The effect of DanHong injection combined with Clopidogrel hydrogen sulphate tablets on the serum inflammatory factors, platelet activation and vascular endothelium function

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ARTICLE INFO

Article history:
Received 7 Jul 2016
Received in revised form 17 Jul 2016
Accepted 12 Jul 2016
Available online 24 Jul 2016

Keywords:
Acute coronary syndrome in patient
DanHong injection
Clopidogrel hydrogen sulphate tablets
Inflammatory factors
Platelet activation
Vascular endothelium function

ABSTRACT

Objective: Treated the patients with acute coronary syndrome by the DanHong injection combined with Clopidogrel hydrogen sulphate tablets, and defined the effect of this combined treatment on the serum inflammatory factors, the level of platelet activation and the vascular endothelium function. Methods: Selected 102 ACS patients who were admitted in our hospital from December 2014 to April 2016 as the research subjects, and divided them into the control group and observation group according to the data sheet method, each group was composed of 51 cases. The control group was treated with conventional therapy and Clopidogrel hydrogen sulphate tablets, the observation was given DanHong injection additionally on the basis of control group. The treatment period was 2 months. Detected the change level of related indexes of all patients before and after treatment, which contained the serum inflammatory factors (IL-6, TNF-α, hs-CRP), the level of platelet activation (sCD40L, CD62p, GPIIb/IIa receptor compound), and the vascular endothelium function (NO, ET-1, and vWF). Results: It was showed that each index of this two groups was no statistical significant (P>0.05) before treatment. After treatment, the level of IL-6, TNF-α, hs-CRP, sCD40L, CD62p, GPIIb/IIa receptor compound, ET-1 and vWF were decreased dramatically compared with that before treatment, it was statistical significant difference (P<0.05); Moreover, these indexes in the observation group was lower than the control group, there was statistical significant difference between this two groups (P<0.05). The NO level of all patients was increased significantly after treatment (P<0.05), and the level in observation group was increased more obviously than the control group, the interlock difference was statistical significant (P<0.05). Conclusions: It was confirmed that the DanHong injection combined with Clopidogrel hydrogen sulphate tablets could ameliorate the level of serum inflammatory factors effectively, depress the blood platelet activation, and improve the vascular endothelium function to a great extent, it was worthy of clinic treatment.

1. Introduction

The acute coronary syndrome was caused by the thrombus which resulted from the plaque disruption or invasion of coronary atherosclerosis[1]. In recent years, the morbidity and mortality increased continually, and this would severely impact the health and life quality of patients. Dan Hong injection is a common drug for ischemic cardio-cerebrovascular diseases, whose main compounds are DanShen and Safflower, it was reported that this drug could improve effectively microcirculation, decrease the myocardial oxygen consumption, and depress the thrombus formation[2-4]. Clopidogrel hydrogen sulphate tablets are a kind of platelet aggregation inhibitor. The efficacy of this combination therapy was effective in treatment for unstable angina pectoris[5], however, this mechanism was undefined. Therefore, this study was aimed to discuss the effect of this Chinese-Western medicine combined treatment on serum biochemical indicators in patients with ACS.
2. Materials and methods

2.1. Research objects

102 cases of ACS patients who were admitted in our hospital from December 2014 to April 2016 were selected, condition of all patients were consistent with the incorporation and exclusion criteria that were developed by this research. All subjects were divided into the control group and the observation group, according to the data table method, each group contained 51 cases. In the control group, 32 males and 19 females; the ages were 41–72 years old; and the acute myocardial infarction patients was 29 cases (ST segment elevation 17 cases, non-ST elevation 12 cases), unstable angina pectoris 22 cases. In the observation group, 31 males and 20 females; the ages were 41–75 years old; acute myocardial infarction patients was 27 cases (ST segment elevation 16 cases, non-ST elevation 11 cases), unstable angina pectoris 24 cases. There were no statistical significant difference in the general data of this two group patients (P>0.05). This study was accorded with the hospital ethics criteria and approved by the hospital ethics committee, all patients and their family members accepted and signed the informed consent, in addition, all the clinical data was complete.

