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Effect of folic acid combined with routine drugs on Hcy metabolism, inflammatory response and plaque properties in patients with H−type hypertension complicated by carotid atherosclerosis

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ABSTRACT

Objective: To explore the effect of folic acid combined with routine drugs on Hcy metabolism, inflammatory response and plaque properties in patients with H-type hypertension complicated by carotid atherosclerosis. **Methods:** A total of 68 patients with H-type hypertension complicated by carotid atherosclerosis who received treatment in our hospital between January 2014 and September 2016 were collected and divided into control group (n=34) and observation group (n=34) according to random number table. The control group received routine therapy and the observation group received folic acid combined with routine drug therapy. The differences in Hcy metabolism, inflammatory response and plaque properties were compared between the two groups of patients before and after treatment. **Results:** Before treatment, differences in serum Hcy contents, pro-inflammatory and anti-inflammatory mediator contents, and ultrasound plaque property parameter levels were not statistically significant between two groups of patients. After treatment, serum Hcy content of observation group was lower than that of control group; serum pro-inflammatory factors IL-1, IL-6, IL-8 and CRP contents were lower than those of control group; serum anti-inflammatory factors IL-4, IL-10 and IL-13 contents were lower than those of control group; ultrasound plaque property parameter strain value was lower than that of control group while plaque strain rate was higher than that of control group. **Conclusion:** Folic acid treatment based on routine treatment can effectively accelerate the Hcy metabolism, reduce systemic inflammatory response and increase the plaque stability in patients with H-type hypertension complicated by carotid atherosclerosis.

1. Introduction

H-type hypertension is a special type of hypertension that is complicated by hyperhomocysteinemia, increased blood level of Hcy is an independent risk factor for atherosclerosis, so the probability of hypertension with atherosclerosis is extremely high, and it is also is the main cause of long-term cardiovascular events[1,2]. For H-hypertension patients with carotid atherosclerosis, lowering blood pressure, regulating lipid and other basic means contribute to the stability of the disease, but they are limited in reversing plaques properties, reducing cardiovascular events and other aspects, and other drugs are needed to improve the curative effect. Folic acid is a necessary substance during methionine generation by Hcy remethylation, its deficiency can lead to methionine synthesis blocking, Hcy accumulation and hyperhomocysteinemia, and therefore, adding exogenous folic acid is expected to become a reliable way to optimize the condition in patients with H-type hypertension complicated by carotid atherosclerotic[3,4]. In the study, folic acid was introduced in treatment of patients with H-type hypertension complicated by carotid atherosclerosis, and its application value was explored from Hcy metabolism, inflammatory response, plaque properties and other aspects, now reported as follows.

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2. Information and methods

2.1 General information

A total of 68 patients with H-type hypertension complicated by carotid atherosclerosis who received treatment in our hospital between January 2014 and September 2016 were selected as the research subjects, patients or family members signed informed consent, and then they were divided into control group (n=34) and observation group (n=34) according to random number table. Control group included 18 men and 16 women that were 48-76 years old; observation group included 19 men and 15 women that were 50-78 years old. The gender and age distribution of the two groups were similar (P>0.05), and the hospital ethics committee approved the study.

2.2 Inclusion and exclusion criteria

Inclusion criteria: (1) in accordance with the diagnostic criteria for H-type hypertension and carotid atherosclerosis; (2) taking pressure and lipid-lowing drugs regularly for 6 months; (3) cooperating with the treatment and examination and with complete data. Exclusion criteria: (1) with the history of folic acid allergies; (2) with the history of cerebral infarction and cerebral hemorrhage; (3) associated with severe heart, liver and kidney insufficiency.

2.3 Therapy

The control group received regular drug therapy, including reducing blood pressure, antiplatelets, regulating lipid, etc. Observation group of patients, on the basis of routine treatment, received folic acid treatment, which was as follows: folic acid tablets (Hangzhou Aoyi Baoling Pharmaceutical Co., Ltd., approved by H20123159) 0.8 mg/time, 1 time/d, taken orally, for 3 months.

2.4 Hcy content

Before and after treatment, 2.0 mL of fasting cubital venous blood was extracted from two groups of patients, anti-coagulated and then centrifuged at low speed to get upper serum, and chemiluminescence was used to detect the levels of homocysteine (Hcy).

2.5 Inflammation indexes

Before and after treatment, peripheral blood serum was obtained from two groups of patients in the same way, and serum levels of pro-inflammatory factors interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and C-reactive protein (CRP) as well as anti-inflammatory factors interleukin-4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13) were determined by enzyme-linked immunosorbent assay.

