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Original Article

Effects of Danhong injection on patients with acute cerebral infarction

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Abstract: Objective: To explore the therapeutic effects of Danhong injection on acute cerebral infarction (ACI) patients, including its effects on nerve function, quality of life, coagulation function and hemorheology. Methods: One hundred and fifty patients with ACI were selected as our research subjects. The patients were separated into the experimental group and the control group according to a digital random table. Routine treatment, including analgesia, dehydration and anticoagulation, were given to the patients in the control group for one month. Apart from the routine treatment, additional intravenous drip of 40 mg Danhong was applied to the patients in the experimental group, once a day for one month. The curative effect between the two groups was observed and compared. Besides, the National institute of health stroke scale (NIHSS) scores, coagulation function index, hemorheology index and SF-36 scale scores of the two groups before and after treatment were also compared. Results: The total effective rate of the experimental group was much higher than that of the control group (93.3% vs 78.7%, P=0.010). After treatment, the NIHSS scores in the two groups were both significantly decreased over those before treatment (P<0.001) and the NIHSS scores of the experimental group was evidently lower than that of the control group (P<0.001). Compared with corresponding index before treatment, levels of activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) all increased markedly and the levels of fibrinogen (FIB) decreased sharply in the two groups after treatment (P<0.001). At the same time, PT, APTT and TT levels in the experimental group were all markedly higher than those in the control group, and FIB levels showed the contrary trend (P<0.05). In addition, the whole blood viscosity, platelet aggregation rate and plasma viscosity of the two groups were all clearly decreased through the treatment (P<0.001) and these indices in the experimental group were sharply lower than those of the control group (P<0.001). What is more, the scores of SF-36 in the two groups were both elevated by the treatment (P<0.001) and as expect, the scores of SF-36 in the experimental group were still substantially higher than those in the control group after treatment (P<0.001). Conclusion: Danhong injection can significantly improve the clinical effect, neurological function and quality of life of ACI patients, which is mainly achieved by improving the coagulation function and hemorheology index of the patients.

Keywords: Acute cerebral infarction, Danhong injection, therapeutic effects, coagulation function, hemorheology

Introduction

Acute cerebral infarction (ACI) is a common clinical ischemic cerebrovascular disease. Due to its rapid onset, rapid progression, fairly high disability rate and mortality rate, ACI greatly threatens the life and health of patients [1, 2]. In the clinic, atherosclerosis and other factors which induce acute cerebral vascular stenosis or even occlusion are the main causes of ACI. They give rise to a lack of blood supply, and then lead to cerebral ischemia and hypoxia, which further induces edema and necrosis, eventually inducing neurological damage, language or limb dysfunction [3]. Some studies have shown that changes in coagulation function such as increased blood viscosity is a main inducer of ACI. These studies point out that about 80%-90% of cases of ACI are caused by thrombus and other emboli blocking cerebral arteries [4]. Thus, the focus of clinical treatment of ACI is to restore the blood and oxygen supply of brain tissue as soon as possible, save the dying brain cells, improve the coagulation function and hemorheology indexes of brain; only through which we can avoid damage to brain function [5].

Some studies have shown that microcirculation disorders and thrombosis in the brain are

closely related to hemorheology and coagulation [6, 7]. Danhong injection, as a kind of compound preparation of Traditional Chinese Medicine, is mainly composed of Salvia miltiorrhiza and safflower. Danhong injection helps to promote blood circulation and remove blood stasis, dredge blood vessels and relax collaterals, thus it has great effects on acute thrombus events [8, 9]. At present, Danhong injection has already been extensively used in the treatment of ischemic vascular diseases [10]. However, up to now, there are few studies about the therapeutic effects of Danhong Injection on ACI, especially in the improvement of neurological function, quality of life, coagulation function and hemorheology. In order to provide an experimental basis and new strategies for the clinical treatment of ACI, this study mainly discusses the therapeutic effect of Danhong Injection on patients with ACI and its effects on the neurological function, quality of life, coagulation function and hemorheology indexes.

Materials and methods

General materials

One hundred and fifty patients with ACI were selected from the Department of Neurology of Affiliated Hospital of Chengde Medical University during January 2017 to July 2019. They were separated into an experimental group and a control group according to a digital random table. The patients in the experimental group received Danhong injection (Purchased from Heze bubo Pharmaceutical Co., Ltd., China. No.: Z20026866. Specification: 10 mg/bottle) in addition to the routine treatment. Intravenous drip treatment: 10 mg Danhong injection was diluted with 250 mL normal saline, 40 mL of the mixture was injected each time, once a day for one month.