2.2. Incorporation and exclusion criteria

Incorporation criteria: (1) accorded with the acute myocardial infarction and unstable angina pectoris diagnosis standard developed by ACC/AHA: The duration time of ischemic chest discomfort surpassed 30 min, with more than 2 adjacent precordial leads ST segment elevation ≥0.2 mV (or ST segment elevation in limb leads ≥0.1 mV); blood CK-MB >10% or cardiac-specific blood troponin I >2 ng/mL, diagnosed patients who were conformed to the above requirements as ST segment elevation acute myocardial infarction. Otherwise, if the duration time of ischemic chest discomfort surpassed 30 min, but the CK-MB and cardiac-specific troponin I was normal, diagnosed the patients as unstable angina pectoris[6]; (2) All the information of patients was complete.

Exclusion criteria: (1) the patients with severe hepatorenal dysfunction, tumor, severe electrolyte disturbance and autoimmune disease; (2) the patients with acute and chronic infectious disease; (3) the patients underwent revascularization in the past (coronary artery bypass grafting or stent implantation); (4) patients had surgery or trauma in one month, used the steriod drug and other immunoregulation drugs; (5) patients with cerebral ischemia, periphery vascular disease, and serious coagulation disorders; (6) with incomplete clinical data[7].

2.3. Treatment methods

The control group: was treated with conventional therapy, included anti-platelet drugs, nitrates drugs, calcium channel antagonist and β receptor blocker etc, Clopidogrel hydrogen sulphate tablets (Sanofi pharmaceutical Co., Ltd., approved by J20130083 75 mg/tablet ) 75 mg oral drug, one time/day, one course of treatment was 2 weeks, total 2 months.

The observation group: on the basis of control group, in addition, 250 mL of saline solution and 40 mL of DanHong injection (Heze Buchang pharmaceutical Co., Ltd., approved by Z20026866,10 mL/tube), were used for intravenous infusion one time/day, one course of treatment was 2 weeks, the treatment time was same as control group.

2.4. Observation indexes and measurement methods

4–5 mL of fasting periphery venous blood were collected before and after treatment, obtained serum through centrifugation, then stored in a freezer at -70℃ to detect the inflammatory factors, plasma soluble cluster of differentiation 40 ligand (sCD40L) and the vascular endothelium function. The inflammatory factors included the interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), hypersensitivity C reaction protein (hs-CRP) and plasma soluble cluster of differentiation 40 ligand (sCD40L), detected by enzyme linked immunosorbent assay, that kits were supplied by Beijing Jingmei bio-engineering Co., Ltd.; The indexes of vascular wall endothelium functions contained serum nitric oxide (NO), endothelin-1(ET-1) and von Willebrand Factor (vWF), the double-antibody solid sandwich ELISA was applied to detect vWF (the kits were supplied by Shanghai Sun bio-technology Co., Ltd.), Nitrate reductase colorimetry assay and Radioimmunoassay was applied to measure the NO and ET-1 respectively, the kits were supplied by Shenzhen Jingmei bio-engineering Co., Ltd. All procedures were carried out strictly according to the kits instructions.

The level of platelet membrane glycoprotein CD62p and GPIIb/IIIa receptor compound were detected, 3 mL of periphery anticoagulant venous blood were collected before and after treatment, obtained serum through centrifugation, then stored in a freezer at -70℃ to detect the inflammatory factors, plasma soluble cluster of differentiation 40 ligand (sCD40L) and the vascular endothelium function. The inflammatory factors included the interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), hypersensitivity C reaction protein (hs-CRP) and plasma soluble cluster of differentiation 40 ligand (sCD40L), detected by enzyme linked immunosorbent assay, that kits were supplied by Beijing Jingmei bio-engineering Co., Ltd.; The indexes of vascular wall endothelium functions contained serum nitric oxide (NO), endothelin-1(ET-1) and von Willebrand Factor (vWF), the double-antibody solid sandwich ELISA was applied to detect vWF (the kits were supplied by Shanghai Sun bio-technology Co., Ltd.), Nitrate reductase colorimetry assay and Radioimmunoassay was applied to measure the NO and ET-1 respectively, the kits were supplied by Shenzhen Jingmei bio-engineering Co., Ltd. All procedures were carried out strictly according to the kits instructions. The count data was presented by positive expression rate.

