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Original Article

Influence of tanshinone on coagulation function, hemorheology and neurological function in patients with acute cerebral infarction

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Abstract: Objective: The purpose of this study was to investigate the influence of tanshinone on coagulation function, hemorheology and neurological function in patients with acute cerebral infarction. Methods: A prospective study was conducted in 100 patients with acute cerebral infarction. These patients were randomly divided into the experimental group and the control group. For the control group, patients were treated with conventional therapy. Patients in the experimental group received intravenous drip of tanshinone and conventional therapy. The duration of treatment was 2 weeks. Therapeutic effects of both groups were observed. Comparisons were conducted between the two groups on coagulation function indexes, hemorheology indexes (capillary plasma viscosity and erythrocyte aggregation index), blood lipid levels, NIHSS score and SF-36 scale. Results: The total effective rate in the experimental group increased significantly compared with that in the control group (82.00% vs 60.00%, P<0.001). Comparison of coagulation function indexes, blood lipid levels, capillary vascular plasma viscosity, erythrocyte aggregation index, NIHSS score and SF-36 scale in both groups before and after treatment indicated that the differences were statistically significant (all P<0.001). After treatment, levels of fibrinogen (FIB), D-dimer, total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), capillary plasma viscosity, erythrocyte aggregation index and NIHSS score in the experimental group were decreased more than those in the control group (all P<0.001, except for FIB at P<0.05), while SF-36 scale showed additional increase (P<0.001). Conclusion: Tanshinone can improve the therapeutic effect in patients with acute cerebral infarction, and raise the life quality. These benefits may be related to the improvement of coagulation function, blood lipid levels and hemorheology.

Keywords: Acute cerebral infarction, tanshinone, clinical effect, fibrinogen, D-dimer, blood lipid, hemorheology

Introduction

Acute cerebral infarction is a kind of ischemic cerebrovascular disease commonly seen in clinical practice. The mortality rate is about 5%-15%, and the disability rate in surviving patients is about 50%. This means that it is a severe threat to human health and quality of life [1, 2]. The pathogenesis is that cerebral atherosclerosis and other factors initiate acute cerebrovascular obstruction and cause the interruption of blood supply, then resulting in acute cerebral ischemia and neurological functional impairments [3, 4]. According to one report [5], the coagulation and fibrinolytic system plays an important role in the development and progression of acute cerebral infarction, about 80%-90% of acute cerebral infarction are caused by cerebral artery occlusion resulting from emboli like thrombus. The treatment principle concerning acute cerebral infarction is to improve the cerebral circulation in the acute phase, rescue dying brain cells, and prevent the progression of thrombosis and cerebral edema. The research on an effective prevention and treatment method for cerebral infarction has become a hotspot in this field, and it has attracted more and more research attention.

At present, the treatments of cerebral infarction are mainly focused on improving brain

microcirculation and inhibiting the recurrence of thrombus. Microcirculation disturbance and thrombosis are related to hemorheology and coagulation function of patients [6]. Tanshinone is a water-soluble substance obtained by sulfonating diterpene quinone compounds extracted from Salvia miltiorrhiza Bunge and a commonly used Chinese medicine for promoting circulation and removing stasis clinically. Zhang S et al [7] reported that perioperative intravenous drip of tanshinone in patients with non-cardiovascular surgery could significantly inhibit thrombosis and reduce the occurrence of thromboembolism. Another study suggested that tanshinone could significantly alleviate local microcirculation, improve coagulation function and prevent recurrence of thrombus for patients with illnesses like thromboangiitis obliterans, acute myocardial infarction, and acute deep vein thrombosis in lower extremities [8]. Thereby, tanshinone plays an important role in the treatment of microcirculation disturbance and prevention of thrombosis. However, there are few studies on the treatment of acute cerebral infarction with tanshinone, and results of these reports are inconsistent. Here, we studied the treatment efficacy of tanshinone in patients with acute cerebral infarction in order to provide more evidence for the clinical use of tanshinone in the treatment of acute cerebral infarction.

