Clinical study of Butylphthalide combined with Xue Shuan Tong on serum inflammatory factors and prognosis effect of patients with cerebral infarction

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Abstract: To investigate the effect of Butylphthalide and Xue Shuan Tong on serum inflammatory factors and prognosis of patients with cerebral infarction. One hundred and twenty patients with acute cerebral infarction were randomly divided into control group, Butylphthalide group and Xue Shuan Tong group, with 40 patients in each group. Conventional therapy was performed in the control group; On the basis of conventional therapy, 100ml Butylphthalide intravenously twice a day was administrated among patients in Butylphthalide group; On the basis of conventional therapy, 250ml 0.9% NaCl intravenously once a day was conducted among patients in Xue Shuan Tong group. A treatment course of continuous 7 days was takin in the three groups. The serum levels of IL-2 and CGRP were detected for patients in the three groups before and after treatment. Carotid plaque thickness and size as well as intima-media thickness were detected by ultrasonic testing for patients in three groups before treatment and 90 days after follow-up. The NIHSS, Barthel and MRS scoring were performed for all the patients after 90-day follow-up to evaluate the prognosis. After treatment, differences in the levels of IL-2 and CGRP for patients in the three groups showed statistical significance (P<0.05), while the levels of IL-2 and CGRP in Xue Shuan Tong group were significantly higher than those in the other two groups (P<0.05). After 7-day treatment, plaque size and thickness in Xue Shuan Tong group and Butylphthalide group were significantly reduced, compared with those before treatment (P<0.05), but no significant differences was shown in the plaque size and thickness between Xue Shuan Tong group and Butylphthalide group (P>0.05) .The CA-IMT in Xue Shuan Tong group and Butylphthalide group was significantly reduced after treatment, and that in Butylphthalide group was significantly larger than that in Xue Shuan Tong group (P<0.05). After 90-day follow-up, NIHSS scores in Butylphthalide group were significantly less than those in the other two groups (P<0.05). After 90-day follow-up, Barthel scores in Butylphthalide group and Xue Shuan Tong group were significantly larger than those in control group (P<0.05), while differences between Butylphthalide group and Xue Shuan Tong group indicated no statistical significance (P>0.05). There were significant differences in MRS scores among patients in the three groups after 90-day follow-up (P<0.05). Butylphthalide and Xue Shuan Tong are clinically effective in treating acute cerebral infarction. Butylphthalide has significant efficacy in inhibiting inflammation and improving prognosis of neurological function, while Xue Shuan Tong has obvious effect in improving carotid intima-media thickness.

Keywords: Butylphthalide; Xue Shuan Tong; acute cerebral infarction; prognosis.

INTRODUCTION

Acute cerebral infarction is a common and frequently-occurring disease in neurology department, with higher disability rate and case-fatality rate. It is also one of the important diseases threatening middle-aged and elderly people's health (Chinese Neuroscience Society, 1996). Acute cerebral infarction is also named acute ischemic cerebral apoplexy. If the blood circulation of brain tissues in ischemic regions can be recovered as soon as possible at acute phase, the brain tissue injury in ischemia is able to obtain reversal in a certain degree. Thrombolysis and neuroprotective therapy are also gradually called the two vital approaches to treat cerebral infarction (Osawa *et al*, 2013). Butylphthalide has the effect to improve nerve injury and protect blood vessels (Li, 2009). Moreover, Xue Shuan Tong, has the effect in promoting blood circulation to remove blood stasis, anti-thrombosis, improving microcirculation, augmenting peripheral blood vessel perfusion flow as well as carotid artery volume flow *et al*, widely used in the treatment of acute cerebral infarction (Li and Wei, 2010). This study is to probe the clinical efficacy and prognosis of Butylphthalide and Xuexhuantong in the treatment of acute cerebral infarction, providing more effective regimens in the clinical treatment for these diseases.

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MATERIAL AND METHOD

General information

One hundred and twenty patients, hospitalized in the First Affiliated Hospital of Zhengzhou University and diagnosed as acute cerebral infarction from November 2013 to May 2014, were selected, with 72 males and 48 females, age ranging from 50 to 84 years old and an average age of 70.5±10.1 years old. Inclusive criteria: (1) Through head CT and MRI examination within 48 hours, all patients was confirmed with acute cerebral infarction,

in accordance with the diagnostic code formulated in the fourth national cerebrovascular academic conference (1995) and in the Chinese acute ischemic stroke treatment guidelines (2010); (2) Through carotid artery color doppler detection on patients, the carotid intima-media thickness (CA - IMT) was ascertained at least 1.2 mm. Exclusive criteria: (1) Carotid artery ultrasound indicated that plaques in lumen leaded to serious obstruction of blood flow.; (2) Combined severe cardiopulmonary insufficiency and severe arrhythmia; (3) Severe hepatic and renal dysfunction; (4) Serious infection and malignant tumor; (5) Acute coronary syndrome; (6) Allergic constitution or drug allergy patients; (7) Pregnancy or females in lactation.