Inclusion criteria: According to the results of clinical manifestations and imaging examination, ACI was diagnosed as the first time. The diagnosis standard is in accordance with the guidelines for ACI issued by the European Stroke Promotion Association in 2000 [11]; Onset time is longer than 6 hours; accompanied by different degrees of movement and sensory dysfunction, but without significant disturbance of consciousness.

Exclusion criteria: Severe organ dysfunction, such as heart, liver and kidney; combined with acute cerebral hemorrhage, transient ischemic attack and autoimmune diseases; patients with a large area of cerebral infarction; existing hypersensitivity or contraindications to the drugs in Danhong injection; patients who have taken drugs affecting coagulation function or have undergone craniocerebral surgery within the past 3 months; patients without complete clinical data or who could not cooperate with this study.

The implementation of this study was reviewed by the Ethics Committee of the Affiliated Hospital of Chengde Medical University, and informed consent was signed by all patients or their guardians.

Treatment methods

All the selected patients were treated with routine analgesia, dehydration, anti-coagulation, maintenance of internal environment balance, brain protection and neuronutrition. Routine treatment interventions were conducted on patients in the control group, including bed rest, oxygen inhalation, oral aspirin anticoagulation (Purchased from Bayer medical and health Co., Ltd., Germany. No.: J20171021). Patients with hypertension were given drugs orally such as loxorubicin (Purchased from Pfizer Pharmaceutical Co., Ltd., USA. No.: H10950224) to control blood pressure and Lipitor (Purchased from Pfizer Pharmaceutical Co., Ltd., USA. No.: H20051408) to adjust blood lipid levels. Metformin (Purchased from Shanghai Squibb Pharmaceutical Co., Ltd., China, No.: H20023371) and other drugs were taken orally to control blood glucose levels in patients with diabetes. The experimental group had an additional Danhong injection (Purchased from Hezebao Pharmaceutical Co., Ltd., China. After diluted with 250 mL normal saline, take 40 mg Danhong injection once a day through intravenous drip for one month) in addition to the same medication as the control group.

Outcome measures

Main outcome measures: Compare the therapeutic effects of the two groups: After being treated for one month, the therapeutic effects of the two groups were evaluated [12]. Invalid:

There was no change in the patients' condition before and after treatment, and no improvement in muscle strength. Effective: The patient's symptoms and signs were both improved, and the muscle strength recovered to level 2. Markedly effective: the symptoms and signs of the patients were significantly improved, most of them were able to take care of themselves in daily life, and their muscle strength recovered to above level 2. Cure: all the symptoms and signs of the patient disappear, the muscle strength returns to normal, and patients can take care of themselves in daily life. Total effective rate was calculated according to the following formula: cases of (effective + effective + cure)/Total cases × 100%.

Comparison of neurological function and mental state between the two groups after 1 month of treatment: National institute of health stroke scale (NIHSS) was used to check the neurological function and mental state of all patients. NIHSS has 11 items, including consciousness level, gaze, visual field, facial paralysis, upper limb movement, lower limb movement, limb freeing movement, sensation, language, dysarthria and neglect. The score range is 0-42 points. The higher the score is, the more serious the nerve damage is and vice versa.

Secondary outcome measures: Activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT) and fibrinogen (FIB) were compared between the two groups. One day before the treatment and one month after the treatment, the coagulation function indexes (APTT, PT, TT and FIB) of the two groups were detected by the Automatic Coagulation Analyzer (purchased from Sysmex company of Japan, Type CA7000), and corresponding average value was taken to compare the differences between the two groups.

Hemodynamic indexes including plasma viscosity, whole blood viscosity and platelet aggregation rate were compared between the two groups. One day before treatment and one month after treatment, the hemorheology indexes of all patients, such as plasma viscosity, whole blood viscosity and platelet aggregation rate were examined by the full-automatic Hemorheology analyzer (Beijing SECCO Sid Technology Co., Ltd., Type SA-6000), and the average value was taken to compare the differences between the two groups.

Comparing the quality of life of the two groups before and after treatment: SF-36 scale was used to check the quality of life of patients one day before and one month after treatment. The SF-36 scale included physical and mental health. Physical health includes physical pain, physical activity, work efficiency and overall health. Mental health includes social ability, mental state, vitality and emotional state. The total score of SF-36 is 100. The higher the score is, the better the quality of life is, and vice versa.

