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The effect of different doses of fluvastatin on inflammatory markers in the early phase of acute coronary syndrome

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Abstract

Background: Inflammation promotes acute coronary syndromes (ACS) and ensuing clinical complications. It is well known that statins decrease the risk of coronary events and may benefit the stabilization of atherosclerotic plaque with their anti-inflammatory effects. We investigated the effects of different doses of fluvastatin on serum concentrations of high-sensitive C-reaction protein (hs-CRP) and tumor necrosis factor-α (TNF-α) in the early phase of ACS.
Methods: We prospectively randomized 60 patients with ACS to 3 groups: (1) group A ($n=20$): were given routine therapy; (2) group B ($n=20$): were administrated routine therapy with 40 mg/d oral fluvastatin; (3) group C ($n=20$): received routine therapy with 80 mg/d oral fluvastatin. Twenty patients with stable coronary heart disease served as controls. The following-up period was 7 days. By immunoturbidimetric assay and ELISA methods the serum concentrations of hs-CRP and TNF-α were measured before and after therapy.
Results: (1) The serum concentrations of hs-CRP and TNF-α in patients with ACS was significantly higher than those in the control group ($P<0.05$). (2) After 1 week of therapy, the serum concentrations of hs-CRP and TNF-α were significantly lower in group B and group C (all $P<0.01$), especially in group C. (3) The serum concentrations of hs-CRP and TNF-α did not correlate to the concentrations of TC, TG, LDL-C, or HDL-C.
Conclusion: Early fluvastatin intervention decreases dose-dependently the serum concentrations of hs-CRP and TNF-α of patients with ACS. The high-dose fluvastatin invention may play a stronger anti-inflammatory effect in ACS patients. The anti-inflammatory effect of fluvastatin may be beyond the lipid lowering.

Keywords: Acute coronary syndrome; Fluvastatin; High-sensitive C-reactive protein; Tumor necrosis factor-α

1. Introduction

Cardiovascular events typically arise from the disruption of atherosclerotic plaques that contain numerous inflammatory cells. Inflammation is an established consequence of myocardial ischemia and necrosis, and is a possible pathogenetic component that may be responsible for the sudden onset of coronary instability [1–4]. Systemically detectable signs of inflammation, represented by elevated concentrations of circulating C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and serum amyloid A protein, are commonly detected in patients with acute coronary syndromes (ACS) [5,6].

CRP synthesized in the liver, is a typical acute-phase reactant and a sensitive inflammatory marker [7,8]. Large prospective studies have demonstrated that high-sensitive CRP (hs-CRP) is an independent predictor of future coronary events in apparently healthy individuals or in patients with established cardiovascular disease 5,9–15]. TNF-α is an important proinflammatory cytokine primarily produced by monocytes/macrophages which may play a role in the development of cardiovascular disease. Recent observational data indicate that the concentrations of acute

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phase reactant in patients with ACS may relate to the risk of subsequent cardiovascular events [7,16].

Lipid-lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been shown to significantly reduce the incidence of cardiovascular events in patients with coronary heart disease (CHD) [10,17–20] and seems to be effective in reducing the concentration of CRP in subjects free of overt cardiovascular disease or in patients with stable coronary disease, even when lipid concentrations are relatively low [21–23]. However, the effects of statins on blood concentrations of hs-CRP and TNF-α in the early phase of ACS and the relationship between the anti-inflammatory effects and their doses remain unclear. The present study was designed to investigate the effects of different doses of fluvastatin on serum concentration of hs-CRP and TNF-α in the early phase of ACS.

2. Subject and methods

2.1. Subject and protocol

The study included 60 patients admitted within 24 h of onset of ACS without percutaneous coronary intervention and 20 patients with stable coronary heart disease (SCHD) who were admitted to the Second Xiangya Hospital of Central South University and Zhanjiang Center Hospital Affiliated to Guangdong Medical College between August 2003 and December 2004. ACS was defined as high-risk unstable angina, non-ST elevated myocardial infarction (MI) or ST-elevated MI. The diagnosis of unstable angina required new or dynamic ST-segment or T-wave changes in at least 2 contiguous ECG leads or a new wall motion or myocardial perfusion abnormality. The diagnosis of myocardial infarction (include non-ST-elevated myocardial infarction or ST-elevated myocardial infarction) required increased serum creatine kinase or its MB fraction concentration exceeding 2 times the upper limit of normal. The patients gave written informed consent to participate before randomization study entry. The diagnosis of SCHD is according to the nomenclature and criteria for the diagnosis of ischemic heart disease reported by the ISFC/WHO in 1979.