2.6 Ultrasound plaque property parameters

Before and after treatment, the plaque properties were assessed by intravascular ultrasound elastography, including the strain value and strain rate of the plaques.

2.7 Statistical processing

Statistical software was SPSS 21.0. The inflammatory factors, plaque property parameters and so on belong to measurement data and were in terms of mean ± standard deviation, and the comparison was by t test. P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Hcy contents

Serum Hcy content of observation group was (20.71±3.42) μmol/L before treatment, and serum Hcy content of control group was (21.05±3.52) μmol/L before treatment; serum Hcy content of observation group was (9.59±0.98) μmol/L after treatment, and serum Hcy content of control group was (20.73±2.61) μmol/L after treatment. Serum Hcy contents were not significantly different between two groups of patients before treatment (P> 0.05); compared with that before treatment, serum Hcy content of observation group decreased significantly after treatment (P<0.05), and serum Hcy content of control group didn't change significantly after treatment (P>0.05); meanwhile, compared with that of control group, serum Hcy content of observation group decreased significantly after treatment (P<0.05).

3.2 Pro-inflammatory factors

Comparison of serum pro-inflammatory factors IL-1 (pg/mL), IL-6 (pg/mL), IL-8 (pg/mL) and CRP (mg/L) contents between two groups of patients before and after treatment was as follows: serum IL-1, IL-6, IL-8 and CRP contents were not statistically different between two groups of patients before treatment (P>0.05); compared with those before treatment, serum IL-1, IL-6, IL-8 and CRP contents of observation group decreased significantly after treatment (P<0.05), and serum IL-1, IL-6, IL-8 and CRP contents of control group didn't change significantly after treatment (P>0.05); meanwhile, compared with those of control group, serum IL-1, IL-6, IL-8 and CRP contents of observation group decreased significantly after treatment (P<0.05), shown in Table 1.

Table 1.

Comparison of serum pro-inflammatory factor contents between two groups of patients before and after treatment.

Groups	n	Time	IL-1	IL-6	IL-8	CRP
Control group	34	Before treatment	15.83±2.19	25.48±3.52	17.39±2.13	5.82±0.69
		After treatment	15.16±1.93	25.36±3.41	17.16±2.09	5.65±0.63
Observation group	34	Before treatment	15.79±2.06	25.37±3.78	17.14±1.98	5.76±0.64
		After treatment	8.23±0.91$^{*\#}$	10.84±1.92$^{*\#}$	6.43±0.85$^{*\#}$	2.11±0.24$^{*\#}$

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

Table 2.

Comparison of serum anti-inflammatory factor contents between two groups of patients before and after treatment (pg/mL).

Groups	*n*	Time	IL-4	IL-10	IL-13
Control group	34	Before treatment	3.28±0.46	1.29±0.15	14.72±1.85
		After treatment	3.21±0.39	1.22±0.17	14.24±1.63
Observation group	34	Before treatment	3.31±0.45	1.31±0.14	13.94±1.79
		After treatment	1.76±0.23$^{*\#}$	0.97±0.11$^{*\#}$	6.36±0.78$^{*\#}$

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

3.3 Anti-inflammatory factors

Comparison of serum anti-inflammatory factors IL-4, IL-10 and IL-13 contents between two groups of patients before and after treatment was as follows: differences in serum anti-inflammatory factors IL-4, IL-10 and IL-13 contents were not statistically significant between two groups of patients before treatment ($P>0.05$); after treatment, serum anti-inflammatory factors IL-4, IL-10 and IL-13 contents of observation group were lower than those before treatment ($P<0.05$), and serum anti-inflammatory factors IL-4, IL-10 and IL-13 contents of control group were not significantly different from those before treatment ($P>0.05$); Meanwhile, serum anti-inflammatory factors IL-4, IL-10 and IL-13 contents of observation group were lower than those of control group after treatment ($P<0.05$), shown in Table 2.

3.4 Plaque properties

Comparison of ultrasound plaque property parameter plaque strain value ($\times 10^{-3}$) and plaque strain rate levels between two groups of patients before and after treatment was as follows: before treatment, differences in ultrasound plaque property parameter plaque strain value and plaque strain rate levels were not statistically significant between two groups of patients ($P>0.05$); after treatment, plaque strain value of observation group was lower than that before treatment while plaque strain rate was higher than that before treatment ($P<0.05$), and the plaque strain value and plaque strain rate levels of control group were not significantly different from those before treatment ($P>0.05$); meanwhile, plaque strain value of observation group was lower than that of control group while plaque strain rate was higher than that of control group ($P<0.05$), shown in Table 3.

Table 3.

Comparison of ultrasound plaque property parameter levels between two groups of patients before and after treatment.

