Original article

Effect of pravastatin on endothelial dysfunction in children with medium to giant coronary aneurysms due to Kawasaki disease

Chao Duan, Zhong-Dong Du, Yu Wang, Li-Qun Jia

Beijing, China

Background: **Ongoing low-grade inflammation and endothelial dysfunction persist in children with coronary lesions diagnosed with Kawasaki disease (KD). Statins, frequently used in the management of high cholesterol, have also shown to improve surrogate markers of inflammation and endothelial dysfunction. This study was undertaken to investigate the efficacy and safety of pravastatin in children with coronary artery aneurysms due to KD.**

Methods: **The study enrolled 14 healthy children and 13 male children, aged 2-10 years, with medium-to-giant coronary aneurysms for at least 12 months after the onset of KD. Pravastatin was given orally to the KD group at a dose of 5 mg/day for children under 5 and 10 mg/day for children older than 5 years. To determine the effects of pravastatin on endothelial function, high-frequency ultrasound was performed before the start of the study and 6 months after pravastatin therapy. The parameters measured were brachial artery flow-mediated dilation (FMD), non-flow mediated dilation (NMD), and carotid artery stiffness index (SI). High sensitive C-reactive protein (hs-CRP) levels, the circulating endothelial progenitor cells (EPCs) number, and serum lipid profiles were also determined at baseline and after 6 months of pravastatin treatment.**

Results: **Before treatment, the KD group had significantly decreased FMD ($P<0.05$) and increased SI and hs-CRP levels ($P<0.05$) compared with controls. After 6 months of pravastatin therapy, FMD improved significantly compared to the baseline KD group (3.16±6.49 to 10.05±7.74, $P<0.05$), but remained significantly less than that in the control group with no significant changes in NMD and SI. There were significant decreases in markers of inflammation after treatment. The hs-CRP levels decreased significantly from 2.93±0.81 mmol/L to 2.14±0.82 mmol/L ($P<0.05$) and the serum apo-B and apo-B/apo-A1 ratio were also reduced ($P<0.05$) in the KD group. However, the circulating EPC number was not significantly different between baseline and that following pravastatin treatment in the KD group and the control group ($P>0.05$). No significant complications were noted with paravastatin therapy.**

Conclusions: **Pravastatin improves endothelial function and reduces low-grade chronic inflammation in patients with coronary aneurysms due to KD. Children with coronary aneurysms due to KD may benefit from statin therapy.**

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Key words: **coronary aneurysm;**
endothelial function;
endothelial progenitor cells;
Kawasaki disease;
statins

Introduction

Kawasaki disease (KD) is an acute systemic febrile illness that predominantly affects children under 5 years of age. Initially described in Japan in 1967 by Tomisaku Kawasaki, KD has become the leading cause of acquired heart disease among children in the developed world.[1] In addition, children with giant coronary aneurysms due to KD are at risk for stenosis, thrombotic occlusion and progression to ischemic heart disease.[2-4]

Previous studies[5-7] have shown that ongoing low-grade inflammation and endothelial dysfunction persist in children with coronary lesions due to KD. Recent trials of cholesterol-lowering agents[8-10] have demonstrated that 3-hydroxy-3-methylglutaryl-coenzyme

Author Affiliations: Department of Hematology/Oncology, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China (Duan C); Department of Cardiology, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China (Du ZD); Department of Ultrasonography, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China (Wang Y, Jia LQ)

Corresponding Author: Zhong-Dong Du, MD, PhD, Department of cardiology, Beijing Children's Hospital, Nan Li Shi Road, Beijing 100045, China (Tel: 86-10-59616643; Fax: +86-10-59616643; Email: zhongdong_du2012@126.com)

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(HMG-CoA) reductase inhibitors (statins) not only reduce cholesterol levels, but also improve surrogate markers of inflammation and endothelial dysfunction. Subsequently, the administration of statins has been shown to be safe and effective in children.[11-13] These resultsshowed that statins may delay the progression of late arterial lesions by improving endothelial dysfunction and suppressing inflammation in children with coronary aneurysm due to KD.

Additionally, the integrity and functional activity of the endothelial monolayer is essential for the protection against atherosclerosis. Circulating endothelial progenitor cells (EPCs) are regarded as having a key role in the maintenance of endothelial integrity and the replacement of apoptotic or damaged endothelial cells.[14] Therefore, we systematically evaluated changes in EPC number in KD patients with medium to giant coronary aneurysms.

