



Effect of Dan seven soft capsule adjuvant therapy on serum inflammatory factors, coagulation function and blood rheology indexes in patients with acute hemorrhagic cerebrovascular disease

Shu-Hua Gui, Ling-Ling Hu[✉], Ting-Gang Wang, Chen-Yan Sui, Xiao-Jing Yin, Liang Kong

Department of Neurology, Wuxi integrated traditional Chinese and Western medicine hospital, Wuxi, Jiangsu 214000, China

ARTICLE INFO

Article history:

Received 28 Jul 2017

Received in revised form 9 Aug 2017

Accepted 19 Aug 2017

Available online 28 Aug 2017

Keywords:

Acute hemorrhagic cerebrovascular disease

Dan seven soft capsule

Inflammatory factors

Coagulation function

Blood rheology

ABSTRACT

Objective: To investigate the effect of Dan seven soft capsule on the treatment of acute hemorrhagic cerebrovascular disease and the influence of serum inflammatory factors, coagulation function and blood rheology indexes. **Methods:** A total of 112 cases of patients with acute hemorrhagic cerebrovascular disease, according to the random data table were divided into the control group ($n=57$) and observation group ($n=55$), the patients in the control group received routine treatment combined with edaravone, on the basis of the treatment of the control group, the observation group was treated with Dan seven soft capsule. The serum levels of inflammatory factors, coagulation function and blood rheology indexes were compared between the two groups before and after treatment. **Results:** Before treatment, there were no significant difference in the inflammatory factors (hs-CRP, TNF- α and IL-6), blood coagulation function (FIB, PT and APTT) and hemorheology (high cut whole blood viscosity, low cut whole blood viscosity and plasma viscosity) levels between the control group and observation group. Compared with the levels of the same group before treatment, two groups of hs-CRP, TNF- α , IL-6, FIB, high cut whole blood viscosity, low cut whole blood viscosity and plasma viscosity level after treatment were significantly decreased, and levels in the observation group were significantly lower than those in the control group; Compared with the group before treatment, the levels of PT and APTT in the two groups were significantly increased, and the observation group was significantly higher than the control group. **Conclusion:** Dan seven soft capsule in the treatment of acute hemorrhagic cerebrovascular disease can effectively reduce the level of serum inflammatory factors, improve coagulation function and blood rheology index, it has an important clinical value.

1. Introduction

Acute hemorrhagic cerebrovascular disease is a common emergency in clinic. Its incidence, mortality and disability rate are higher. In recent years epidemiological studies indicate that there is an upward trend in the occurrence of the disease, the main cause for cerebral vascular thrombosis and bleeding caused by rupture, serious illness caused disturbance of consciousness and limb paralysis, a serious threat to patient safety[1,2]. Edaravone is a kind of medicine used to treat cerebral hemorrhage and cerebral infarction

at present. It has better effect on acute hemorrhagic cerebrovascular disease[3,4]. Studies have pointed out that the combination of traditional Chinese medicine treatment on the basis of conventional treatment can effectively improve the clinical symptoms of acute hemorrhagic cerebrovascular disease and reduce the incidence of complications[5,6]. The purpose of this study is to investigate the clinical efficacy of Dan seven soft capsule in the treatment of acute hemorrhagic cerebrovascular disease. The details are as follows.

2. Research objects and research methods

2.1. General information

Selection of 112 patients with acute hemorrhagic cerebrovascular diseases as the research object from April 2013 to May 2017 treated in Wuxi Hospital of traditional Chinese medicine and Western

[✉]Corresponding author: Ling-Ling Hu, Department of Neurology, Wuxi Integrated Traditional Chinese and Western Medicine Hospital, Wuxi, Jiangsu 214000, China.

Tel: 15301516361

E-mail: guishuhua448@163.com

Fund Project: Research Project of Jiangsu Provincial Health Bureau (816172).