The software SPSS 17.0 was applied to all data analysis, t test and chi-square analysis were used for the measurement data and count data respectively, P<0.05 was defined as statistical significant difference.

3. Results

3.1. Comparison the change of serum inflammatory factors level

Before treatment, the serum inflammatory factors: IL-6, TNF-α and hs-CRP were no statistical significant difference (P>0.05).
After treatment, the level of IL-6, TNF-α and hs-CRP were (105.08±27.92), (9.97±2.09) and (5.08±2.06) ng/L in the observation group, and that in the control group were (133.51±29.94), (16.45±2.67) and (11.52±2.95) ng/L respectively. All these three levels in two groups were decreased dramatically compared with that before treatment, moreover, the levels in observation group was decreased more significantly than the control group (P<0.05). See Table 1.

3.2. Comparison the change of platelet activation markers level

There was no significant difference in the platelet activation markers which included sCD40L, CD62p and GPIIb/IIIa receptor compound before treatment in observation and control group (P>0.05). The sCD40L, CD62p and GPIIb/IIIa receptor compounds of all patients in this two groups were decreased dramatically, the value of this three markers in the observation group after treatment, were (2.09±0.36) ng/mL, 10.3±2.4 and (28.4±7.1)% respectively, the level in observation group was lower than the control group (P<0.05). See Table 2.

3.3. Comparison the related indexes of vascular endothelium function before and after treatment

NO, ET-1 level of two group patients was no statistical significant difference before treatment (P>0.05), after treatment, the NO level was (65.57±14.29) and (81.37±12.68) µmol/L respectively in the observation group and control group, increased obviously, and it was statistical significant difference (P<0.05). NO in the observation group was higher than control group (P<0.05), ET-1 and vWF of all patients were decreased dramatically after treatment, it showed statistical significant difference (P<0.05), this two levels in observation group was more significant than the control group (P<0.05). See Table 3.

4. Discussion

Atherosclerosis is pathological basis of ACS, the hemodynamics change, body inflammatory reaction, oxidative stress and vascular endothelium function were the important risk factors which resulted in unstable Atherosclerosis plaque[8,9]. The main pathogenesis of ACS was coronary atherosclerosis plaque disruption or invasion, it would release a lot of platelet activation factors and inflammatory

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment time</th>
<th>IL-6 (ng/L)</th>
<th>TNF-α (ng/L)</th>
<th>hs-CRP (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>170.31±47.82</td>
<td>27.54±4.34</td>
<td>12.29±5.32</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>133.51±29.94</td>
<td>16.45±2.67</td>
<td>11.52±2.95</td>
</tr>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>170.27±49.82</td>
<td>28.16±3.64</td>
<td>12.16±5.01</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>105.08±27.92</td>
<td>9.97±2.09</td>
<td>5.08±2.06</td>
</tr>
</tbody>
</table>

* compared with before treatment in the same group, P<0.05;   * compared with control group, P<0.05.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment time</th>
<th>sCD40L (ng/mL)</th>
<th>CD62p</th>
<th>GPIIb/IIIa (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>3.41±0.46</td>
<td>17.1±2.9</td>
<td>62.9±9.2</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>2.93±0.38</td>
<td>14.1±2.5</td>
<td>28.4±7.1</td>
</tr>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>3.39±0.51</td>
<td>16.8±2.7</td>
<td>63.4±8.6</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>2.09±0.36</td>
<td>10.3±2.4*</td>
<td>16.1±6.7*</td>
</tr>
</tbody>
</table>

