Clinical evaluation on treatment of acute cerebral thrombosis with decocted turtle shell pills

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Received December 14, 2015; Accepted May 17, 2016; Epub May 15, 2017; Published May 30, 2017

Abstract: Objective: Decocted turtle shell pill is a traditional Chinese medicine used for promoting blood circulation and removing blood stasis. The effect of decocted turtle shell pills on acute cerebral thrombosis was examined in 30 cases of cerebral ischemic infraction patients. Method: Sixty patients confirmed with cerebral thrombosis by clinical and imaging examinations were randomly divided into test group (n=30) and control group (n=30). Patients in control group were treated with standard procedure according to guidelines; while patients in test group took decocted turtle shell pills in addition to the standard procedure basis. Treatment efficiency was compared between the two groups at 1 week, 1 month and 3 months after stroke onset; neurological deficit (ND) score and activities of daily living (ADL) score after treatment for 3 months, and laboratory indicators after 1 month of treatment. Results: No significant difference was observed after 1 week of treatment (P>0.05, for all observed indicators). After treatment for 3 months, ND score and ADL score of patients receiving decocted turtle shell pill were significantly improved than control. Triglyceride, cholesterol and fibrinogen level were significantly decreased compared with control group. Conclusion: Addition of decocted turtle shell pills based on standard procedure helps acute stroke patients recover by relieving neurological deficit and improving daily living activities.

Keywords: Decocted turtle shell pills, acute cerebral infarction, treatment outcome

Introduction

Cerebral infarction usually involves the formation of thrombosis due to atherosclerosis and vascular wall lesions such as arteritis, which leads to decreased or disrupted local blood supply of the brain and causes neurological disorders due to ischemia, hypoxia, softening and necrosis of nerve tissues. Multiple factors including lipid metabolism, vascular endothelial dysfunction, hypertension, hemorrhology and hemodynamic changes contribute to this pathogenesis. Formation of thrombosis is the most common cause of cerebral infarction, which is featured by high incidence, complex pathogenesis and high disability rate. Thrombolysis is the therapy that has explicit effect against thrombosis, but its application is restricted to a narrow time window after the onset. It is necessary to find more applicable therapy against cerebral thrombosis.

Decoction turtle shell pill has the effect of softening and resolving hard mass, unblocking the collaterals and unbinding painful obstructions. It is first described in Synopsis of Prescriptions of the Golden Chamber by Zhang Zhongjing, the medical sage in ancient China. Turtle shell is the “monarch drug” (major ingredient) in the prescription, and the drugs for promoting blood circulation, removing stasis and inducing diuresis are the “ministerial drugs” (subsidiary ingredients), which include Cortex Moutan, Chinese herbaceous peony, rhubarb, Scutellaria baicalensis and ginseng, all are known for their effect in activating blood circulation, dispelling stasis, softening and resolving hard mass. The root of herbaceous peony can effectively inhibit ADP-induced platelet aggregation. Paeonol and paeoniflorin in Cortex Moutan have long been known as inhibitor for platelet aggregation induced by different aggregating agents. This pill has been used to treat many diseases in China. From April 2011 to April 2012, 30 cases...
Decocted turtle shell pills for acute cerebral thrombosis were treated by decocted turtle shell pills with explicit effect.

**Subjects and methods**

**Study protocol**

The flow chart of this study was shown in Figure 1. Sixty patients with cerebral infarction treated at our hospital from April 2011 to April 2012 were recruited. The initial inclusion criteria consisted of the following: patients younger than 80 years with clinical and CT evidence of acute cerebral infarction and signs of local brain swelling; confirmed as cerebral infarction according to the criterion of the Fourth National Cerebrovascular Disease Academic Meeting of China Medical Association with the inquiry of medical history, and receiving examination of the nervous system; patients received treatment within 72 hours from stroke onset and have no previous history of stroke. Patients satisfying any of the following conditions were excluded from study: with temporary cerebral ischemia and cerebral embolism; asymptomatic and silent stroke; cerebral hemorrhage and concurrent cerebral hemorrhage; subarachnoid hemorrhage; existing impairment and disability before onset or combined with severe heart, lung, liver and kidney diseases, heart failure or recent history of myocardial infarction.

Among the recruited patients, 7 cases had a history of temporal cerebral ischemia in the recent 6 months; 22 subjects had complete paralysis of the right limbs; 12 subjects had incomplete paralysis of the right limbs; 7 subjects were combined with aphasia; 18 subjects had complete paralysis of the left limbs; 8 subjects had incomplete paralysis of the left limbs. All subjects received head CT scan.

Subjects were equally and randomly divided into two groups: the test group treated with standard procedure plus decocted turtle shell pills, and control group only treated with routine procedure. The test group enrolled 18 males and 12 females aged 40-81 (average, 65.24±10.21). NIHSS score was 13.6±3.1 and activities of daily living (ADL) score was 34.9±24.8. The control group recruited 20 males and 10 females aged 42-82 (average, 67.56±9.87). Neurological deficit (ND) score was 11.8±2.9 and ADL score was 35.6±24.3. The two groups were comparable in age, gender, concurrent diseases, previous history scoring or baseline ND score ($P>0.05$). The study was approved by the local ethics committee. Written consent was obtained from every enrolled patient.