medicine, all diagnosed by CT and MRI, were consistent with the diagnostic criteria of cerebrovascular disease onset[7], and 24 h of onset of treatment, patients with normal swallowing function; exclude: (1) severe liver and kidney dysfunction, myocardial infarction, blood and autoimmune diseases and cancer; (2) the recently received immunosuppressive drugs; (3) the patients with mental disorders. All the subjects were divided into the control group ($n=57$) and the observation group ($n=55$) according to the random data table. In the control group, 34 cases of male patients and 23 female patients; age from 48 to 77. The bleeding sites included 18 cases of basal ganglia hemorrhage, 15 cases of thalamic hemorrhage, 13 cases of brain stem hemorrhage, 7 cases of intraventricular hemorrhage, and 4 cases of subarachnoid hemorrhage. There were 33 males and 22 females in the observation group. The age was from 47 to 76 years. The bleeding site types were 17 basal ganglia hemorrhage, 14 thalamic hemorrhage, 13 brain stem hemorrhage, 6 intraventricular hemorrhage, and 5 subarachnoid hemorrhage. The sex structure, age composition and incidence type of the two groups of objects were similar, the difference was not significant ($P>0.05$), and it was comparable. The content and process of this study with the hospital ethics committee of relevant standards, obtain permission for all objects and their families were informed and signed the informed consent, voluntary treatment after admission and complete clinical data.

2.2 Therapeutic method

Two groups of patients were given conventional treatment, including: keep quiet, bed rest, maintaining water, electrolyte, and nutrient balance, blood pressure control and nutritional therapy and cerebral edema (mannitol, diuretic and glycerin fructose), anti-infection treatment. The control group on the basis of routine treatment for Edaravone Injection (Bicun, Nanjing Xianshengdongyuan Pharmaceutical Co. Ltd., Zhunzi H20050280, packaging specifications 20 mL: 30 mg) treatment, taking medicine 30 mg solution intravenous infusion in 0.9% saline diluted after the infusion time shall not exceed 30 min, 2 times a day. Patients in the observation group were treated with Dan seven soft capsule (Beijing the Great Wall pharmaceutical factory, GZ20050031, 30 x s 0.6), and treated with 4 to 6 granules, 3 times a day, in the control group on the basis of treatment. The two groups were treated with 14 d.

Table 1.

Comparison of serum inflammatory factors before and after treatment in two groups.

Group	n	Time	hs-CRP (mg/L)	TNF- α (ng/L)	IL-6 (ng/L)
Control group	57	Before treatment	12.99 \pm 3.05	95.38 \pm 17.55	129.59 \pm 56.62
		After treatment	8.85 \pm 2.33 [*]	67.68 \pm 13.46 [*]	87.43 \pm 31.62 [*]
Observation group	55	Before treatment	13.12 \pm 3.09	95.32 \pm 21.28	132.94 \pm 57.66
		After treatment	5.59 \pm 1.89 ^{*#}	48.93 \pm 10.92 [#]	51.72 \pm 19.79 [#]

Note: compared with the group before treatment, ^{*} $P<0.05$; compared with the control group after treatment, [#] $P<0.05$.

2.3 Index detection

The fasting peripheral venous blood 3-5 mL was extracted from all patients before and after treatment at 14 d, and was detected in two sections. A part of centrifuged and serum treatment, patients to detect the levels of inflammatory factors, including high sensitivity C reactive protein (hs-CRP), tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6), using the corresponding ELISA detection kit, method for the ELISA method, ELISA kit was provided by Shanghai biological technology limited. Another part of the MEN-C100 automatic hematology analyzer to detect blood coagulation function and blood rheology index, the former including fibrinogen (FIB), prothrombin time (PT) and prothrombin time (APTT); blood rheology: including high shear whole blood viscosity, low shear whole blood viscosity and plasma viscosity. All operations are carried out in strict accordance with the operating instructions.

2.4 Statistical analysis

The raw data in the study is processed by SPSS 17.0 statistical software, inflammatory factors and coagulation function and blood rheology and other biochemical indexes accord with the normal distribution, the Mean \pm SD said that each index level between groups and within groups were compared using independent samples t test and paired t test. Statistical results were expressed by $P<0.05$, and the difference was statistically significant.

3. Result

3.1 Comparison of serum inflammatory factor levels between the two groups

The serum inflammatory factors hs-CRP, TNF- α and IL-6 were detected in the two groups before and after treatment as shown in table 1. From the table, the results of hs-CRP, TNF- α and IL-6 in the two groups before treatment were relatively close, the difference was not statistically significant, and there was no statistical significance ($P>0.05$). After treatment, the control group hs-CRP, TNF- α and IL-6 levels were respectively (8.85 \pm 2.33) mg/L, (67.68 \pm 13.46) ng/L and (87.43 \pm 31.62) ng/L, the observation group respectively (5.59 \pm 1.89) mg/L, (48.93 \pm 10.92) ng/L and (51.72 \pm 19.79) ng/L. Two groups of treatment after the levels were significantly lower than the same group before treatment ($P<0.05$), and the observation group after treatment, hs-CRP, TNF- α and IL-6 were significantly lower than the control group ($P<0.05$).

