Effect of folic acid adjuvant therapy on Hcy as well as lipid metabolism and endothelial injury in coronary heart disease patients with stable angina pectoris

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ARTICLE INFO

Objective: To analyze the effect of folic acid adjuvant therapy on Hcy as well as lipid metabolism and endothelial injury in coronary heart disease patients with stable angina pectoris. Methods: A total of 98 cases of coronary heart disease patients with stable angina pectoris who received treatment in our hospital from March 2014 to August 2015 were selected as research subjects and randomly divided into observation group 49 cases and control group 49 cases. Control group received conventional clinical treatment, observation group received folic acid adjuvant therapy, and then differences in levels of Hcy, lipid metabolism, endothelial injury and adhesion molecules were compared between two groups after treatment. Results: Hcy, TC, LDL-C and ApoB values of observation group were lower than those of control group while HDL-C and ApoA1/ApoB values were higher than those of control group; Flow-vel and FMD values of observation group after treatment were higher than those of control group; serum E-selectin, ICAM-1, VCAM-1 and sICAM-1 values of observation group after treatment were lower than those of control group. Conclusion: Folic acid adjuvant therapy for coronary heart disease patients with stable angina pectoris can reduce plasma Hcy level and optimize lipid metabolism, further protects vascular endothelium, and has positive clinical significance.

1. Introduction

High homocysteine (Hcy) in blood has already been confirmed as an independent risk factor leading to high incidence of cardiovascular disease, and is equally important with hyperlipidemia, hypertension and hyperglycemia. Folate is the coenzyme of Hcy metabolism, its deficiency will directly lead to plasma Hcy level rise, so the clinical scholars have use the folic acid as the new auxiliary method to cure coronary heart disease, which actively intervenes Hcy levels to further affect the body’s overall state[1,2]. In this study, the effect of folic acid adjuvant therapy on Hcy as well as lipid metabolism and endothelial injury in coronary heart disease patients with stable angina pectoris was mainly analyzed. 98 cases of patients who received treatment in our hospital from March 2014 to August 2015 were selected as research subjects, and specific report was as follows.

2. Information and methods

2.1 Case information

A total of 98 cases of coronary heart disease patients with stable angina pectoris were included in the research, and the exclusion criteria were as follows: 1) those complicated with hematological diseases and severe malnutrition; 2) those complicated with diabetes and thyroid diseases; 3) those with familial high homocysteine (Hcy); 4) those with severe liver and kidney dysfunction; 5) pregnant or breast-feeding women.

According to different treatment regimens, patients were divided into observation group 49 cases and control group 49 cases. Control group included 27 male cases and 22 female cases, they were 35-71 years old, the average age was (58.82±7.06) years, the course
of disease was 1-12 years, the average course was (6.28±2.95) years, the body mass index (BMI) was 23-29, the average was (25.48±3.17), 35 cases were complicated with hypertension and 29 cases were complicated with hyperlipemia; observation group included 26 male cases and 23 female cases, they were 33-73 years old, the average age was (57.72±7.59) years, the course of disease was 2-13 years, the average course was (6.73±2.81) years, the body mass index (BMI) was (BMI) 23-28, the average was (25.27±3.49), 38 cases were complicated with hypertension and 31 cases were complicated with hyperlipemia. The research was presented to, reviewed and approved by the hospital ethics committee, patients themselves learned about the research process and then signed informed consent forms, and differences in baseline information were not significant between two groups (P>0.05), and they could be further compared.

2.2 Treatment regimens
Control group were informed to change the way of life, pay attention to rest at ordinary times, give up smoking and drinking, and take nitrates, angiotension-converting enzyme inhibitor, enteric-coated aspirin and other drugs where appropriate according to the illness. Observation group received folic acid treatment on the basis of conventional treatment, specifically as follows: folic acid tablets 5 mg/d, oral administration, once daily for consecutive 6 months.

2.3 Plasma Hcy levels
Before treatment and 6 months after treatment, 5 mL of fasting peripheral venous blood was drawn from two groups in the morning, anticoagulated with EDTA for half an hour and then sent to lab for testing. Blood specimens were cooled to 4°C and centrifuged for 10 min with 5 000 r/min, and fluorescence polarization immunoassay (FPIA) was used to detect plasma Hcy levels.

2.4 Lipid metabolism
After receiving treatment, both groups were fasting for 12 h, and then 5 mL cubital venous blood was collected to determine serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoAB) and ApoA1/ApoAB respectively.