Methods

Grouping and treatment

According to patients' admission time, they were randomly divided into control group, Butylphthalide group and Xuexhuantong group by adopting random number method, with 60 cases in every group. Diet control, moderate exercise therapy and health education were administrated among patients in the three groups after hospitalization. Control group: 80mg sodium ozagrel plus 250ml 0.9% sodium chloride solution, intravenous drip, once a day; 0.5g aceglutamide plus 250 ml 0.9% sodium chloride solution, intravenous drip, once a day; 30mg edaravone plus 100ml 0.9% sodium chloride solution, intravenous drip, twice a day; 5000 U low molecular heparin calcium, subcutaneous injection, twice a day; 0.1g Bayaspirin tablets, oral administration, once a day; 100mg Atorvastatin calcium tablets, once a day; continuous treatment in 7 days, mannitol was appropriately used on patients for dehydration treatment. On the basis of therapeutic regimens in control group, 100 ml Butylphthalide intravenously twice a day in continuous 7 days was conducted among patients in Butylphthalide group, while 500mg Xue Shuan Tong injection plus 250ml 0.9% sodium chloride solution intravenously once a day in continuous 7 days was conducted among patients in Xue Shuan Tong group.

Collection for patients' general data and detection on serological indicators

Baseline information for all patients like ages, genders, smoking history, BMI, blood pressure and others was recorded. 10ml fasting venous blood from the morning for all patients were selected on admission and after treatment and placed into the anticoagulative tube. After centrifugation (3000 r/min) under 4^{o}C, supernatant was selected to obtain blood serum. Then blood plasma was placed into EP tube and preserved for standby application under -20□. By adopting fully automatic biochemistry analyzer, the serum levels of total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL - C) and others in patients were detected.

Detection on IL-2 and calcitonin gene related peptide (CGRP) levels: operations were performed step -by-step according to ELISA kit introduction (purchased from Invitrogen company). Standard curve was drawn by standard substance. OD value of samples to be tested was measured. Standard curves were compared to calculate the protein concentration of samples to be tested.

Detection on carotid plaque size and intima-media thickness

Color doppler ultrasonic diagnosis apparatus and peripheral vascular high frequency probe, with probe frequency from 6 to 12 MHz, were adopted on all patients on admission and after treatment, with detection range including internal carotid, common carotid, external carotid artery and their branches. Three sites with largest plaque were selected for measurement and the average size of plaque was recorded. Meanwhile, the intima-media thickness at the 2cm from the bifurcate of the common carotid artery was measured.

Neurological score

Follow-up in 90 days was conducted on all patients after discharge from hospital. NIHSS scores, Barthel indexes and modified Rankin scale (MRS) scores for patients on admission and in the 90th day after discharge from hospital were evaluated and recorded. These three scores were evaluated and approved to complete by 3 high qualification doctors.

STATISTICAL ANALYSES

SPSS 17.0 statistical software was applied. ± s was represented for measurement data. Variance analysis was adopted for multiple group data. x^2 test was used for rate comparison and Pearson correlation test for correlation analysis. $P<0.05$ was considered statistically significant difference.

RESULTS

Comparison of general data for patients among three groups

No statistically significant difference was shown in ages, gender rate, blood pressure, BMI, smoking history, blood lipid and other indicators for patients among three groups ($P>0.05$), showing a comparison in data (table 1).

Comparisons between IL-2 and CGRP levels for patients among three groups

There was no statistically significant difference in the serum levels of IL-2 and CGRP for patients among three groups on the admission before treatment ($P>0.05$). While, after treatment, differences in the serum levels of IL-2 and CGRP for patients among three groups showed statistical significance ($P<0.05$). IL-2 and CGRP levels for patients in Xue Shuan Tong group was higher than

Table 1: Comparisons of general data for patients among three groups (n = 60, $\bar{x}$ ±s)