Adverse reactions in these two groups were observed.

Statistical analysis

SPSS 21.0 was used to compare and analyze the research data. The measurement data is expressed by mean ± standard deviation. Paired t-test is suitable for the comparison of patients in the same group before and after treatment, and independent sample t-test is suitable for the comparison between two groups. Enumeration data is expressed by percentage or rate and Chi square test is applicable to the comparison between two groups. $P<0.05$ is considered as a significant difference.

Results

Comparison of general data between patients in the two groups

There was no significant difference in age, the proportion of men and women, the time from onset to treatment, basic diseases and the location of cerebral infarction between the two groups ($P>0.05$) (**Table 1**).

Comparison of clinical effects between patients in the two groups

After treated for one month, total effective rate of the experimental group was 93.3%, while that of the control group was 78.7% with a statistically significant difference ($P=0.010$) (**Table 2**).

Table 1. Comparison of basic data

Index	Experimental group	Control group	T value/χ^2 value	*P* value
Cases	75	75	-	-
Male/Female (case)	43/32	45/30	0.110	0.740
Age (year)	57.6±4.1	58.1±4.3	0.729	0.467
BMI (kg/m^2)	22.9±0.6	23.1±0.8	1.732	0.085
Hypertension (case)	31	29	0.111	0.739
Hyperlipemia (case)	17	14	0.366	0.545
Diabetes (case)	10	13	0.462	0.497
Time from onset to treatment (hour)	11.2±1.5	10.9±1.3	1.309	0.193
Location of cerebral infarction (case)			0.784	0.853
Nucleus basalis	37	35		
Brainstem	5	3		
Cerebellum	8	9		
Lobes	25	28		

Note: BMI: Body Mass Index.

Table 2. Comparison of clinical effects (cases)

Group	Cases	Invalid	Effective	Markedly effective	Cure	Total effective rate
Control group	75	16	22	19	18	78.7%
Experimental group	75	5	20	24	26	93.3%
χ^2 value						6.700
P value						0.010

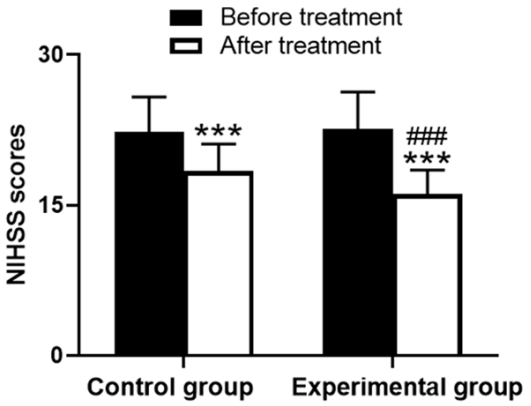

Figure 1. Comparison of NIHSS scores. Compared with patients in the same group before treatment, ***P<0.001; compared with the control group after treatment, ###P<0.001; NIHSS: National institute of health stroke scale.

Comparison of NIHSS scores between patients in the two groups

Before treatment, no significant difference in NIHSS scores was found between the two groups. After being treated for 1 month, the NIHSS scores of the two groups were both significantly decreased (P< 0.001). What is more, the NIHSS scores of the experimental group were much lower compared with the control group after one month of treatment (t=5.274, P<0.001) (**Figure 1**).

Comparison of coagulation indexes between the two groups

Comparing to that before treatment, PT, APTT and TT levels were markedly increased and level of FIB was dramatically decreased in the two groups after 1 month of treatment (P<0.001). Before treatment, no significant difference was shown in PT, APTT, TT and FIB coagulation levels between the two groups (P>0.05). However, levels of APTT, TT and PT in the experimental group all increased substantially, and FIB level decreased evidently comparing to that of the control group through treatment (P<0.05) (**Table 3**).

Comparison of hemodynamic indexes between the two groups

No significant difference in whole blood viscosity, platelet aggregation rate and plasma viscosity between the two groups was shown before treatment. The above indexes of the two groups all decreased significantly after 1 month of treatment, and there was a significant difference comparing to that of before treatment (P<0.001). Simultaneously, the abo-

