Int J Clin Exp Med 2016;9(8):16517-16522
www.ijcem.com /ISSN:1940-5901/IJCEM0022544

Original Article

Efficacy of pravastatin on carotid artery atherosclerosis plaque after cerebral infarction and the change of C-reactive protein level

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Received December 22, 2015; Accepted April 3, 2016; Epub August 15, 2016; Published August 30, 2016

Abstract: Cerebral infarction is featured with atherosclerosis and is often accompanied with elevated C-reactive protein (CRP) levels. This study applied pravastatin on acute cerebral infarction patients complicated with carotid artery atherosclerosis, and observed the pattern of atherosclerosis plaque, serum CRP level and blood lipid, in an attempt to evaluate the treatment efficacy of pravastatin. Cerebral infarction patients complicated with carotid artery atherosclerosis were randomly divided into pravastatin, diet control and negative control groups. Aspirin was given to all individuals, while pravastatin was given in the first group and low-salt, low-fat diet was introduced in the second group. The plaque of carotid artery was examined by ultrasound, while blood lipid and CRP level were tested and analyzed for their correlations with artery plaque. After pravastatin treatment, artery plaque score, blood lipid and CRP levels were significantly lowered than those in other two groups ($P<0.05$). A positive relationship existed between plaque score and CRP level, while the plaque was negatively correlated with high density lipoprotein (HDL) level ($P<0.05$) but not for other parameters ($P>0.05$). The application of pravastatin in treating cerebral infarction with carotid artery atherosclerosis can effectively decrease the plaque size, suppress blood lipid and CRP levels.

Keywords: Pravastatin, artery atherosclerosis, cerebral infarction, C-reactive protein

Introduction

Artery atherosclerosis (AS) is the major pathological alternation in various cerebral-/cardiac-vascular diseases. As the most commonly affected site, carotid artery is one risk factor for cerebral infarction and severely affects patients' health and life quality [1]. The rupture of artery atherosclerosis may rupture under the direction of inflammation [2]. The tissues injury may release C reactive protein (CRP), which is a non-specific reactive protein to participate in pathological processes including endothelial cells dysfunction and inflammation [3]. This study recruited cerebral infarction patients in our hospital and gave them pravastatin followed the detection of plaque in carotid artery and assays of blood lipid and CRP levels, in an attempt to analyze its treatment efficacy.

Materials and methods

Clinical information

A total of 150 cerebral infarction patients complicated with artery atherosclerosis were recruited in this study. All patients received primary treatment in our hospital between January 2014 and January 2015. There were 80 males and 70 females in the disease group, aging between 31~80 years old (average = 45.6 years old). Those patients were randomly divided into three groups: (1) Pravastatin group (30 males and 20 females, average age = 45.1 years old); (2) Diet control group (25 males and 25 females, average age = 44.8 years old); and (3) Negative control group (25 males and 25 females, average age = 45.7 years old). The diagnosis of cerebral infarction was confirmed by head MRI

Table 1. Clinical information and laboratory results of patients

Parameter	Negative control	Diet control	Pravastatin
Male/female (N)	20/20	22/18	20/20
Age (year)	36.4±1.4	41.2±1.3	39.2±1.7
Disease course (year)	7.8±3.3	8.1±2.9	8.7±3.5
BMI (kg/m^2)	25.1±2.1	24.2±2.4	22.9±2.6
SBP (mmHg)	125.2±19.4	127.1±17.5	131.5±18.9
DBP (mmHg)	75.2±8.1	73.9±8.7	76.1±8.9

Note: BMI, body-mass index; SBP, systolic blood pressure; DBP, diabolic blood pressure.

Table 2. Carotid artery plaque integration in all patients

Group	N	Carotid artery plaque integration		
		Before treatment	1 month after	3 months after
Diet control	50	4.76±2.31	5.06±2.38[a,b,c]	6.13±1.89[d]
Pravastatin	50	4.88±2.32	4.47±2.26[a,b]	4.02±2.03[a,d]
Negative control	50	4.91±2.56	5.23±2.65[b]	6.37±3.01[d]

Note: [a]*P*<0.05 compared to the negative control group at the same time point; [b]*P*<0.05 compared to that before treatment in the same group; [c]*P*<0.05 compared to both diet control and negative control groups at the same time point; [d]*P*<0.05 compared to that at 1 month post-treatment in the same group.

or CT examination, while carotid artery atherosclerosis was checked by color Doppler sonography. The three groups had no significant difference regarding sex, age or disease course (P>0.05) and were thus comparable. The experimental protocol has been pre-approved by the ethical committee of our hospital and written consents have been obtained from all patients and healthy volunteers. General information of patients was shown in **Table 1**.