Materials and methods

General information

This study was conducted in 100 patients diagnosed with acute cerebral infarction in The First Hospital Affiliated with Shandong First Medical University from January 2016 to December 2018. Based on a random number table, patients were divided into the experimental group and the control group (50 patients in each group).

Inclusive criteria: Acute cerebral infarction was first diagnosed according to the Diagnostic Criteria for Acute Cerebral Infarction developed by the American Heart Association/American Stroke Association in 2018 and confirmed by head MRI or CT [9]; the onset time was longer than 6 hours; patients were accompanied by dyskinesia, sensory disturbance, disturbance of consciousness or other dysfunction.

Exclusive criteria: Severe liver and kidney dysfunction; acute cerebral hemorrhage, transient ischemic attack or large area cerebral infarction; autoimmune disease; allergy to tanshinone; administration of lipid-lowering drugs or medicines affecting coagulation function within 3 months prior to enrollment. Informed consent was signed by all enrolled patients. This study was approved by the Ethics Committee of The First Hospital Affiliated with Shandong First Medical University.

Interventions

Patients in the control group received conventional therapy, including bed rest, oxygen inhalation, antiplatelet drug (bayaspirin, Bayer HealthCare, Germany) for anticoagulation, oral administration of lipitor (Pfizer Inc., USA) to adjust blood lipid level, patients accompanied by hypertension were orally administered drugs like norvasc (Pfizer Inc., USA) to control blood pressure, patients with diabetes orally took metformin (Sino-US Shanghai Squibb Pharmaceutical Co., Ltd.) and other drugs to control blood glucose level. Patients in the experimental group were treated with tanshinone (Shanghai No. 1 Biochemical & Pharmaceutical Co., Ltd., China) plus conventional therapy applied in the control group. Tanshinone was diluted with 250 mL normal saline and dripped intravenously at a dose of 80 mg once a day for 2 weeks.

Outcome measures

A comparison concerning the treatment efficacy, which was evaluated by the degree of recovery at the end of 2-weeks of treatment [10], was conducted between patients in the two groups. A score of an Invalid patient was indicated by patients with an unchanged condition and muscle strength after the treatment. Effective patients consisted of patients with improved symptoms and signs and restored muscle strength (level 2). Obviously effective patients were patients with significantly improved symptoms and signs and restored muscle strength (above level 2); and they could take care of most of their daily life. Cured patients included patients with totally improved symptoms and signs and normal muscle strength; and they could take care of themselves in daily life. Total effective rate = (number of cured patients + number of obviously effective patients + number of effective patients)/total number of patients * 100%.

Coagulation function indexes including activated partial thromboplastin time (APTT), pro-

Table 1. Comparison of basic data

Group	Experimental group	Control group	t/χ^2 value	*P* value
Number (n)	50	50		
Male/female (n)	30/20	32/18	0.170	0.680
Age (years)	58.4±3.7	59.2±4.1	0.933	0.353
Hypertension (n)	29	26	0.364	0.547
Diabetes (n)	8	11	0.585	0.444
NIHSS score	10.92±5.78	11.05±6.11	0.109	0.913
Onset to treatment time (hours)	10.87±1.24	11.02±1.68	0.508	0.613
Site of cerebral artery lesions (n)			0.300	0.861
Anterior cerebral artery	18	17		
Middle cerebral artery	25	24		
Posterior cerebral artery	7	9		

thrombin time (PT), platelets (PLT), FIB and D-dimer in the two groups were detected by PUN-2048B automatic coagulation analyzer (Nanjing Perlong Medical Equipment Co., Ltd., China) the day before treatment and at the end of 2-weeks of treatment and were then compared.

Blood lipid indexes in each group were tested by an automatic biochemical analyzer (Model 7600, Hitachi, Japan) the day before treatment and at the end of a 2-week treatment period to compare blood lipid levels in the two groups.

Hemorheology indexes including capillary plasma viscosity and erythrocyte aggregation index in the two groups were measured by LB-2A PLUS automatic hemorheometer (Tianjin Tangyu Medical Instrument Technology Co., Ltd., China) the day before treatment and at the end of a 2-week treatment period and then compared.