Table 2.

Comparison of coagulation function indexes between the two groups.

Group	n	Time	FIB (g/L)	PT (s)	APTT (s)
Control group	57	Before treatment	5.42±0.69	9.52±0.57	40.38±3.83
		After treatment	4.21±0.23 [*]	10.94±0.32 [*]	43.11±4.16 [*]
Observation group	55	Before treatment	5.51±0.58	9.65±0.64	40.17±3.84
		After treatment	2.93±0.26 ^{*#}	12.42±0.26 ^{*#}	46.31±3.15 ^{*#}

Note: compared with the group before treatment, ^{*}P<0.05; compared with the control group after treatment, [#]P<0.05.

Table 3.

Comparison of blood rheology indexes between two groups.

Group	n	Time	High cut whole blood viscosity (mPa·s)	Low cut whole blood viscosity (mPa·s)	Plasma viscosity (mPa·s)
Control group	57	Before treatment	6.19±1.59	11.36±1.35	2.23±0.38
		After treatment	4.92±0.26 [*]	9.78±1.23 [*]	1.64±0.23 [*]
Observation group	55	Before treatment	5.99±1.38	11.57±1.34	2.25±0.39
		After treatment	4.36±0.16 ^{*#}	7.66±1.28 ^{*#}	1.26±0.11 ^{*#}

Note: compared with the control group after treatment, [#]P<0.05; compared with the group before treatment, ^{*}P<0.05.

3.2 Comparison of coagulation function indexes between the two groups

The coagulation function indexes of the two groups were measured before and after treatment, as shown in table 2. By the table, before treatment, the two groups of FIB, PT and APTT levels were not statistically significant ($P>0.05$). After treatment, the control group and the observation group FIB levels were (4.21 ± 0.23) g/L and (2.93 ± 0.26) g/L, were significantly lower than in the group before treatment, and the observation group was significantly lower than the control group ($P<0.05$). The observation group PT and APTT level (12.42 ± 0.26) s, (46.31 ± 3.15) s, which is significantly higher than the treatment group before and after treatment and was significantly higher than that of the control group (10.94 ± 0.32) s, (43.11 ± 4.16) s, the difference was significant ($P<0.05$).

3.3 Comparison of blood rheology indexes between two groups

Two groups of patients before and after treatment of blood rheology related indicators, the results shown in table 3. Before treatment, the observation group compared with the control group of patients with high blood viscosity, low shear whole blood viscosity and plasma viscosity levels, no significant difference was not statistically significant ($P>0.05$). The control group after treatment level of viscosity and plasma viscosity high shear whole blood viscosity, low shear whole blood (4.92 ± 0.26) mPa·s, (9.78 ± 1.23) mPa·s and (1.64 ± 0.23) mPa·s, the observation group level (4.36 ± 0.16) mPa·s, (7.66 ± 1.28) mPa·s and (1.26 ± 0.11) mPa·s, the three index level of two groups were significantly lower than in the group before treatment ($P<0.05$), and the observation group was significantly lower than the control group ($P<0.05$).

4. Discussion

Acute hemorrhagic cerebrovascular disease is one of the most common cerebrovascular diseases, with the characteristics of rapid onset and rapid development, the disease is more common among the middle-aged and elderly, and the incidence of male is higher than that of women[8,9]. Hypertension is the main cause of the disease, in addition, chess, activities, quarrels, overwork, smoking,

alcoholism and other factors can also lead to the occurrence of the disease[10]. Treatment guidelines point out that the treatment of this disease is mainly based on medical treatment, including the control of hypertension, cerebral edema, proper rest, maintenance of water, electrolyte and nutritional balance[11]. In recent years, relevant studies have pointed out that the conventional treatment is not very satisfactory, and the recurrence rate is high[12]. Edaravone is a potent free radical scavenger and antioxidant, its mechanism is mainly by scavenging free radicals in the brain tissue, inhibiting lipid peroxidation, to prevent brain damage of vascular endothelial cells, etc. In addition, it can also reduce the synthesis of leukotrienes, reduce the inflammatory response, prevent further damage to neurons[13]. The use of this drug does not increase the risk of bleeding and kidney damage, and has high safety. It has been widely used in the clinical treatment of cerebral infarction, cerebral edema and cerebral hemorrhage[14,15].