Items	Control group	Butylphthalide group	Xuetongshuan group	*P* value
Gender (cases, male/female)	25/15	23/17	24/16	>0.05
Age (years)	71.1±9.15	69.31±10.38	70.53±10.02	>0.05
Systolic pressure (mm Hg)	137.15±13.38	137.01±14.1	136.93±13.05	>0.05
Diastolic pressure (mm Hg)	76.56±9.34	76.32±9.76	77.01±9.11	>0.05
BMI (kg/m^2)	25.28±3.31	25.64±3.54	24.92±3.28	>0.05
Smoking history (cases)	24	25	22	>0.05
HDL-C (mmol/L)	0.86±0.32	0.89±0.12	0.84±0.42	>0.05
LDL-C (mmol/L)	3.08±0.93	3.14±0.76	2.97±0.69	>0.05
TC (mmol/L)	4.57±0.71	4.65±0.73	4.58±0.86	>0.05
TG (mmol/L)	2.38±3.13	2.31±2.01	2.45±1.08	>0.05

Table 2: Comparisons of IL-2 and CGRP levels for patients in the three groups (n = 60, $\bar{x}$ ±s)

Items	Control group	Butylphthalide group	Xueshuantong group
IL-2 (ng/ml)			
Before treatment	1.27±0.12	1.26±0.21	1.24±0.67
After treatment	0.81±0.34	0.32±0.16 *	0.57±0.21 *#
CGRP (pg/L)			
Before treatment	56.33±9.61	58.07±0.16	57.36±9.21
After treatment	28.11±10.17	35.18±9.26	41.48±10.31 *#

Table 3: Comparisons of carotid plaque thickness and size as well as intima - media thickness in the three groups (n = 60, $\bar{x}$ ±s)

Items	Control group	Butylphthalide group	Xueshuantong group
Plaque size (mm2)			
Before treatment	23.05±7.51	23.46±8.12	24.01±6.91
After treatment	20.4±6.48	17.08±5.91	17.26±4.97 *
Plaque thickness (mm)			
Before treatment			
After treatment	2.31±0.58	2.32±0.78	2.33±0.18
CA-IMT (mm)	1.89±0.51	1.61±0.31*	1.73±0.57 *
Before treatment			
After treatment	1.61±0.61	1.68±0.47	1.64±0.43
	1.4±0.58	1.29±0.31 *	1.17±0.28 *#

those in control group and Butylphthalide group (*P*<0.05) (table 2).

Carotid plaque size and thickness as well as intima-media thickness

Differences in plaque size and thickness as well as carotid intima-media for patients before treatment among three groups indicated no statistical significance. After treatment in 7 days, plaque size for patients was distinctly reduced in Xuetongshuan group, showing significant difference compared that before treatment (*P*<0.05), while no statistically significant difference was shown on the plaque size for patients between Butylphthalide group and Xue Shuan Tong group (*P*>0.05). After treatment, plaque thickness of patients in the three groups indicated a remarkable reduce compared that before treatment, while no statistically significant difference was shown for patients between Butylphthalide group and Xue Shuan Tong group (*P*>0.05), significantly smaller than those in control group (*P*<0.05) (table 3).

Comparisons of prognoses score for patients in the three groups

Before treatment, NIHSS and Barthel scores for patients in the three groups indicated a statistically significant difference (*P*>0.05). On the 90^{th} day of follow-up, there were statistically significant difference in patients among three groups (*P*<0.05), while NIHSS score for patients in Butylphthalide group was significantly smaller than that in the other two groups (P<0.05). On the 90^{th} day, Barthel score for patients in Butylphthalide group and Xue Shuan Tong group was distinctly larger than that in control group (P<0.05), but no statistically significant difference was shown in those 2 groups (P>0.05). After 90 days of follow-up for patients in 3 groups, differences in MRS showed statistical significance (P<0.05) (tables 4 and 5).

Table 4: Comparisons of NIHSS and Barthel scores foe patients before and after treatment in the three groups (n=60, $\bar{x}$ ±s)

Items	Control group	Butylphthalide group	Xueshuantong group
NIHSS			
Before treatment	9.61±3.62	20.21±4.01	19.61±3.81
90 d	16.2±4.28	11.58±3.69 *	12.61±4.31 *#
Barthel			
Before treatment	54.31±21.23	55.43±19.59	56.21±20.19
90 d	61.53±23.29	79.41±24.47 *	74.29±22.87 *

Table 5: Comparisons of proportions of MRS for patients after 90-day follow - up in the three groups (n = 60, case (%))

MRS proportions	Control group	Butylphthalide group	Xueshuantong group	*P* value
MRS 0 ~ 1	14 (35.00)	26 (65.00)	23 (57.50)	< 0.05
MRS 2 ~ 3	12 (30.00)	10 (25.00)	13 (32.50)	
MRS 4 ~ 5	14(35.00)	4 (10.00)	4 (10.00)	

DISCUSSION

Pathological characteristics of acute cerebral infarction are the neuronal cell necrosis induced by acute hypoxia and ischemia which occurred in different regions of brain tissues and the mitochondrial function impair of necrosis or impair cells, resulting in aggregation augment of cell toxic products, cellular edema *et al*. Moreover, mitochondrial dysfunction also has the ability to induce overloading due to the internal flow of calcium ion, the augment of inflammatory factors and others, identically inducing the necrosis of neuronal cells. Around cerebral infarction, there always existed ischemic penumbra. Saving timely this section of neuronal cell function is the key to the treatment of acute cerebral infarction, acting crucial role in the later neurological function among patients (Wang *et al*, 2013).