Inclusive criteria: (1) Diagnosed with cerebral infarction by CT or MRI; (2) Within 3 days of the primary onset; (3) No major illness of critical organs; (4) No history of thrombolysis treatment; (5) No mental illness.

Exclusive criteria: (1) Taking other lipid lowering agents; (2) With severe complications such as systemic infection or deep venous thrombosis. (3) Allergy to statin medications.

Treatment plan

Pravastatin group: Patients were told to have low-salt, low-lipid diets, along with regular daily schedule. Pravastatin (Sino-American Shanghai Squibb Pharmaceuticals Ltd) was orally introduced for 10 mg daily, along with aspirin (100 mg daily) for three months.

Diet control group: Patients were told to have low-salt, low-lipid diets, along with regular daily schedule. Aspirin (100 mg daily) was given for three months.

Negative control group: Aspirin (100 mg daily) was given for three months.

Clinical examination

Color sonography was used to examine bilateral common carotid artery, internal carotid artery and external carotid artery. The existence, size and thickness of artery plaque were measured for calculating carotid artery plaque integration as previously described [4].

Fasted blood samples were collected from all patients before treatment, one month and three months afterwards. Serum lipid indexes including total cholesterol (TC), tri-glycerol (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were measured. Meanwhile serum CRP level was tested by automatic biochemical analyzer (Beckman, US).

Statistical analysis

SPSS 17.0 software package was used to analyze all collected data, of which measurement data were presented as mean ± standard deviation (SD) and compared by analysis of variance (ANOVA). Enumeration data, however, were analyzed by chi-square test. Logistic regression model was utilized to perform multivariable analysis. A statistical significance was defined when *P*<0.05.

Results

Carotid artery integration after treatment

Color sonography was used to examine the plaque of carotid artery before the treatment, and 1 month or 3 months after the treatment. Results (**Table 2**) showed no significant difference of plaque integration index across all three groups (*P*>0.05). One-month treatment using pravastatin, however, significantly decreased the plaque integration, whilst both diet or

Table 3. Blood lipid indexes in all patients

Group	N	Blood lipid index			
		TC (mM)	TG (mM)	HDL (mM)	LDL (mM)
Diet control	50				
Before		4.63±1.28	1.46±0.76	1.25±0.61	2.54±0.87
1 month		4.71±1.06	1.51±0.65	1.27±0.52	2.61±0.75
3 months		4.74±1.21	1.56±0.59	1.28±0.89	2.58±0.42
Pravastatin	50				
Before		4.61±1.32	1.43±1.12	1.25±0.83	2.59±0.79
1 month		4.13±1.06[a,c]	1.23±0.56[a,c]	1.62±0.71[a,c]	2.12±0.23[a,c]
3 months		2.76±2.31[b,c]	0.76±0.32[b,c]	1.83±0.58[b,c]	1.45±0.11[b,c]
Control	50				
Before		4.66±1.22	1.47±0.58	1.24±0.43	2.58±0.96
1 month		4.82±1.26	1.52±0.67[c]	1.27±0.09	2.67±0.79
3 months		4.81±1.31	1.57±0.88[c]	1.23±0.26	2.82±0.69

Note: [a], $P<0.05$ compared to the negative control group at the same time point; [b], $P<0.05$ compared to that before treatment in the same group; [c], $P<0.05$ compared to both diet control and negative control groups at the same time point.