Excluded criteria were as follows: malignancy, any acute infection 4 weeks before enrollment, history of diabetes, thyroid disease, stroke, severe hepatic or renal dysfunction, administration of lipid-lowering drugs (statin, clofibrate, probucol or analog, nicotinic acid, or other prohibited drug) 4 weeks before enrollment. Patients were instructed to avoid using nonsteroidal anti-inflammatory agents while participating in the study.

2.2. Study design

Sixty patients with ACS were randomly separated into 3 groups immediately at the time of hospital admission: (1) group A ($n=20$): were given routine therapy including aspirin, metoprolol, angiotensin-converting enzyme inhibitor, nitrates, heparin and ticlopidine; (2) group B ($n=20$): were administrated routine therapy with oral fluvastatin 40 mg/d; (3) group C ($n=20$): received routine therapy with oral fluvastatin 80 mg/d (both fluvastatins are the same drug: Lescol, Novartis Pharma AG). The total following-up period was 7 days. Twenty patients with SCHD were used as control group.

Blood samples were immediately taken from patients for examination of inflammatory markers at the time of hospital admission. And after 12 h of overnight fasting, venous blood samples were collected after 2 and 8 days in patients with ACS and after the second day in patients with SCHD. All serums were separated at 4 °C and then stored at −70 °C. The paired baseline and 8 day samples were shipped to the laboratory and measured in batches. Serum lipid, hs-CRP and TNF-α were performed at the core laboratory for clinical study in the Second Xiangya Hospital, Changsha, China.

2.3. Lipid measurements

Fasting serum total cholesterol (TC), triglyceride (TG), HDL-C, LDL-C concentrations were measured on a Hitachi 7170A analyzer by a specialist who was unaware of the study assignment. Serum TC and TG concentrations were measured by enzymatic methods, and HDL-C and LDL-C concentrations were measured by direct methods. The Apo A-1 and Apo B concentrations were assessed using an immunoturbidimetric method. The reagents were provided by Daiichi Pure Chemicals Co. Ltd. The inter- and intra-assay CVs were within 5.5% and 3.5%, respectively.

2.4. Measurement of inflammatory markers

Hs-CRP was measured at 550 nm by a particle enhanced immunoturbidimetric assay (Orine Diagnostica) on a Hitachi 7170A analyzer. The lower limit of detection for the methods is 0.3 mg/l. TNF-α was measured by enzyme linked immunosorbent assays (ELISAs) technique according to the manufacturer (serum TNF-α ELISA kit, Jingmei Engineering, China). The reproducibility of the assays over the study period was 5.0% for CRP and 9.6% for TNF-α 9.6%.

2.5. Statistical analysis

Data were analyzed with SPSS (ver. 11.0) and are presented as the mean ± SD unless other indicated. Because the distributions of the inflammatory markers were skewed, log-transformation was made for distribution-dependent analyses. Difference between the intra- and inter-group means was analyzed by t-test or one-way ANOVA. Coefficients of correlation (r) were calculated by Pearson correlation analysis. General linear regression analysis with

Table 1
Baseline characteristics of 4 groups ($X \pm SD$)

	SCHD ($n=20$)	ACS		
		Routine ($n=20$)	Fluvastatin 40 mg ($n=20$)	Fluvastatin 80 mg ($n=20$)
Age (y)	63.0±10.5	63.5±9.4	64.2±9.7	64.1±10.9
Gender (M/F)	13/7	13/7	12/8	11/9
BMI (kg/m^2)	22.6±1.9	23.5±2.4	22.9±1.9	23.1±2.7
HR (beat/min)	70.9±7.9	73.6±12.1	71.4±8.6	73.7±9.3
NSTACS/STEMI	–	14/6	14/6	15/5
SBP (mm Hg)	132.1±16.7	131.1±16.4	132.3±16.3	131.5±19.6
DBP (mm Hg)	78.4±10.6	76.2±9.3	77.9±11.3	76.7±12.8
FBS (mmoL/l)	5.56±0.65	5.31±0.89	5.61±0.87	5.25±0.73
TC (mmoL/l)	5.25±0.82	5.28±0.83	5.16±1.03	5.13±0.93
TG (mmoL/l)	1.63±0.38	1.52±0.49	1.48±0.49	1.55±0.93
LDL-C (mmoL/l)	3.17±0.86	3.72±0.69	3.34±0.91	3.62±0.76
HDL-C (mmoL/l)	1.04±0.20	1.04±0.22	1.02±0.26	1.12±0.17
Apo A-1 (g/l)	1.24±0.26	1.36±0.26	1.27±0.22	1.20±0.27
Apo B (g/l)	1.09±0.31	1.23±0.27	1.16±0.26	1.15±0.22
WBC ($\times 10^9$)	6.38±1.33	9.26±2.02*	8.49±1.56*	8.62±2.24*
CKMB	8.38±5.49	35.64±54.9*	33.32±47.5*	38.3±58.4*
Hs-CRP (mg/l)	2.44±2.27	14.55±14.98*	14.69±14.08*	14.24±12.12*
TNF-α (pg/ml)	10.23±6.59	22.74±15.78*	22.88±12.36*	23.01±12.57*

SCHD = Stable Coronary Heart Disease; ACS = Acute Coronary Syndrome; NSTACS = Unstable angina and non-ST-elevation MI; STEMI = ST-elevation MI; Date are presented as means±SD. *$P<0.05$ when compared with the SCHD group. Abbreviations are as defined in text.

adjustment for differences in baseline variants was performed to assess the effect of fluvastatin treatment. Statistical significance was defined as $P<0.05$.