Groups	*n*	Time	Strain value	Strain rate
Control group	34	Before treatment	2.73±0.35	4.38±0.57
		After treatment	2.68±0.31	4.49±0.54
Observation group	34	Before treatment	2.78±0.32	4.36±0.54
		After treatment	0.92±0.11$^{*\#}$	9.72±1.18$^{*\#}$

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

4. Discussion

Hcy is an important metabolic intermediate of methionine and cysteine, blood Hcy level > 10 μmol/L in patients with hypertension is called H-type hypertension, and its harm to the body is far more than that of normal hypertension[5,6]. Studies both at home and abroad have confirmed that the hyperhomocysteinemia is an independent risk factor for atherosclerosis, it can directly damage vascular endothelial cells, affect smooth muscle cell migration and proliferation, promote local vascular plaque calcification and macrophage aggregation, and finally lead to atherosclerosis, the probability of long-term cardiovascular events in such patients is also higher than that in patients with normal hypertension[7,8]. How to optimize the disease and reduce the final stroke, myocardial infarction and critically ill diseases in patients with H-type hypertension complicated by carotid atherosclerosis is the focus and hot spot of current clinical research. Folic acid is an important coenzyme of methionine cycle, it is degraded into tetrahydrofolic acid in the body to provide methyl donor for the degradation of Hcy, and study abroad has also confirmed that the exogenous folic acid supplementation can effectively reduce the level of Hcy and improve endothelial function[9]. In the study, folic acid was taken as a adjuvant therapy drug and introduced in the treatment of patients with H-type hypertension complicated by carotid atherosclerosis, blood Hcy levels were first compared between two groups of patients, and it was found that compared with control group, observation group were with lower serum level of Hcy after treatment, confirming that folic acid has the function of degrading Hcy, but its impact on inflammatory response and plaque properties remains to be researched.

Hypertension can damage vascular endothelium directly and is the start step of atherosclerosis formation, and inflammatory mediators are the necessary materials involved in atheromatous plaque formation, and play the roles of accelerating the plaque formation and aggravating atherosclerosis disease[10,11]. Meanwhile, Hcy damage to the vascular endothelial cells and its stimulation to the immune system make IL-1, IL-6, IL-8, CRP and other pro-inflammatory factors increase, make local blood vessels and whole body form inflammatory response, further activate the anti-inflammatory system and make the mononuclear macrophages secrete the anti-inflammatory factors such as IL-4, IL-10 and IL-13[12,13]. The imbalance of pro-inflammatory/anti-inflammatory system is the core mechanism causing the body's inflammatory

reaction, anti-inflammatory factor secretion increases in the acute phase of inflammation, but it cannot completely neutralize the effects of excessively produced pro-inflammatory factors, and therefore, the body is still in the state of inflammatory lesions[14]. In the study, serum levels of pro-inflammatory and anti-inflammatory factors were compared between two groups of patients, and it was found that compared with control group, the observation group of patients were with lower serum contents of pro-inflammatory factors IL-1, IL-6, IL-8 and CRP as well as lower contents of anti-inflammatory factors IL-4, IL-10 and IL-13, this is associated with the weakened activating effect of pro-inflammatory factors on anti-inflammatory secretion system, and the above results suggest that adjuvant folic acid therapy can effectively inhibit the systemic inflammatory response in patients with H-type hypertension complicated by carotid atherosclerosis after it accelerates decomposition of Hcy.

Plaques are divided into stable and unstable plaques, and unstable plaques include soft plaques and mixed plaques, which can rupture at any time and cause acute stroke; hard plaques belong to stable plaques, and will normally not cause acute cerebrovascular events, so the effect of plaque properties on the outcome of clinical patients is enormous [15–16]. Ultrasonic elastography can reflect the tissue hardness, it has been successfully applied in the diagnosis of mammary gland diseases, the technology was used for the judgment of the properties of the carotid plaques in the study, and it was found that compared with control group, the observation group were with lower plaque strain value and higher plaque strain rate after treatment. In ultrasonic elastography, plaque strain value is negatively correlated with plaque hardness, plaque strain rate is positively correlated with plaque hardness, and therefore, the above results show that adjuvant folic acid therapy can effectively increase the plaque stability in patients with H-type hypertension complicated by carotid atherosclerotic, which is speculated to be directly related to the decreased serum Hcy levels and the relieved inflammatory reaction in patients.

Folic acid combined with conventional drug therapy for patients with H-type hypertension complicated by carotid atherosclerosis can effectively accelerate the catabolism of Hcy, also reduce the systemic inflammatory response and increase plaque stability, and is expected to become the reliable way to improve the clinical outcome and decrease the occurrence of long-term cardiovascular and cerebrovascular emergency in such patients.

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