Table 3. Comparison of coagulation indexes

Index	Control group	Experimental group	t value	*P* value
Cases	75	75	-	-
PT (s)				
Before treatment	10.1±2.4	9.8±2.0	0.832	0.407
After treatment	12.5±3.2***	13.7±3.6***	2.158	0.033
TT (s)				
Before treatment	13.9±3.5	14.2±3.9	0.496	0.621
After treatment	14.9±4.1***	16.6±4.5***	2.418	0.017
APTT (s)				
Before treatment	30.1±3.8	30.5±4.2	0.612	0.542
After treatment	32.7±4.7***	34.6±5.2***	2.348	0.020
FIB (g/L)				
Before treatment	4.9±1.1	5.1±1.3	1.017	0.311
After treatment	3.9±0.8***	3.2±0.6***	2.598	0.010

Note: PT: prothrombin time; TT: thrombin time; APTT: activated partial thromboplastin time; FIB: fibrinogen. Compared with the same group before treatment, ***P<0.001.

ve indices of the experimental group all decreased significantly comparing with the control group with a significant difference (P<0.001) (**Figure 2**).

Comparison of SF-36 scores between the two groups

No significant difference in SF-36 was found between the two groups before treatment. After treatment, the scores of SF-36 in the two groups were both significantly elevated with significant difference (P<0.001). Concurrently, scores of SF-36 in the experimental group were much higher than those in the control group with significant difference after the treatment (P<0.001) (**Figure 3**).

Comparison of adverse reactions between the two groups

No serious adverse reactions happened in either group. Two cases of rash, one case of facial flush and one case of nausea and vomiting appeared in the experimental group. After continuous administration, the symptoms improved, and there was no effect on the treatment and observation process of the patients. No significant difference existed in the incidence of adverse reactions between the treatment group and the control group.

Discussion

Acute cerebral infarction (ACI) is a common acute and severe disease found in the clinic. Due to different onset areas and different degrees of brain tissue damage, and different clinical manifestations of ACI, resulting in a complex presentation of symptoms most patients may miss the best opportunity for thrombolysis at the time of consultation. Therefore, effective drug treatment is necessary to reduce the area of ACI, decrease the morbidity and mortality, and improve the prognosis of patients. From the point of view of Traditional Chinese Medicine (TCM), ACI belongs to the category of "stroke". The pathogenesis of ACI is considered as Qi and blood disorder induced by choking of cerebral vessels. Thus, a focus of the treatment is to relax the blood channels and collaterals by promoting blood circulation and removing blood stasis. It has been reported that Danhong injection helps to activate blood circulation and dredge meridians, disperse blood stasis and relieve pain [13]. As such, we set out to explore whether the Danhong injection has therapeutic effect on ACI.

Danhong injection is a new type of pure Chinese herbal injection agent, which is processed and synthesized by Salvia miltiorrhiza and Carthamus tinctorius. It is one of the main TCMs which is conducive to promote blood circulation and remove blood stasis [14]. The results of this study show that the total effective rate of the experimental group is much higher than that of the control group, with a significant difference of 93.3% compared to 78.7%. The above results indicate that Danhong injection can significantly improve the clinical effect of patients with ACI, which is consistent with the research report of Wang et al [15]. At present, quality of life is one of the important indices used to evaluate the prognosis of cerebral infarction patients [16]. The SF-36 scale was used in this study to assess quality of life by evaluating the subjective feelings and activity ability of the human body. The results showed that, the SF-36 scale scores of the experimental group increased significantly with statistical differences compared to that of the control group after treatment; indicating that Danhong injection can significantly improve the quality of life of patients with ACI. In addition, NIHSS scale, as one of the important indexes to ev-