The neurological function and mental state in the two groups were compared at the end of 2-weeks of treatment. The degree of neurological impairment of patients was assessed by the NIHSS score. The maximum points of the NIHSS score was 42. A higher NIHSS score was consistent with more severe neurological impairment [11]. The assessment included the following 11 items: level of consciousness, horizontal extraocular movements, visual field, facial palsy, upper limb motor drift, lower limb motor drift, limbs ataxia, sensation, language/aphasia, dysarthria and extinction/inattention.

SF-36 scales were compared between the two groups. SF-36 scale consisted of 8 items: role physical, physical functioning, bodily pain, general health, vitality, role emotional, social functioning and mental health [12]. The score ranged from 0 to 100 points. The higher the score is, the better the quality of life is. The life quality of patients was evaluated by SF-36 scale the day before treatment and at the end of 2-weeks of treatment.

Statistical processing

All data were analyzed using SPSS statistical software version 21.0. The enumeration data were calculated as number/percentage (n/%); comparison was conducted using chi-square test. The measurement data were calculated as mean ± standard deviation ($\bar{x}$ ± sd); paired t-test was applied for the intergroup before-after comparison, and independent sample t test was used for comparison between the two groups. The difference was statistically significant when the *P* value was less than 0.05.

Results

Comparison of basic data

As shown in **Table 1**, there were no differences concerning gender, age, onset to treatment time, underlying disease, and NIHSS score at admission between the two groups (all P>0.05).

Comparison of therapeutic effect

Total effective rate in the experimental group was significantly higher than that in the control group at the end of 2-weeks of treatment (82.00% vs 60.00%, χ^2=18.540, P<0.001, **Table 2**).

Comparison of coagulation function indexes

As displayed in **Table 3**, coagulation function indexes in the two groups at the end of 2-weeks of treatment were significantly changed compared with those before treatment (all P<0.001). There were no significant differences concerning coagulation function indexes between the two groups before treatment. FIB level in the experimental group after treatment

Table 2. Comparison of treatment effect (n)

Group	Total number	Invalid patients	Effective patients	Obviously effective patients	Cured patients	Total effective rate
Experimental group	50	9	13	16	12	82.00%
Control group	50	20	12	10	8	60.00%
χ^2 value						18.540
P value						<0.001

Table 3. Comparison of PT, TT, APTT and FIB

Group	Experimental group	Control group
Number (n)	50	50
PT (s)		
Before treatment	11.49±2.25	11.58±2.31
After treatment	12.78±2.36***	12.15±2.28***
TT (s)		
Before treatment	14.17±3.21	14.25±3.16
After treatment	14.93±3.42***	14.84±3.31***
APTT (s)		
Before treatment	29.41±4.36	29.57±4.41
After treatment	30.69±4.15***	30.54±4.23***
FIB (g/L)		
Before treatment	4.55±1.22	4.52±1.28
After treatment	3.10±0.97***,##	3.65±1.01***

Note: Compared with the same group before treatment, ***P<0.001; compared with the control group, ##P<0.01. PT: prothrombin time; TT: thrombin time; APTT: activated partial thromboplastin time; FIB: fibrinogen.

was significantly lower than that in the control group (t=2.777, P=0.007).

As shown in **Figure 1**, there was no significant difference concerning the level of D-dimer between the two groups before treatment. D-dimer levels in the two groups after treatment were significantly decreased compared with those before treatment (P<0.001). D-dimer level in the experimental group was significantly lower than that in the control group at the end of 2-weeks of treatment (P<0.001).

Comparison of blood lipid levels

There was no significant difference concerning blood lipid levels between the two groups before treatment. Total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) levels in the two groups after treatment were significantly lower, while HDL-C levels was significantly higher than those before treatment (all P<0.001). TC, TG and LDL-C levels in the experimental group were significantly lower than those in the control group after treatment (all P<0.001). Details were displayed in **Table 4**.