* compared with before treatment in the same group, P<0.05;   * compared with control group, P<0.05.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment time</th>
<th>NO (µmol/L)</th>
<th>ET-1 (ng/L)</th>
<th>vWF (×10^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>Before treatment</td>
<td>51.83±12.31</td>
<td>78.17±7.22</td>
<td>99.86±7.94</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>65.57±14.29*</td>
<td>65.28±5.31</td>
<td>84.39±6.41*</td>
</tr>
<tr>
<td>Observation group</td>
<td>Before treatment</td>
<td>51.66±11.52</td>
<td>77.85±7.12</td>
<td>101.22±7.86</td>
</tr>
<tr>
<td></td>
<td>After treatment</td>
<td>81.37±12.68*</td>
<td>56.14±6.49*</td>
<td>65.06±5.77*</td>
</tr>
</tbody>
</table>

* compared with before treatment in the same group, P<0.05;   * compared with control group, P<0.05.
factors, the former could accelerate the platelet to adhere and aggregate, form white thrombus eventually. Otherwise, the latter could induce thrombus formation through up-regulating the expression of procoagulant compounds, then result in acute vascular occlusion, at last trigger the myocardial ischemia[10]. The inflammation and activated platelet are the primary factors that cause thrombus formation after PCI surgery and in-stent restenosis of later period in ACS patients[11]. Therefore the research emphasis was that how to ameliorate the level of inflammatory factors, platelet activation and vascular endothelium function, further improve the prognosis of patients.

DanHong injection is a compound preparation which is mainly composed of Salvia miltiorrhiza and safflower. The function of Salvia miltiorrhiza is following:(1) invigorating the circulation of blood, it can expand coronary artery, increase its blood flow, expand the periphery blood vessel, ameliorate the microcirculation, shorten the recovery time of erythrocyte and ferroheme and promote tissue repair; (2) preventing thrombus formation, that plays role in anticoagulation, promotes fibrinolysis and depresses platelet aggregation; (3) reducing the blood lipid; (4) decreasing blood sugar, improves the ability of enduring the oxygen deficit, enhances immunological function[12,13].

It was demonstrated that safflower is able to activate the blood circulation and stimulate meridians, the safflower extraction can inhibit activation of intrinsic coagulation at a certain extent[14]. It was manifested that combination of DanHong injection and Clopidogrel hydrogen sulphate tablets could decrease the level of platelet activation, including that could reduce the level of sCD40L, CD62p and GPIIb/IIIa receptor compound, CD62p and GPIIb/IIIa receptor compound were activated platelet membrane glycoprotein which was the characteristic marker that could reflect the platelet activation level, as well the perfect indicator of detecting platelet activation in clinical[19]. As the main stimulation factor of T and B lymphocyte activation, sCD40L anticipated in the cellular and humoral immunity response, it was critical for the early prevention of plaque disruption in clinical, and detection of sCD40L at early stage is helpful to recognize the unstable plaque early[20]. This study pointed out that this combined therapy could inhibit effectively the level of platelet activation, reduce the risk of thrombus formation, this mechanism might be related to that the DanHong injection was able to stabilize the plaque by depressing the platelet aggregation[21].

NO and ET-1 were the primary vasodilation factors which were generated by vascular endothelium, this two molecules secretion level were unbalanced, when the endothelium function was damaged, this would cause vasodilation dysfunction, then resulted in accelerating thrombus mechanism. vWF level was the sensible indicator of endothelium damage. The detection of NO, ET-1 and vWF was significant for estimation of thrombus formation, the severity of condition and prognosis[22]. It was indicated that combination of DanHong injection and Clopidogrel hydrogen sulphate tablets could increase the NO level and decrease the level of ET-1 and vWF dramatically. These results were conformed to the previous researches[23], this showed DanHong injection combined therapy could ameliorate effectively the vascular endothelium function.

In summary, the combination of DanHong injection and Clopidogrel hydrogen sulphate tablets for treatment of ACS patients was worthy of clinical application, which could ameliorate the level of serum inflammatory factors distinctly, depress the level of platelet activation, improve the vascular endothelium function effectively.

References