Currently, there are a number of methods available to indirectly measure vascular function and inflammation, two key parameters in the development of atherosclerosis. Flow-mediated dilation (FMD) of the brachial artery indirectly reflects the action of nitric oxide liberated by the endothelium, which is considered a marker for endothelial function. Non-flow mediated dilation (NMD) of the brachial artery reflects vasodilation mediated by vasoactive agents and does not require the endothelium to be morphologically and functionally intact. In addition, high sensitivity C-reactive protein (hs-CRP), a marker of chronic, low-grade inflammation, is a reliable predictor of chronic cardiovascular disease. As a result of the limited studies on the effects of statins on the progression of atherosclerosis, we investigated the effect of oral pravastatin on endothelial function, EPC and inflammatory markers in children with coronary aneurysms due to KD.

Methods

Subjects

Thirteen males between the ages of 2 and 10 years (mean, 5.8±2.1 years) with medium to giant coronary aneurysms that met the 5th revised edition of KD diagnostic criteria and the American Heart Association classification of coronary aneurysms[15] were consecutively enrolled in the study. All children were patients of Beijing Children's Hospital, had persistent aneurysms for at least 12 months, and had routine electrocardiograms (ECG) and echocardiograms before the start of treatment and at each follow-up visit. The echocardiograms detected a stenotic lesion of the right coronary artery in 2 patients. No coronary artery aneurysm (CAA) regression or ischemic cardiac events were observed in any of the patients. One patient had an axillary artery aneurysm.

Patients were excluded from the study if they had confounding risk factors for endothelial damage, such as an infectious disease, chronic inflammatory disease, snoring, malignant disease, family history of premature cardiovascular disease, or history of taking vasoactive medications.

The control group consisted of 14 boys aged 3-11 years (mean, 5.5±2.3 years). These subjects were recruited from the Children's Health Center of Beijing Children's Hospital. All participants underwent a routine physical examination and blood work. The study was approved by the institutional ethics committee of the hospital, and an informed consent was obtained from all the patient's parents.

Study protocol

A general physical examination was performed on all patients. Their height, weight, and right arm blood pressure were recorded. Blood samples were initially collected for baseline measurements, monthly to monitor liver enzymes, and at end of the protocol. Samples were used to determine the EPC number, as well as high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), triglycerides (TG), total cholesterol (TC), apolipoprotein A1 (apo-A1), and apolipoprotein B (apo-B) levels, hs-CRP levels were assessed using an ELISA (ADL, USA).

The KD group was administered oral pravastatin (Sino-American Shanghai Squibb Pharmaceuticals Ltd.) 5 mg/day for children under 5 years of age and 10 mg/day for children older than 5 years. Pravastatin was administered 30 minutes after their evening meal for 6 months. During this period, the enrolled KD patients underwent monthly laboratory tests for creatine kinase (CK), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to monitor kidney and liver functions. In addition, the KD patients received intravenous gamma globulin treatment during the acute phase (2 g/kg or 1 g/kg for 2 consecutive days). All patients diagnosed with persistent CAA recieved a low dose of aspirin (3 to 5 mg/kg per day) and dipyridamole (5 mg/kg per day). Clinical events and adverse effects were monitored and recorded during the follow-up visits.

Assessment of FMD and NMD

FMD was assessed using the method described by Corretti et al.[16] Room temperature was maintained at 24ºC-25ºC and all of the measurements were performed by the same operator blinded to the study groups. Patients rested in a supine position 15 minutes prior to obtaining the measurement. B-mode ultrasound images of the brachial artery were obtained with a 7 MHz linear-array transducer (GE logic Q9) in longitudinal sections 2 to 15 cm above the elbow. After an optimal longitudinal image of the brachial artery wall was obtained, the baseline end-diastolic vessel diameter

(D0) was measured. A pneumatic tourniquet was then inflated distal to the arterial segment being imaged to a pressure of 200 mmHg for 5 minutes. The cuff was deflated and a second scan (D1) was then recorded within 60-90 seconds of cuff deflation. After an additional rest period of 15 minutes to permit vessel recovery, sublingual nitroglycerine was administered (250 μg). The final scan (D2) was recorded 5 minutes later. All vessel diameters were calculated as the average of 3 measurements. The ECG was monitored continuously throughout the study, and the end-diastolic vessel diameter was measured concurrently with the onset of the QRS complex. FMD was calculated as follows: FMD = [(D1-D0)/D0]×100%. NMD was calculated as follows: NMD = [(D2-D0)/D0] ×100%.