**Treatment**

Both two groups received standard therapy (management of blood pressure and blood lipids, improving blood circulation, anti-platelet therapy, alleviating cerebral edema): (1) oral...
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Table 1. ND and ADL scores in two groups before and after treatment (x±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>N(M/F)</th>
<th>Age (years)</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test group</td>
<td>30(18/12)</td>
<td>65.24±10.21</td>
<td>13.6±3.1</td>
<td>6.2±2.8^{1,2}</td>
</tr>
<tr>
<td>Control group</td>
<td>30(20/10)</td>
<td>67.56±9.87</td>
<td>11.8±2.9</td>
<td>6.6±3.1</td>
</tr>
<tr>
<td>ADL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test group</td>
<td>30</td>
<td>-</td>
<td>34.9±24.8</td>
<td>67.7±24.3^{1,2}</td>
</tr>
<tr>
<td>Control group</td>
<td>30</td>
<td>-</td>
<td>35.6±24.3</td>
<td>51.4±25.6^{1}</td>
</tr>
</tbody>
</table>

Note: ^1Statistically significant difference compared with that before treatment (P<0.05); ^2Statistically significant difference compared with the control group (P<0.05).

Table 2. Comparison of outcome cases (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cure rate</th>
<th>Marked response rate</th>
<th>Response rate</th>
<th>Failure rate</th>
<th>Overall response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Week</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test group</td>
<td>10 (33.3)</td>
<td>3 (10)</td>
<td>2 (6.7)</td>
<td>15 (50)</td>
<td>15 (50)</td>
</tr>
<tr>
<td>Control group</td>
<td>8 (26.7)</td>
<td>3 (10)</td>
<td>2 (6.7)</td>
<td>17 (56.7)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>1 Month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test group</td>
<td>12 (40)</td>
<td>7 (23.3)</td>
<td>5 (16.7)</td>
<td>6 (20)</td>
<td>24 (80)^1</td>
</tr>
<tr>
<td>Control group</td>
<td>9 (30)</td>
<td>5 (16.7)</td>
<td>3 (10)</td>
<td>13 (40.3)</td>
<td>17 (59.7)</td>
</tr>
<tr>
<td>3 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test group</td>
<td>14 (46.7)</td>
<td>7 (23.3)</td>
<td>6 (20)</td>
<td>3 (10)</td>
<td>27 (90)^1</td>
</tr>
<tr>
<td>Control group</td>
<td>10 (33.3)</td>
<td>8 (23.3)</td>
<td>5 (16.7)</td>
<td>8 (26.7)</td>
<td>22 (73.3)</td>
</tr>
</tbody>
</table>

Note: ^1Statistically significant difference compared with that before treatment (P<0.05).

Observation of indicators

ND score and ADL score of the two groups were compared before and after 3 months of treatment. The cure rate, overall response rate, response rate and failure rate after treatment of 1 week, 1 month and 3 months were compared between the two groups. The platelet count, blood lipid level and fibrinogen before and 1 month after treatment were also compared for observation of any possible side effect.

Blood sample collection

Blood samples were obtained before treatment and every follow-up visit at 1 Week, 1 Month, and 3 Months after treatments. Collected samples were immediately placed on ice, and centrifuged within 30 minutes. Plasma was aspirated

Statistical analysis

Statistical analysis was performed using SAS (version 9.3). Data were reported as mean ± standard deviation (x±s). The treatment effect was compared using X^2 analysis, with P<0.05 indicating statistical significance.

Results

There were neither dropouts nor deaths in the both two groups during the study.

Decocted turtle shell pill significantly improved ND and ADL scores

Neurological deficit (ND) and activities of daily living (ADL) score in both groups significantly improved compared with baseline level before treatment. Yet the ND and ADL in test group were significantly better than control group aspirin 100 mg qd, atorvastatin 20 mg qd; (2) venoruton 400 mg iv. qd, 10ds for one period, 1-2 periods; (3) citicoline 0.5 g iv. qd, 10ds for one period, 1-2 periods; (4) antihypertensive drugs for cases with hypertension, and 20% mannitol for cases combined with cerebral edema in acute stage. For the test group, turtle shell powder was prescribed (3 g each time, tid, for 1-3 months).
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Comparison of outcome

At Week 1 of treatment, the overall response rate for control and test group were 50.0% and 43.3%, respectively, indicating no significant difference ($P>0.05$). While after 1 month and 3 months of therapy, the overall response rate for test group were 80.0%, 90.0%, and 59.7%, 73.3% in control group, respectively. The outcomes of test group at both time points were significantly improved compared with control ($P<0.05$) (Table 2).

Hematological indicators

Hematological indicators were compared before and 1 month after treatment. Significant decrease triglyceride, cholesterol and fibrinogen were observed in test group compared with baseline detected at arrival of hospital ($P<0.05$) (Table 3).