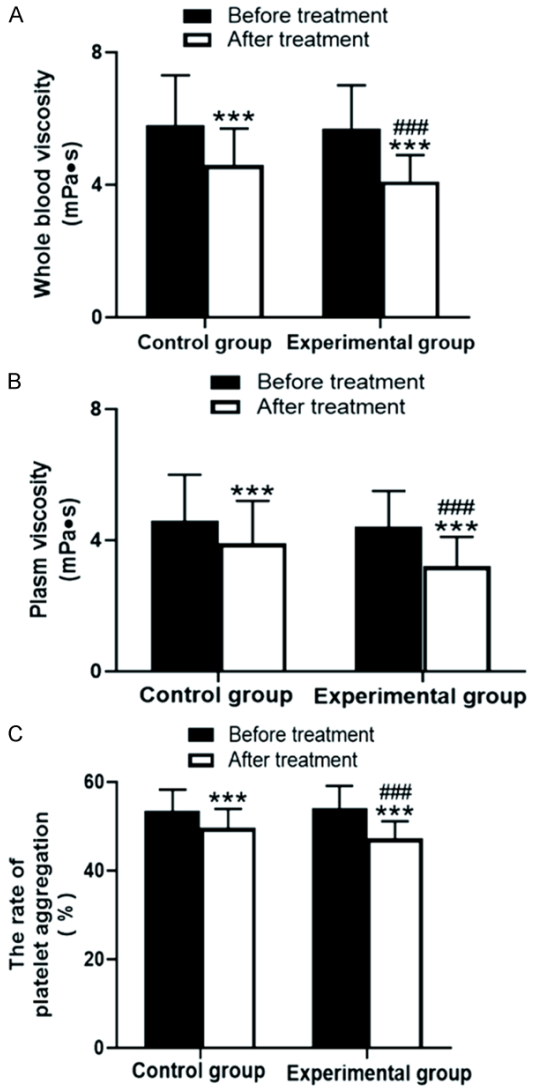

Figure 2. Comparison of hemodynamic indices. Compared with patients in the same group before treatment, ***P<0.001; compared with the control group after treatment, ###P<0.001; A: Whole blood viscosity; B: Plasma viscosity; C: Platelet aggregation rate.

aluate the neurological function and mental state of patients, has been widely used in clinical practice [17]. The results of our study showed that compared with the control group after treatment, the NIHSS scores of the experimental group sharply decreased, indicating that Danhong injection also had obvious effect on improving the neurological function and mental state of patients with cerebral infarction.

Some studies have shown that the main pathogenesis of ACI is cerebral vascular thrombosis. PT, APTT, TT and FIB are widely used in clinic as the monitoring indicators of the coagulation function in the body [18]. Results of our study showed that, after being treated for one month, the PT, APTT and TT levels of the experimental group were significantly increased, and the FIB level was significantly decreased compared with the control group with a significant difference. These above results indicate that Danhong injection could significantly improve the coagulation function of the patients, relieve the hypercoagulable state of patients, and reduce the formation of thrombus, which are consistent with the previous results reported by Fan et al [19]. In addition, FIB has been demonstrated to be crucial in the pathogenesis of ACI. High level of FIB induces damage of blood vessel walls and increases blood viscosity, laying the basis for thrombosis and atherosclerosis. Moreover, FIB level is also an important factor affecting hypercoagulability in patients with cerebral infarction [20]. Evaluation of blood flow status and properties in patients is mainly based on hemorheology indexes. It has been reported that high viscosity caused by abnormal hemorheology is closely related to the occurrence and development of ACI [21]. Results of this study showed that, compared with the control group after one month of treatment, the plasma viscosity, whole blood viscosity and platelet aggregation rate of the experimental group were all markedly reduced with significant differences. Our study suggests that Danhong injection can effectively improve

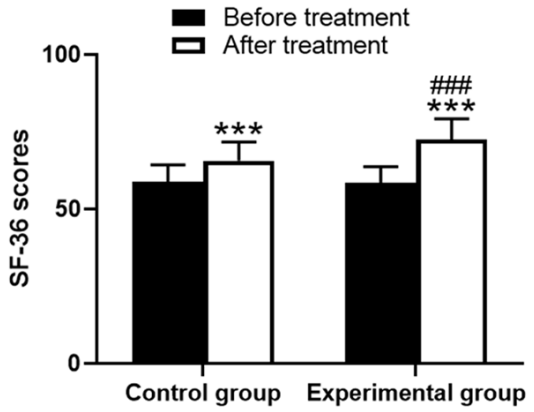

Figure 3. Comparison of SF-36 scores between the two groups. Compared with patients in the same group before treatment, ***P<0.001; compared with the control group after treatment, ###P<0.001.

the blood viscosity of the patients, which is basically similar to the results of Jiang et al [22]. Taken together, it can be seen that Danhong injection can improve the hypercoagulable state of patients by increasing levels of PT, APTT and TT and reducing the level of FIB, thus affecting the prognosis of patients with ACI.

There are still some limitations in this study, such as small sample size, single center study, lack of long-term follow-up results, etc. In our follow-up study, we will increase the sample size and carry out a multi-center randomized controlled prospective study. In addition, we will further confirm the results through observing the changes of index values at multiple time points, studying the effects of different doses of Danhong injection and conducting a long-term follow-up.

In conclusion, Danhong injection can significantly improve the treatment efficiency of ACI. Danhong injection helps to largely improve the quality of life and promote the recovery of nerve function, which is mainly because it can effectively improve the coagulation function and hemorheology indices in ACI patients.

Disclosure of conflict of interest

None.

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