Assessment of carotid stiffness index

The carotid stiffness index (SI) was measured using B-mode with a 7.0 MHz linear transducer. Patients were positioned in a supine position with a lateral head tilt. Images were obtained within 1 cm of the junction of the right common carotid artery. The vascular diameter of the vessel was determined during systole (Ds) and diastole (Dd). The SI was calculated as follows: SI=[systolic pressure/diastolic pressure]/[(Ds-Dd)/Dd].

EPC number

EPCs were quantified by phenotype in whole blood samples using flow cytometry. The cells were directly stained and analyzed for phenotypic expression of surface antigens using anti-human monoclonal antibodies. The EPCs were defined as CD34+/CD133+/KDR+ cells. EDTA anticoagulant peripheral whole blood (100 μL) was stained with antibodies [anti-CD34-FITC (Becton Dickinson, Oxford, UK), anti-CD133-APC (Miltenyl Biotech, Germany) and anti-KDR (VEGFR2)-PE (R&D Systems, Minneapolis, USA)] for 20 minutes in the dark at room temperature. Appropriate isotype controls were stained to establish positive stain boundaries. Erythrocytes were lysed (Becton Dickinson, Oxford, UK), and samples were centrifuged at 1500 g for 5 minutes at room temperature. Cells were collected, washed, and re-suspended in 500 μL of phosphate-buffered saline (PBS) without cations. Acquisition was performed by technicians blinded to subject identity using a FACS Valieur analyzer (Becton Dickison). Analysis was performed by gating lymphocytes and monocytes on the basis of light-scattering properties. We acquired 100 000 events per gate. EPCs were quantified based on the percentage of CD34+CD133+KDR+ triple positive leucocytes and expressed as the number of cells per 10^5 mononuclear cells.

Safety examination

ALT, AST and CK levels were measured monthly during the study. If the ALT and AST levels increased more than 3-fold of the upper limit of the normal range or the CK levels increased more than 10-fold of the upper limit, the patient was terminated from the study. Other monitored side effects of pravastatin were included rash, nausea, vomiting, headache, and chest pain.

Statistical methods

Data were analyzed using SPSS 12.0 (Chicago, IL, USA) and expressed as the median (Q1, Q3). The differences in serum lipid profile, endothelial function and EPC number between the KD group and control group were analyzed by the rank-sum test (Tables 1 and 3). The above values before and after statin therapy in the KD group were compared by Wilcoxon's signed-rank test (Tables 2 and 4). $P<0.05$ was considered statistically significant.

Table 1. Baseline serum lipid profile and endothelial function in the KD and control groups

Variables	KD group (n=13)	Healthy controls (n =14)	P value
HDL-C (mmol/L)	1.32 (1.07, 1.53)	1.27 (1.02, 1.57)	0.880
LDL-C (mmol/L)	2.57 (2.05, 2.89)	2.11 (1.81, 2.62)	0.204
TG (mmol/L)	1.11 (0.47, 1.43)	0.61 (0.51, 0.96)	0.390
TC (mmol/L)	4.30 (3.77, 4.26)	4.17 (3.84, 4.32)	0.204
apo-A1 (g/L)	1.10 (1.00, 1.35)	1.10 (1.00, 1.20)	0.762
apo-B (g/L)	0.60 (0.50, 0.80)	0.60 (0.50, 0.70)	0.614
apo-B/apo-A1	0.56 (0.48, 0.62)	0.55 (0.42, 0.86)	0.323
hs-CRP (mg/L)	2.89 (1.66, 7.01)	1.75 (1.02, 3.74)	0.013
FMD (%)	4.20 (-1.71, 8.16)	11.10 (8.80, 16.40)	0.001
NMD (%)	24.40 (11.2, 30.65)	24.13 (18.62, 30.86)	0.545
SI	3.12 (3.02, 3.37)	2.93 (2.67, 3.15)	0.032

HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TG: triglycerides; TC: total cholesterol; apo-A1: apolipoprotein-A1; apo-B: apolipoprotein-B; hs-CRP: high sensitivity C-reactive protein; FMD: flow-mediated dilatation; NMD: non-flow mediated dilatation; SI: stiffness index; KD: Kawasaki disease.