Discussion

Cerebral thrombosis is the obstruction of brain vessels due to various reasons, leading to functional damage and neurological symptoms. Arteriosclerosis is the underlying reason for thrombosis, with the results of platelet adhesion and aggregation and activation of platelets and coagulation system. The initiation of coagulation cascade will cause risk of forming potential thrombosis which may lead to blood vessel stenosis and obstruction and finally ends up with neurological ischemia injury in the corresponding blood supply area of the brain.

Cerebral thrombosis, or stroke, is most commonly seen in elderly people. According to the theory of traditional Chinese medicine, the pathological basis of thrombosis is deficiency of “qi” and blood, imbalance of internal organs function and excess of either yin or yang. The inducing factors may include the emotional experience of sorrow and anger, excessive drinking, eating or sex, and invasion of external evil. All these will lead to imbalance of yin and yang, disorder and obstruction of qi and blood, and lack of nourishment of orifices and limbs. In Synopsis of Prescriptions of the Golden Chamber, disorder of qi and blood is the pathogenic factor; qi deficiency is the cause and blood deficiency finally leads to the disease. Depression caused by such disorder will manifest externally in the skin, causing numbness and weakness of the limbs. Internal depression will obstruct qi and collaterals of internal organs. Due to stirring of liver wind, the patient will feel dizziness and headache. The disorder of qi and blood will generate fire, which burns the yin. The mind is nourished by the body fluid and blood. Once yin is burned, the patient will suffer from insomnia and dreaminess, red coating on the tongue, yellow and greasy fur of the tongue, and tight pulse.

There are more than 100 traditional medicines in use for stroke therapy in China. Some of their therapeutic effects in stroke have been confirmed by recent clinical studies. Decocted turtle shell pill is the major prescription in Synopsis of Prescriptions of the Golden Chamber (for malaria) and has long been used against malarial nodule with a history over 2000 years, and the compatibility of drugs has been proved effective in activating blood circulation, dispelling stasis, softening and resolving hard mass. Its ingredients Cortex Moutan and Chinese herbaceous peony can inhibit platelet aggregation in vitro, which was considered the main effective component. Turtle shells, the major ingredient in the prescription, can soften and resolve the hard mass, thus dredging the collaterals. Rhubarb, tree peony root bark and peach kernel can break and expel blood stasis. Dung beetle, honeycomb, Armadillidium vulgare,
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Belamcanda chinensis and red niter are known to promote circulation, eliminate toxic substances, dispel wind, activate the collaterals and reduce the pain in traditional Chinese medicine. Radix bupleuri and Mangnolia officinalis can promote qi and relieve depression and resolve depression. Pinellia ternata, Poria cocos, Roripa montana, Dianthus superbus and Pyrosia lingua can dispel phlegm and remove dampness. Dried ginger, Scutellaria baicalensis, Cassia twig and Chinese herbaceous peony are used to coordinate yin and yang. Ginseng and donkey-hide gelatin can replenish qi and blood. The prescription has the effect of breaking blood stasis and activating the collaterals, regulating qi and eliminating phlegm, replenishing qi and blood and regulating yin and yang. By facilitating qi movement, dispelling phlegm and stasis and eliminating cold sensation of the genitalia, the prescription can achieve balance of yin and yang and unobstructed of heart meridian.

Modern pharmacological research has demonstrated that the rhubarb, peach kernel and ginseng have the effect of reducing blood lipids and blood viscosity and improving microcirculation. The active ingredients in Cortex Moutan have antiplatelet and anti-coagulation effect; besides, they can reduce blood pressure and enhance anti-oxidative capacity, thus protecting the myocardium from ischemia/reperfusion injury. Rhubarb can decrease total cholesterol, triacylglycerol, ApoB, cholesterol content of the aorta and atherogenic index in rats with hypercholesterolemia, while increasing the level of HDL-C. Peach kernel can dilate blood vessels and increase tissue blood flow with anti-coagulation and antithrombotic effect. However, till now research on decocted turtle shell pills is few and we searched on pubmed with “decocted turtle shell pill” as keyword and found no hit. Studies published on local journals indicated that this drug can significantly decrease the high-shear and low-shear whole blood viscosity, total cholesterol and increase the level of HDL-C in rats fed with high-fat diet; it also increases the platelet cAMP level, inhibit platelet aggregation and release, and facilitate thrombolysis. Based on previous study, we investigated the medicine under real-world condition and confirmed with ischemic infarction patients with improved outcome.

In summary, patients treated by decocted turtle shell pills in addition to routine medicinal procedure showed significantly improved outcome measured with neurological deficit (ND) and activities of daily living (ADL) scores compared with patients received only routine treatment. Decoction turtle shell pills can be used as supplementary drugs against acute cerebral thrombosis clinically. The sample volume in the study was limited (30 subjects in each group), however significant effect have already been observed. Further mechanism study is expected for more specific information to explain such clinical benefits.

Disclosure of conflict of interest

None.

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