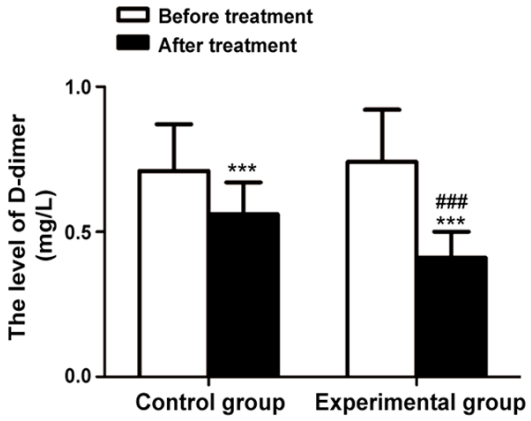

Figure 1. Comparison of D-dimer. Compared with the same group before treatment, ***P<0.001; compared with the control group, ###P<0.001.

Comparison of capillary plasma viscosity and erythrocyte aggregation index

As illustrated in **Figure 2**, there were no significant differences concerning capillary plasma viscosity and erythrocyte aggregation index between the two groups before treatment. Capillary plasma viscosity and erythrocyte aggregation index in the two groups at the end of 2-week treatment significantly decreased compared with those before treatment (both P<0.001). Capillary blood viscosity and erythrocyte aggregation index in the experimental group after treatment were significantly lower than those in the control group (both P<0.001).

Comparison of NIHSS scores

As displayed in **Figure 3**, there was no significant difference concerning NIHSS score between the two groups before treatment. NIHSS scores in the two groups at the end of

Table 4. Comparison of blood lipid levels

Group	Experimental group	Control group
Number (n)	50	50
TC (mmol/L)		
Before treatment	5.89±1.35	5.78±1.42
After treatment	3.68±1.17***,###	4.23±1.28***
TG (mmol/L)		
Before treatment	2.27±0.32	2.19±0.28
After treatment	1.47±0.30***,###	1.65±0.31***
HDL-C (mmol/L)		
Before treatment	0.72±0.14	0.78±0.16
After treatment	1.26±0.17***	1.15±0.15***
LDL-C (mmol/L)		
Before treatment	4.35±1.52	4.42±1.57
After treatment	3.18±1.34***,###	3.75±1.45***

Note: Compared with the same group before treatment, ***P<0.001; compared with the control group, ###P<0.001. TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

2-weeks of treatment declined significantly compared with those before treatment (both P<0.001). NIHSS score in the experimental group was significantly lower compared with that in the control group at the end of 2-weeks of treatment (P<0.001).

Comparison of SF-36 scale

As shown in **Figure 4**, there was no significant difference concerning SF-36 scale between the two groups before treatment. SF-36 scales in the two groups after treatment increased significantly compared with those before treatment (both P<0.001). SF-36 scale in the experimental group after treatment was significantly improved compared with that in the control group (P<0.001).

Discussion

Acute cerebral infarction is a common type of cerebrovascular disease found in the clinic. The incidence, mortality and disability rate have increased year by year. Most patients in clinical practice have missed the optimal time window of thrombolysis (within 6 hours). Therefore, it is extremely meaningful to apply effective drugs to minimize the cerebral infarction area as much as possible, to reduce the disability and mortality rate, and to improve the prognosis of patients.

From the perspective of traditional Chinese medicine (TCM), acute cerebral infarction belongs to stroke and endogenous wind. TCM doctors believe that the pathogenesis is caused by disorders of vital energy and blood, as well as cerebral vessel blockage stasis. The treatment principle is mainly to promote blood circulation, remove blood stasis, and eliminate phlegm and free channels. According to one report [13], Salvia miltiorrhiza Bunge plays a role in removing blood stasis and relieving pain induced by dysmenorrhea. As an extract of Salvia miltiorrhiza Bunge, tanshinone is a novel type of injected pure Chinese herbal medicine preparation, with significant effect on promoting blood circulation and removing blood stasis [14]. In this study, the result showed that the total effective rate in the experimental group was higher than that in the control group, which was consistent with the study reported by Wang et al and Tang et al [15, 16]. The NIHSS score can reflect patients' neurological function and is widely applied in clinical practice. Our result suggested that the NIHSS scores in the experimental group after treatment were significantly lower than those in the control group, indicating that tanshinone could significantly improve the neurological function of patients with acute cerebral infarction. In addition, life quality has become one of the important indicators for evaluating clinical efficacy [17]. The assessment of life quality mainly consists of the subjective feelings and mobility of the human body. The result showed that SF-36 scale in the experimental group after treatment was significantly higher than that in the control group, suggesting that tanshinone could significantly improve the life quality of patients with acute cerebral infarction. Hence, tanshinone could help to alleviate the symptoms of patients with acute cerebral infarction, promote the recovery of patients' neurological function and improve the life quality of patients.