The motherland medicine thinks, acute hemorrhagic cerebrovascular diseases belong to the category of stroke, this virtual standard physical disease, its treatment for promoting blood circulation to remove blood stasis[16]. Dan seven soft capsule main ingredients of salvia miltiorrhiza and notoginseng, both with promoting blood circulation to remove blood stasis. Modern pharmacological studies have pointed out that Danshen has the effects of expanding blood vessels, scavenging oxygen free radicals, lowering cholesterol and inhibiting platelet aggregation. Notoginseng mainly huoxue pain, besides can improve blood circulation, can also be inflammatory stress response after intervention hemorrhage, the vascular endothelium has certain protective effect[17,18]. In this study, three aspects of serum inflammatory factors, coagulation function and blood rheology were discussed, in order to clear the clinical effect of Dan seven soft capsule in the treatment of edaravone.

After acute intracerebral hemorrhage, some cytokines in the site of injury may cause local inflammatory reaction, further aggravate microcirculatory disturbance, and participate in secondary neuronal injury[19]. It is found that the level of serum inflammatory factors in patients with cerebrovascular disease is related to the severity of the disease, the infarct size and the prognosis of the disease[20]. Hs-CRP,

TNF- α and IL-6 are the inflammatory factors which are frequently used in the current study, and their level reflects the degree of acute cerebrovascular disease. The results of this study found that Dan seven soft capsule combined with edaravone and conventional therapy, patients with hs-CRP, TNF- α and IL-6 were significantly decreased, and its level was significantly lower than the control group. It can be explained that Dan seven soft capsule adjuvant treatment can further reduce the inflammatory stress reaction of the body, and the reason may be related to the superposition inhibition effect of Dan seven soft capsule and edaravone on inflammatory factors.

The occurrence and development of senile hemorrhagic cerebrovascular diseases are related to hypertension, transitional inflammatory response, hyperlipidemia and cardiovascular wall disease, but also related to abnormal coagulation function and hemorheological changes[21,22].

Studies have shown that the blood coagulation function and fibrinolytic hypertension, thrombosis and atherosclerosis in patients with abnormal fibrinolytic system, such as PT and APTT were significantly decreased, abnormal high levels of FIB and APTT level respectively, PT reflects the content and activity of exogenous and endogenous coagulation factor, FIB is an important medium of platelet aggregation, with an important role to maintain blood flow in normal[23]. The results of this study found that Dan seven soft capsule adjuvant treatment elevated PT and APTT levels, reduce the level of FIB, its level of improvement was significantly better than the control group treatment, the difference was statistically significant. The results of this study further confirmed that Dan seven soft capsule can promote fibrinolysis, inhibit platelet aggregation, relieve blood viscosity, aggregation and coagulation, and restore blood flow[24]. In addition, the study also compared two after treatment the patient's blood rheology level, the results indicate that the combination of Dan seven soft capsule after treatment, the patient's blood rheology can be further improved, the results reported by Guo Xu[25] and Dan seven soft capsule can reduce blood viscosity, reduce red blood cell aggregation to improve the blood rheology of the content.

To sum up, Dan seven soft capsule auxiliary treatment of acute hemorrhagic cerebrovascular disease, patients can effectively reduce inflammatory stress response, effectively improve the patients' blood coagulation function, reduce blood viscosity, improve blood rheology indicators. It has important clinical value.