3. Results

Baseline characteristics of patients are shown in Table 1. Four groups were similar in regard to age, gender, body mass index, blood pressure, fasting blood sugar concentration. Compared with SCHD group, serum CK-MB, white blood count (WBC), hs-CRP and TNF-α concentration of 3 ACS groups were higher at baseline. Furthermore, there were no significant different in fasting lipids, hs-CRP and TNF-α concentration at baseline among the 3 ACS groups (Table 1).

Table 2 showed the changes of serum levels of fasting lipid, apolipoprotein and inflammatory markers in patients with ACS after 1 week of therapy. The serum TC, LDL-C and Apo B concentrations in group B and C with fluvastatin treatment had decline tendency, but there were no statistical significance compared with the baseline. The concentrations of hs-CRP and TNF-α decreased significantly in group B and C. In the 40 mg/d fluvastatin group, the serum hs-CRP concentrations (14.69±14.08 vs. 6.25±5.15) and TNF-α concentrations (22.87±12.36 vs. 15.19±9.60) after treatment decreased significantly compared with those at baseline. In the 80 mg/d fluvastatin group, the serum hs-CRP concentrations (14.24±12.12 vs. 4.23±3.64) and TNF-α concentrations (23.01±12.57 vs. 13.46±8.30) after treatment decreased significantly compared with those at baseline. A significant reduction in hs-CRP and TNF-α concentrations was only seen in the 80 mg/d fluvastatin group when compared with group A after 7 days of treatment ($P<0.05$) and no significant change in the 40 mg/d fluvastatin group.

Taking all patients with ACS ($n=60$) as a total population, the Pearson correlation analysis was used to calculate the coefficients of correlation. We found no correlation between serum lipid concentrations (TC, TG, LDL-C, HDL-C) and serum inflammatory factors (hs-CRP and TNF-α) at baseline. Also, there was no significant association between the decrease in the fasting LDL-C concentrations and the changes in serum hs-CRP and TNF-

Table 2
Serum lipids and inflammatory markers at baseline and 7-day treatment of ACS patients

	Routine group (A, $n=20$)		Fluvastatin 40 mg (B, $n=20$)		Fluvastatin 80 mg (C, $n=20$)	
	Baseline	7 days	Baseline	7 days	Baseline	7 days
Total cholesterol, mmol/l	5.28±0.83	4.98±0.73	5.16±1.04	4.57±0.81	5.13±0.93	4.41±0.67
Triglyceride, mmol/l	1.52±0.49	1.50±0.40	1.48±0.49	1.39±0.38	1.55±0.41	1.43±0.35
LDL-C, mmol/l	3.72±0.69	3.56±0.62	3.34±0.91	3.02±0.79	3.62±0.76	3.11±0.61
HDL-C, mmol/l	1.042±0.227	1.04±0.206	1.02±0.26	1.06±0.22	1.12±0.17	1.13±0.21
Hs-CRP, mg/l	14.55±14.98	11.48±9.66	14.69±14.08	6.25±5.15*	14.24±12.12	4.23±3.64*$^{\#}$
TNF-α, pg/dl	22.74±15.78	21.55±10.90	22.87±12.36	15.19±9.60*	23.01±12.57	13.46±8.30*$^{\#}$

Values are means±SD; *$P<0.01$ compared with baseline; $^{\#}P<0.05$ for intra-group comparisons to group A by one-way ANOVA.

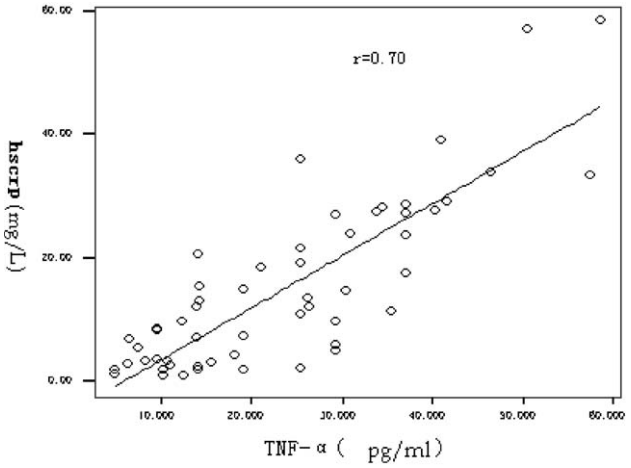

Fig. 1. Correlation between the serum hs-CRP and TNF-α concentrations at baseline and after fluvastatin treatment ($r=0.70$; $P<0.01$).