Butylphthalide, autonomously developed by Chinese scientists, is a chemical drug to treat acute cerebral infarction. The effective constitution is racemic modification 1-3 butylphenol which is a sort of fat - soluble drug and able to develop the pharmacological action through blood brain barrier. Butylphthalide has the ability to reduce the release of pigment C of mitochondria electron transport chain cells in neuronal cells, decrease the activation of caspase - 3 and prevent the apoptosis of neuronal cells (Wu and Chen, 2012). Meanwhile, it also can enhance mitochondria Na-K-ATP enzyme and super oxide dismutase in ischemia anoxic regions in brain tissues to prevent lipid per oxidation. Furthermore, Butylphthalide can play the role in protecting neuron by suppressing the formation of super oxide anion free radicals. Besides, it is also able to suppress the release of glutamic acid, relieve vasospasm and prevent platelet aggregation *et al*. In the ischemic stroke, it is of relatively high therapeutic action (Li *et al*, 2009).

The main component of Xue Shuan Tong is panax notoginseng saponins, with the effects in promoting blood circulation to remove blood stasis, relieving swelling and pain and nourishing *et al*. Some studies have indicated that Xue Shuan Tong has the ability not only to effectively improve microcirculation and suppress platelet aggregation, but also to prevent the thrombus formation and reduce the neuronal necrosis as well as the generation of oxygen -free radicals in ischemic region and peripheral penumbra. Meanwhile, Xushuantong also can reduce the concentration of fibrinogen, alter the deformation of erythrocyte and enhance the amount to reach that in the ischemic and anoxia regions, thus playing the therapeutic effect (Vinod *et al*, 2013; Si *et al*, 2005; Nimura *et al*, 2013; Li *et al*, 2008; Zhang *et al*, 2013).

Patients, hospitalized in the First Affiliated Hospital of Zhengzhou University and diagnosed as acute cerebral infarction, were selected in this study. Different therapeutic methods were adopted. The results suggested that after random grouping, the baseline information for patients in the three groups, such as ages, genders, BMI, smoking history and blood lipid, showed no difference (*P* >0.05), showing a stronger comparability for patients in the three groups after random grouping. The detection of inflammatory factors showed that the levels of IL -2 and CGRP among patients before treatment in the three groups had no statistical difference (*P*>0.05), while after different treatments in 7 days, reduce of the levels of IL - 2 and CGRP to varying degrees was shown in patients among three groups, but the reduce in Butylphthalide was more obvious, superior to that in Xue Shuan Tong group. These indicated that the suppression effect of Xueshuntong in the inflammatory effect induced by acute cerebral infarction was stronger than that of Butylphthalide. Compared the plaque size and thickness as well as the intima - media thickness among patients in the three groups, it found that the improvement in the plaque size and thickness between Butylphthalide group and Xue Shuan Tong group showed no significant difference (*P*>0.05), but was superior to that in the control

group (P<0.05). However, in the improvement of CA-IMT, Butylphthalide was inferior to Xue Shuan Tong. To compared the effects of several therapeutic regimens in the prognosis of patients with acute cerebral infarction, different scoring system was adopted for evaluation. The results indicated that the improvement profile of NIHSS and Barthel scores in Butylphthalide group was the most significant, superior to that in the other two groups. Besides, patients with MRS scores between 0 and 1 value in Butylphthalide group was 60%, significantly larger than that in the other two groups. That suggested that the effect of Butylphthalide in the prognosis was superior to that in the other two groups.

To sum up, both Butylphthalide and Xueshuntong have a better clinical efficacy in the treatment of acute cerebral infarction. Moreover, Butylphthalide has a stronger effect in suppressing inflammation and can take a neuroprotective effect by suppressing inflammation (Zhang *et al*, 2013; Jeong *et al*, 2013; Jaremo *et al*, 2013). While, Xue Shuan Tong is superior to Butylphthalide in the improvement of carotid intima - media thickness. Due to the limited number of selected cases, in the further studies, the range of selected cases will be expanded to observe the differences of Butylphthalide and Xue Shuan Tong in various dosages in the treatment of acute cerebral infarction and find out the dose proportion in optimal efficacy between the two drugs in order to provide more beneficial evidences in the clinical treatment.

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