Reference

- [1] Saver JL, Starkman S, Eckstein M. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *N Engl J Med* 2015; **372**(6): 528-536.
- [2] Yuan Pu, Nie Wenchen. Analysis of risk factors of edema around hematoma in hypertensive intracerebral hemorrhage. *J Clin Neurosurg* 2016; **13**(4): 307-309.
- [3] Ge Lei, Zhao Yuxiao, Chang Yongxia. Effect of low-rTMS in combined with edaravone on the inflammatory cytokines and cerebral metabolites in patients with cerebral infarction and aphasia. *J Hainan Med Univ* 2017; **23**(5): 694-697.
- [4] Jiao Jiao, Jiang Yiqiu, Zhang Xuemeng. The mechanism study of edaravone combined with torasemide for S mechanism of edaravone combined with torasemide for acute intracerebral hemorrhage in senile patient. *J Hainan Med Univ* 2016; **22**(24): 3070-3073.
- [5] Zhang J, Wang D, Liu M. Overview of systematic reviews and meta-analyses of acupuncture for stroke. *Neuroepidemiology* 2014; **42**(1): 50-58.
- [6] Gou Jiayu, Yu Song. Clinical study on sanqi Tongshu Capsules combined with sodium ferulate in treatment of acute ischemic cerebrovascular disease. *Drug Clin* 2016; **31**(12): 1896-1900.
- [7] Chinese society of neurology. Guideline for primary prevention of cerebrovascular disease in China 2015. *Chin J Neurol* 2015; **48**(8): 629-643.
- [8] Steiner T, Al-Shahi Salman R, Beer R. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke* 2014; **9**(7): 840-855.
- [9] Shoamanesh A, Kwok CS, Lim PA. Postthrombolysis intracranial hemorrhage risk of cerebral microbleeds in acute stroke patients: a systematic review and meta - analysis. *Int J Stroke* 2013; **8**(5): 348-356.
- [10] Sun X, Wang Y, Zhang N. Incidence and trends of stroke and its subtypes in Changsha, China from 2005 to 2011. *J Clin Neurosci* 2014; **21**(3): 436-440.
- [11] Hemphill JC, Greenberg SM, Anderson CS. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke* 2015; **46**(7): 2032-2060.
- [12] Kanazawa M, Takahashi T, Nishizawa M. Therapeutic strategies to attenuate hemorrhagic transformation after tissue plasminogen activator treatment for acute ischemic stroke. *J Atherosclerosis Thrombosis* 2017; **24**(3): 240-253.
- [13] Yang J, Cui X, Li J. Edaravone for acute stroke: meta-analyses of data from randomized controlled trials. *Developmental Neurorehabilitation* 2015; **18**(5): 330-335.
- [14] Okamura K, Tsubokawa T, Johshita H. Edaravone, a free radical scavenger, attenuates cerebral infarction and hemorrhagic infarction in rats with hyperglycemia. *Neurological Res* 2014; **36**(1): 65-69.
- [15] Zhang L, Liu H, Cheng W. The clinical efficacy and safety of edaravone combined with GM1 in the treatment of the elderly patients with cerebral infarction. *Int J Clin Exp Med* 2017; **10**(1): 1199-1204.
- [16] Liu Hongbing, Chen Lili, Sun Xingyuan. Mailuoning injection in treatment of different traditional Chinese medicine syndrome types of acute ischemic cerebrovascular disease curative effect comparison. *Chin J Exp Tradit Med Formulae* 2013; **19**(14): 298-300.
- [17] Zhao Xuesong, Chen Zhigang, Gao Fang. Effect of panax notoginseng saponins on brain water content and expression of PAR-1 and MMP-9 in brain tissue of intracerebral hemorrhage rats. *Beijing J Tradit Chin Med* 2016; **35**(9): 851-854+857.
- [18] Wang Ying, Chu Yang, Li Wei. Advances in study on saponins in Panax notoginseng and their pharmacological activities. *Chin Tradit Herbal Drugs* 2015; **46**(9): 1381-1392.
- [19] Chen S, Yang Q, Chen G. An update on inflammation in the acute phase of intracerebral hemorrhage. *Translational Stroke Res* 2015; **6**(1): 4-8.
- [20] Kim JY, Kawabori M, Yenari MA. Innate inflammatory responses in stroke: mechanisms and potential therapeutic targets. *Cur Med Chem* 2014; **21**(18): 2076-2097.
- [21] Appiah D, Fashanu OE, Heckbert SR. Relation of coagulation factor XI with incident coronary heart disease and stroke: the cardiovascular health study. *Blood Coagulation Fibrinolysis* 2017; **28**(5): 389-392.
- [22] Liu Zhenyu, Wang Lihua, Zhou Junying. Influence of edaravone combined with urinary kallidinogenase on blood rheology and function of vascular endothelial cells in acute cerebral infarction. *J Hainan Med Univ* 2014; **20**(3): 337-339.
- [23] Huang X, Moreton FC, Kalladka D. Coagulation and fibrinolytic activity of teneceptase and alteplase in acute ischemic stroke. *Stroke* 2015; **46**(12): 3543-3546.
- [24] Yang Haiyan. Effect of Danqi soft capsule on blood flow and coagulation in patients with coronary arteriosclerosis disease. *Chin J Cardiovasc Rehabil* 2016; **25**(3): 328-331.
- [25] Guo Xu. Myocardial protection effect of Danqi soft capsule and its improving effect on hemorheology in patients with coronary heart disease. *Chin J Cardiovasc Rehabil* 2016; **25**(1): 108-110.