α concentrations after 7 days of treatment. Whereas, there was a significant correlation between the serum hs-CRP and TNF-α concentrations ($r=0.70$; $P<0.01$) (Fig. 1).

4. Discussion

Prospective epidemiologic studies [5,9–15,24,25] have confirmed that hs-CRP and TNF-α concentrations are important predictor of acute coronary events in apparently healthy individuals or in patients with CHD. Ridker et al. [26] showed that CRP may be a stronger predictor of cardiovascular events than LDL-C, and that measurement of hs-CRP adds important prognosis information to that delineated in the Framingham Risk Score. Our study also demonstrated that the serum concentrations of hs-CRP and TNF-α in patients with ACS were significantly higher than those in SCHD group. These results support the role of inflammation in the pathogenesis of atherosclerotic ACS.

Statins have been shown not only to modulate lipid and lipoprotein concentrations, but also have pleiotropic effects as anti-inflammation properties, improvement of endothelial dysfunction, antioxidant effects, stabilization of atherosclerosis plaques. In a randomized double-blind study, CRP increased during the first 5 days of ACS, which could be prevented in those randomized to atorvastatin 80 mg/d [27]. Another study on patients with AMI showed serum sCD40, MMP-9 and CRP concentrations decreased after 3 days of provastatin therapy [28]. In our study, fluvastatin treatment started within 24 h of onset of ACS and after 1 week of therapy showed a significant reduction in serum hs-CRP and TNF-α concentrations. Thus, these data indicated that treatment with fluvastatin may have anti-inflammatory effects in the early phase of ACS.

Several trials have assessed early initiation of statin agents following ACS [19,29,30]. The MIRACL [19] study was the first large-scale clinical trial to investigate whether early treatment with a statin in patients with ACS is beneficial; 3086 patients were randomly assigned within 24 to 96 h of hospital admission. The results showed that, compared to the placebo group, there was 16% reduction in events corresponded to myocardial infarction, resuscitated cardiac arrest, worsening angina or death at 16 weeks period in patients with ACS receiving 80 mg/d of atorvastatin. Recently, Ostadal et al. [29] demonstrated that cerivastatin treatment in patients with non-ST segment elevation ACS starting at the time of hospital admission have shown a decrease in inflammatory markers (CRP, IL-6) by 24 h follow-up, as compared to the non-treated group. In this study, the very early commencement of statin within 24 h of the onset of symptoms of ACS affirms fluvastatin has fast and early anti-inflammatory effects.

Recently, studies continue to show that, compared to low-dose statin, intensive statin therapy not only more effectively modulate serum lipids and improve inflammatory disorder, but also reverses atherosclerotic plaques [31–33]. A recent double-blind, randomized control multicenter trial [31] comparing the effects of 2 different statins administered for 18 months, CRP decreased 5.2% with (40 mg/d) pravastatin and 36.4% with (80 mg/d) atorvastatin ($P<0.001$), intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis, whereas patients treated with pravastatin show progression of coronary atherosclerosis. These data indicated that reverses in atherosclerotic progression were significantly related to greater reductions in the concentrations of both atherogenic lipoproteins and CRP [33]. In our study, serum hs-CRP and TNF-α concentrations were decreased in both the 2 fluvastatin treatment group in a short-term, and the 80 mg/d fluvastatin group had more significant effects, whereas the moderate 40 mg/d fluvastatin group had no significantly difference as compared to routine group. The results indicate that early intensive fluvastatin intervention may exert more anti-inflammatory effect.

In present study, after 1-week fluvastatin treatment, serum lipid concentrations in patients with ACS had no significant change while the serum hs-CRP and TNF-α concentrations significantly lowered. There was no significant association between the decrease in the fasting LDL-C concentrations and the changes in serum hs-CRP and TNF-α concentrations, whereas, there was a positive correlation between the serum hs-CRP and TNF-α concentrations. These data are consistent with similar findings of previous clinical trials [23,32,34–36], confirming the anti-inflammatory effects of statins independent of its lipid-lowering action. This could explain in part the early beneficial effects of statin intervention in ACS.

In summary, we demonstrate that the serum concentrations of inflammatory markers including CRP and TNF-α increase in patients with ACS, and early fluvastatin intervention effectively decreases the serum concentrations of hs-CRP and TNF-α. The high-dose fluvastatin invention may play a stronger anti-inflammatory effect in ACS patients, which is independent of its lipid-lowering effect.

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