It is reported that thrombus formed between damaged blood vessel wall and blood is the basic pathogenesis causing acute cerebral infarction [18]. As the monitoring indicators for coagulation function of the body, PT, APTT, TT and FIB are widely applied in clinic. In this study, the result showed that there were no significant differences concerning PT, APTT and TT between the two groups at the end of 2-weeks of treatment, suggesting that tanshi-

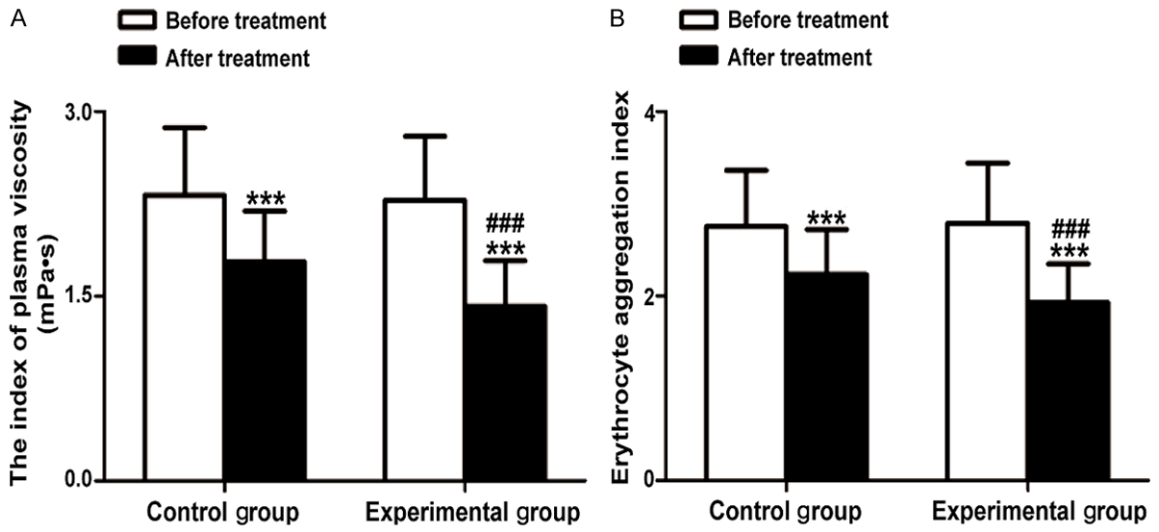

Figure 2. Comparison of hemorheology indexes. A. Comparison of capillary plasma viscosity. B. Comparison of erythrocyte aggregation index. Compared with the same group before treatment, ***P<0.001; compared with the control group, ###P<0.001.

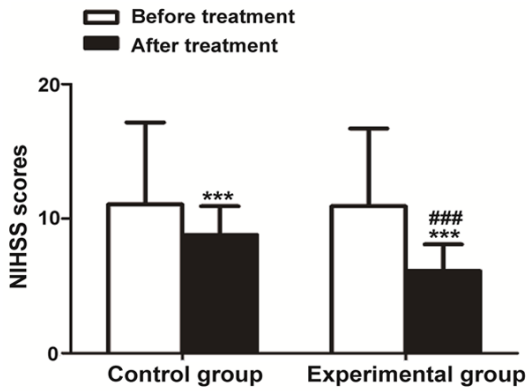

Figure 3. Comparison of NIHSS score. Compared with the same group before treatment, ***P<0.001; compared with the control group after treatment, ###P<0.001.

