neural cells. According to TCM, brain injury promoted by acute ICH is attributed to internal obstruction of blood stasis and dysregulation of qi, which ultimately leads to blood stasis and *qi stagnation* [14]. Therefore, the treatment is to relieve blood stasis, achieve hemostasis, and activate the orifices. Modern pharmacology studies have shown that Angong Niu Huang pills improve microcirculation, protect brain cells, and remove blood stasis, thereby relieving brain pressure and brain damage. Mild therapeutic hypothermia is a physical method to counteract neuroexcitation in brain cells and reduce the degree of cell death [15].

Previous research by Metz suggested that a temperature of 32.5 – 35 °C is conducive to reducing intracranial pressure [16]. In recent years, mild therapeutic hypothermia (with a temperature of 30 - 35 °C) has achieved favorable outcomes in treating cerebral ischemia, cerebral hypoxia, and cerebral hemorrhage [17,18]. The results of the current study indicated that *Angong Niu Huang* Pill/mild therapeutic hypothermia significantly reduced the levels of NSE, S100B, and MBP proteins and mitigated the severity of neuron damage in the bleeding site. Mild therapeutic hypothermia treatment inhibits the generation, release, and uptake of endogenous harmful factors after brain injury [19]. *Angong Niu Huang* Pill excites the cerebral cortex, repaired damaged brain cells, protects the blood-brain barrier, reduces capillary permeability, and improves neurological function, indicating that the combined treatment of *Angong Niu Huang* Pill and mild therapeutic hypothermia alleviates inflammatory responses and lowers the incidence of multiple organ failure in patients.

CONCLUSION

Treatment of patients with acute ICH using a combination of Angong Niu Huang Pills and mild therapeutic hypothermia enhances treatment efficacy and lowers intracranial pressure, blood glucose, and blood pressure in the patients. The combined therapy also improves patients' ability of daily life and reduces incidence of adverse reactions.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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