2.5 Endothelial function
HP Sonos colour to exceed 5500 colour Doppler ultrasound instrument was used to inspect patients’ brachial artery function, patients were fasting and stopped using all kinds of drugs for 24 h, and lay down to rest for 15min, right arm in abducent position. Base vessel diameter value (Base-vel), flow-mediated dilation vessel diameter value (Flow-vel), nitrate-mediated dilation vessel diameter value (Ntg-vel), flow-mediated dilation ratio (FMD) and nitrate-mediated dilation ratio (Ntg-MD) were measured.

2.6 Adhesion molecules
Enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of adhesion molecules, including E-selectin, mononuclear cell adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and soluble intercellular adhesion molecule (sICAM 1).

2.7 Statistical methods
Obtained data was analyzed by SPSS 23.0 software, measurement data was in terms of Mean ± SD, comparison between two groups was by t test and P<0.05 was the standard of statistical significance in differences.

3. Results
3.1 Plasma Hcy
Plasma Hcy value of observation group was (20.18±3.29) umol/L before treatment, plasma Hcy value of control group was (19.76±3.05) umol/L, and differences between groups were not statistically significant (P>0.05); after different treatment, plasma Hcy value of observation group was (9.15±1.02) umol/L, plasma Hcy value of control group was (17.54±2.63) umol/L, and differences between groups were statistically significant (P<0.05).

3.2 Lipid metabolism
Abnormal lipid metabolism is the base of atherosclerosis and coronary heart disease, atherosclerotic plaque is relatively stable in patients with stable angina, but there is still abnormal lipid level in their body, which is used as the reliable index to judge disease
severity and treatment effect. Detection of the research showed that TC, LDL-C and ApoB values in circulating blood of observation group were lower than those of control group while HDL-C and ApoA1/ApoB values were higher than those of control group ($P<0.05$), shown in Table 1.

### 3.3 Endothelial function

Vascular endothelial function damage is the pathological base of coronary heart disease, ultrasound can accurately identify patients’ artery function change, and it is a reliable means to judge the effect of treatment. In the study, ultrasound was used to examine brachial artery in the right arm of two groups 6 months after treatment, and the results showed that Flow-vel and FMD values of observation group after treatment were higher than those of control group ($P<0.05$), and differences in Base-vel, Ntg-vel and NTG-MD values were not statistically significant between groups ($P>0.05$), shown in Table 2.

### 3.4 Adhesion molecule content

In the formation process of coronary atherosclerotic plaque, adhesion molecules are involved in it and play an important role. Adhesion molecules in circulation cane change with the change of coronary heart disease condition, the levels of E-selectin, mononuclear cell adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and soluble intercellular adhesion molecule (sICAM 1) in circulating blood of two groups were detected after treatment, and results showed that serum E-selectin, ICAM-1, VCAM-1 and sICAM-1 values of observation group after treatment were lower than those of control group ($P<0.05$), shown in Table 3.

### 4. Discussion

Coronary heart disease with stable angina is the clinical most common type of cardiovascular disease, and how to stabilize the disease and avoid the further progress of the atheromatous plaque is an important clinical topic. Many researches have shown that folic acid can play a cardioprotective effect, which may be related to its regulation of endothelial function and other disease-correlated factor levels[3]. In this study, folic acid was added in the treatment of coronary heart disease with stable angina, and patients’ plasma homocysteine and lipid metabolism levels as well as endothelial damage degree of target vessels were mainly observed. It is currently recognized that hyperhomocysteinemia is one of the independent risk factors for coronary heart disease, and compared with the healthy people, the risk of coronary heart disease in those with hyperhomocysteinemia is two times more[4,5]. Homocysteine (Hcy) is a sulfur-containing amino acid and is the intermediate product formed in methionine metabolism process in the body, and some scholars think that Hcy levels are closely associated with the degree of coronary artery coronaries. Plasma Hcy levels of two groups were detected in the study at first, and it was found that there was real high Hcy in coronary artery disease patients with stable angina, and plasma Hcy value of observation group greatly reduced after folic acid adjuvant treatment, indicating that folic acid adjuvant therapy could inhibit the constant Hcy rise and the resulting series of side effects in the body.

Coronary heart disease patients are mostly with insulin resistance, and hyperinsulinemia will directly cause lipid metabolism disorders, and lead to coronary heart disease in the long term[5]. Insulin can reduce lipoprotein, promote LDL-C and TG synthesis and reduce HDL-C levels through sympathetic nerve receptor or Angiotensin II. Meanwhile, hyperglycemia caused by insulin resistance can damage vascular endothelial barrier, accelerate fat deposition and platelet aggregation, and promote atherosclerosis[6,7]. In the study, lipid levels of two groups were tested after treatment, and it was found that TC, LDL-C and ApoB values of observation group decreased after treatment while HDL-C and ApoA1/ApoB values increased. Triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoAB) and ApoA1/ApoAB are commonly used indexes to judge lipid metabolism in patients with coronary heart disease, TC, LDL-C and ApoB values are all directly proportional to the degree of lipid accumulation while HDL-C promotes lipid transfer, and the above results suggested that folic acid adjuvant therapy can optimize lipid metabolism, reduce systemic and coronary local lipid accumulation and inhibit atherosclerosis plaque enlargement and rupture process in coronary artery disease patients with stable myocardial infarction[8].