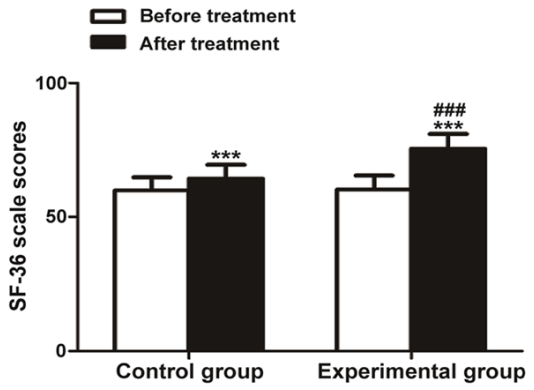

Figure 4. Comparison of SF-36 scale. Compared with the same group before treatment, ***P<0.001; compared with the control group after treatment, ###P<0.001.

none did not make distinct improvements for patients' PT, APTT and TT levels. However, FIB level in the experimental group after treatment was significantly lower than that in the control group. Reports have shown that FIB plays an important role in the pathogenesis of acute cerebral infarction; high level of FIB can injure the vessel wall, make the blood viscosity increase, and may be the basis of thrombosis and atherosclerosis, indicating that FIB level is an essential factor influencing the hypercoagulability of patients with cerebral infarction [19]. As a specific degradation product accumulated in the process of fibrinolysis, high-level D-dimer can damage the intima of blood vessels directly, promote platelet aggregation and interfere coagulation and fibrinolysis function, putting the body in a hypercoagulable state and promoting thrombosis. Therefore, level of D-dimer is important for assessing the condition and prognosis of patients with acute cerebral infarction [20]. This study showed that tanshinone could not only reduce FIB level significantly, but also decrease D-dimer level dramatically, indicating that tanshinone could improve the hypercoagulability of patients through decreasing FIB and D-dimer levels, which are similar to the results reported by Zang et al [21].

Hemorheology indexes can reflect the blood flow condition and properties in human body. The occurrence of acute cerebral infarction is closely related to the high viscosity caused by abnormal hemorheology [22]. The results in this study suggested that plasma viscosity and erythrocyte aggregation index in the experimental group at the end of 2-weeks of treatment were significantly lower than those in the control group, indicating that tanshinone could reduce patients' blood viscosity significantly, which was similar to the results reported by Tan et al [23]. Blood lipid levels are a considerable factor influencing hemorheology indexes. The increase of blood lipid levels can help to induce lipid peroxidation in erythrocyte membranes, reduce the deformability of erythrocytes, and then increase the resistance of erythrocytes passing through the microcirculation of capillaries, which is revealed as the increase of erythrocyte aggregation index and blood viscosity [24, 25]. Here, our results showed that TC, TG and LDL-C levels in the experimental group at the end of 2-weeks of treatment were significantly lower than those in the control group, while there was no significant difference in HDL-C level between the two groups. These results indicated that tanshinone could decline TC, TG and LDL-C levels, while had no significant influence on HDL-C level. A study in a rat model of type II diabetes has shown that tanshinone can reduce the incidence of diabetic complications through decreasing TC, TG and LDL-C levels [26]. In addition, tanshinone can decrease the development and progression of atherosclerosis by reducing the LDL-C presented in plasma [27]. Therefore, tanshinone plays a significant role in the improvement of blood lipid levels.

There are still some limitations existing in this study, such as insufficient sample size, and being a single-center study. Subsequent studies will concentrate on the collection of an increased number of patients, and the multicenter prospective study with follow-up controls. In addition, the effect of different doses of tanshinone will be investigated by observing changes in indexes values at multiple time points, and further confirmed by a long-term follow-up study.

In summary, intravenous drip of tanshinone can significantly enhance the therapeutic effect in patients with acute cerebral infarction, and improve patients' life quality and neurological function status. It may be closely related to the improvement of patients' FIB level, D-dimer level, TG, TC and LDL-C levels, as well as capillary plasma viscosity and erythrocyte aggregation index.

Disclosure of conflict of interest

None.

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