Table 4. Serum CRP levels after treatment

Group	N	CRP (mg/l)
Diet control	50	
Before		16.28±5.13
1 month		15.28±4.76
3 months		15.15±4.02
Pravastatin	50	
Before		16.31±5.22
1 month		7.02±4.01[a,c]
3 months		6.73±2.39[b,c]
Control	50	
Before		16.45±5.04
1 month		15.89±4.78
3 months		15.33±4.37

Note: [a]$P<0.05$ compared to the negative control group at the same time point; [b]$P<0.05$ compared to that before treatment in the same group; [c]$P<0.05$ compared to both diet control and negative control groups at the same time point.

Table 5. Correlation between carotid artery plaque integration and blood lipid/CRP index

Dependent variable	Regression coefficient	*P* value
TP	0.81	0.07
TG	1.27	0.06
HDL	-0.26	0.01
LDL	1.79	0.06
CRP	0.19	0.01

aspirin intervention actually increased the plaque integration index ($P<0.05$ in all cases). Results at 3 month after treatment were consistent, as pravastatin further suppressed plaque integration when compared to that at 1 month post treatment ($P<0.05$). Both diet control and negative control group, however, had further enlarged plaque ($P<0.05$).

Blood lipid levels

Fasted blood were collected from all patients at three time points (before treatment, 1 month after, and 3 months after treatment) and tested for blood lipid indexes including TP, TG, HDL and LDL. As shown in **Table 3**, pravastatin treatment significantly decreased TP, TG and LD levels, whilst increased HDL ($P<0.05$ in all cases) compared to those before treatment. Neither diet control nor negative control group, however, had any significant difference in all those parameters ($P>0.05$). Follow-up surveys found further suppression of TP, TG and LD, along with elevation of HDL in pravastatin group after 3-month intervention ($P<0.05$). The other two groups, however, still had no significant difference ($P>0.05$). In summary, pravastatin treatment significantly decreased blood lipid level when compared to the other two intervention routes.

Serum CRP levels in all patients

We further tested blood CRP contents in all patients at three different time points. Results found significantly suppressed CRP level at 1 month and 3 month after pravastatin treatment (**Table 4**, $P<0.05$ in all cases). The diet control and negative control group, however, only had slightly decreased but not statistically significant CRP level at both time points ($P>0.05$ in all cases).

Correlation between artery plaque integration and blood lipid/CRP contents

Adopting a multi-variant regression model, we tested the correlation of TP, TG, HDL, HDL and CRP with plaque integration index of carotid artery. Results found no significant correlation between plaque integration and TP, TG or LDL (**Table 5**; **Figure 1**, $P>0.05$). The plaque integra-

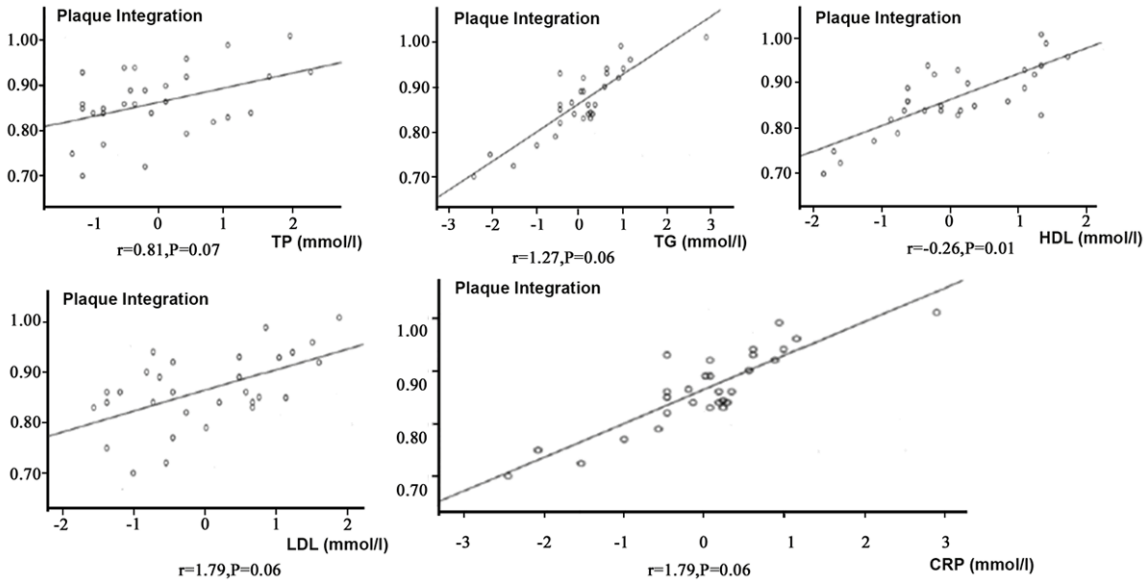

Figure 1. Correlation analysis between plaque integration and blood lipid/CRP indexes.

tion, however, was negatively correlated with HDL and positively correlated with CRP ($P< 0.05$).