### Table 2

Comparison of endothelial function values between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Base-vel</th>
<th>Flow-vel</th>
<th>Ntg-vel</th>
<th>FMD</th>
<th>NTG-MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>4.32±0.53</td>
<td>4.63±0.53</td>
<td>4.62±0.51</td>
<td>12.18±1.93</td>
<td>15.48±2.31</td>
</tr>
<tr>
<td>Control</td>
<td>4.28±0.49</td>
<td>4.17±0.49</td>
<td>4.58±0.57</td>
<td>9.42±0.85</td>
<td>16.37±2.45</td>
</tr>
<tr>
<td>$t$</td>
<td>0.214</td>
<td>5.382</td>
<td>0.193</td>
<td>7.494</td>
<td>0.223</td>
</tr>
<tr>
<td>$P$</td>
<td>$&gt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&gt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&gt;0.05$</td>
</tr>
</tbody>
</table>

### Table 3

Comparison of serum adhesion molecule levels between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>E-selectin</th>
<th>ICAM-1</th>
<th>VCAM-1</th>
<th>sICAM-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>8.15±0.93</td>
<td>104.38±11.27</td>
<td>293.74±34.52</td>
<td>143.84±23.18</td>
</tr>
<tr>
<td>Control</td>
<td>12.84±2.76</td>
<td>192.73±24.28</td>
<td>412.84±53.21</td>
<td>191.76±25.84</td>
</tr>
<tr>
<td>$t$</td>
<td>8.293</td>
<td>9.273</td>
<td>12.473</td>
<td>8.394</td>
</tr>
<tr>
<td>$P$</td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
<td>$&lt;0.05$</td>
</tr>
</tbody>
</table>
Endothelial dysfunction plays an important role in the occurrence and development of coronary heart disease, research has shown that the action of folic acid on endothelial function is earlier than the drop of blood homocysteine concentration, and its specific functional mediator is in vivo active form of folic acid, 5-leucovorin, and in vitro studies have also shown that the endothelial protective effects of folic acid is also related to reducing super-oxygen ion generation and decreasing nitric oxide (NO) inactivation[9,10]. In this study, brachial arteries were selected as target blood vessels, color Doppler ultrasound was used to for endothelial function measurement and the results showed that Flow-vel and FMD values of observation group were higher after treatment. Flow-mediated dilatation ratio (FMD) reflects the inner diameter change rate after vascular congestion, its value is the visual expression of arterial elasticity and endothelial function, flow-mediated dilatation vessel diameter value (Flow-vel) can also reflect the artery wall elasticity, and the above results directly showed that after folic acid adjuvant treatment, large arterial endothelial function was improved in coronary heart disease patients with stable angina. The specific mechanism for folic acid to optimize arterial endothelial function is not clear, but may be associated with the following mechanism: 1) reducing plasma Hcy levels; 2) acting as one carbon group donor to repair and stabilize the genes; 3) improving vascular endothelial oxidative stress[1].

Study in recent years has shown that adhesion molecules are involved in the formation of atheromatous plaque and the incidence of coronary heart disease, and there is significant change in levels of a variety of adhesion molecules in patients with coronary heart disease, which becomes one of the key links in coronary heart disease[12]. In this study, the levels of serum E-selectin, mononuclear cell adhesion molecule (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), soluble intercellular adhesion molecule (sICAM-1) and other adhesion molecules in patients are detected after treatment, and it was found that after folic acid auxiliary therapy, E-selectin, ICAM-1, VCAM-1 and sICAM-1 values of observation group significantly decreased after treatment, indicating that folic acid treatment could significantly intervene the levels of body’s adhesion molecules. ICAM-1 and VCAM-1 can mediate inflammatory cell adhesion in vascular endothelium and promote foam cell formation, and sICAM-1 can promote mononuclear macrophage phagocytosis of lipid, and is precipitating factor of foam cells[13,14]. Folic acid effect on the content of a variety of adhesion molecules in the body has been observed, but its specific functional mechanism needs to be determined by further research.

To sum up, it is concluded as follows: folic acid adjuvant therapy for coronary heart disease patients with stable angina pectoris can reduce plasma Hcy level and optimize lipid metabolism, further protects vascular endothelium, and is worth popularization and application in clinical practice in the future.

References