Discussion

The incidence of cardio-cerebrovascular disease has been increasing in recent years [5]. The pathological feature of such patients is atherosclerosis, especially in the carotid artery, which increases the risk of acute cerebral infarction [6]. The occurrence of carotid artery atherosclerosis has been attributed to metabolic disorder of blood lipid, as elevated serum TC, TG and LDL may reflect the occurrence of atherosclerosis, making them valuable indexes for disease monitor [7].

As one non-antibody protein, CRP was synthesized in hepatocytes after being stimulated by cytokines. It is an acute response protein reflecting body inflammation, and can work as one index for atherosclerosis following cardio-cerebrovascular disease [8]. Previous studies have established the close relationship between acute inflammatory proteins especially CRP, and the severity of cardio-cerebrovascular disease [9, 10]. Both serum CRP level and plaque size/severity are positively correlated with the condition of cardio-cerebrovascular disease [11, 12]. The disposition of CRP on the artery wall may further bind with lipoprotein to facilitate the production of inflammatory factor, causing injury of endothelial vascular walls and even detach of plaque, making it a risk factor underlying cerebrovascular disease [13].

Tatin drug is a speed-liming enzyme in cholesterol synthesis. As the third generation of tatin, pravastatin can prevent the occurrence of atherosclerosis by other means in addition to regulating lipid metabolism [14, 15]. Studies have shown that pravastatin could regulate various inflammatory and immune cells in suppress the production of inflammatory factors, thus suppressing the formation of atherosclerosis plaque and inhibiting the progression of disease [16]. It can inhibit the activation of mononuclear cells, affect the expression of adhesion molecule expression, decrease the production of pro-inflammatory cytokines and major histocompatibility complex (MHC) II, thereby suppression inflammatory response [17, 18]. Due to its significant anti-inflammatory effect, patients after pravastatin treatment had significantly lowered incidence of cerebral infarction complicated with carotid artery atherosclerosis plaque, in addition to lowered serum CRP level [19].

As one commonly used non-invasive examination approach, carotid artery sonography can identify the size, shape and nature of atherosclerosis plaque at its early stage [20]. In this study, we randomly divided acute cerebral infarction patients with atherosclerosis into

three groups, which received pravastatin, diet control and aspirin intervention measures. Using color sonography, we found decreased carotid artery plaque integration index in pravastatin group when compared to diet or control group. These results suggest the effective control of carotid artery plaque by pravastatin when using on cerebral infarction patients complicated with carotid atherosclerosis.

We also examined blood lipid levels in all patients and found lowered TP, TG, LDL contents and elevated HDL concentration in pravastatin treated patients, when compared to the other two groups. The 3-month intervention of pravastatin had even better efficacy than that at 1 month post-treatment. Multivariant regression analysis found negative correlation between plaque integration and HDL, and positive correlation between plaque and CRP. These results collectively suggest the effect of suppressing blood lipid/CRP level, preventing hyperlipidemia and managing the progression of atherosclerosis. Meanwhile, the decreased serum CRP and lipid level also benefit the recovery from atherosclerosis, improving patient prognosis.

In summary, this study showed positive relationship between serum CRP and the progression of atherosclerosis of carotid artery, which was negatively correlated with HDL. The treatment of cerebral infarction complicated with atherosclerosis using pravastatin can effectively decrease the plaque size, lower blood lipid/CRP level, thus managing the progression of atherosclerosis to some extents. Our results suggest the potency of serum CRP in reflecting the condition of atherosclerosis, although its detailed mechanism needs further illustration.

Acknowledgements

This work was supported by the Henan province science and technology research projects (NO. 162102310277).

Disclosure of conflict of interest

None.

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