Table 2. Serum lipid profile and endothelial function before and after pravastatin treatment

Variables	Baseline (n=13)	After treatment (n =13)	P value
HDL-C (mmol/L)	1.32 (1.07, 1.53)	1.30 (0.98, 1.54)	0.294
LDL-C (mmol/L)	2.57 (2.05, 2.89)	1.88 (1.76, 2.43)	0.098
TG (mmol/L)	1.11 (0.47, 1.43)	0.64 (0.51, 0.83)	0.516
TC (mmol/L)	4.30 (3.77, 4.26)	3.53 (3.15, 4.21)	0.019
apo-A1 (g/L)	1.10 (1.00, 1.35)	1.30 (1.20, 1.40)	0.094
apo-B (g/L)	0.60 (0.50, 0.80)	0.40 (0.40, 0.50)	0.010
apo-B/ apo-A1	0.55 (0.42, 0.86)	0.33 (0.31, 0.39)	0.020
hs-CRP (mg/L)	2.89 (1.66, 7.01)	2.12 (1.34, 5.56)	0.022
FMD (%)	4.20 (-1.71, 8.16)	6.46 (4.49, 11.6)	0.009
NMD (%)	24.40 (11.2, 30.65)	23.10 (16.55, 31.95)	0.753
SI	3.12 (3.02, 3.37)	3.05 (2.67, 3.25)	0.575

HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TG: triglycerides; TC: total cholesterol; apo-A1: apolipoprotein-A1; apo-B:apolipoprotein-B; hs-CRP: high sensitivity C-reactive protein; FMD: flow-mediated dilatation; NMD: non-flow mediated dilatation; SI: stiffness index.

Results

ECG and echocardiographic findings in the KD group

Patients in the KD group experienced medium to giant aneurysms 1.5-7 years after the initial diagnosis of KD (3.1±1.7 years). The cohort consisted of 2 patients with medium CAAs and 11 patients with giant CAAs. The aneurysms did not resolve during the study. ECGs showed abnormal Q waves in 3 patients at the beginning of the study, as well as at the end of 6-month study. No other ECG abnormalities were observed. Echocardiography detected 37 CAAs from 78 branches or segments of the patients' coronary arteries. The mean diameter of the CAAs before and after pravastatin was 8.0±2.3 mm and 7.8±3.1 mm, respectively (P=0.53).

Baseline measurements

Age, body mass index, systolic blood pressure, diastolic blood pressure, and serum lipid profiles, including HDL-C, LDL-C, TG, CHO, apo-A1, apo-B, and apo-A1/apo-B levels, between the two groups were not statistically significant (Table 1). Endothelial-dependent FMD (P=0.001) was decreased and SI (P=0.036) and hs-CRP levels (P=0.003) were increased in the KD group compared with the control group. NMD was not statistically significant between the two groups at baseline (P>0.05).

Lipid profiles after 6 months of pravastatin treatment

As shown in Table 2, the mean serum total cholesterol level reduced significantly from 4.24±0.51 mmol/L at baseline to 3.63±0.59 mmol/L 6 months after therapy (P<0.05). The apo-B levels were reduced (0.61±0.34 g/L to 0.47±0.10 g/L) and the apoB/apoA1 ratio decreased (0.60±0.27 to 0.38±0.11 from baseline to 6 months after therapy (P<0.05). The serum apo-A1 levels increased and TG, HDL-C and LDL-C levels lowered after treatment; none of the parameters showed a significant difference (P>0.05).

Changes in endothelial function and hs-CRP levels after treatment

FMD significantly improved after treatment (3.16±6.49 to 10.05±7.74; P<0.05). Other parameters of endothelial function (NMD and SI) were not significantly different after treatment. hs-CRP levels decreased significantly from 2.93±0.81 mmol/L to 2.14±0.82 mmol/L after pravastatin treatment (P=0.020; Table 2).

Circulating EPC number

The number of circulating EPCs between the two groups was not significantly different before the start of therapy. No change was observed between the two groups after 6 months of pravastatin treatment (Table 3 and 4).

Safety monitoring

During the study, one patient presented with slightly elevated CK levels (246 IU/L; upper limit, 200 IU/L), but required no medication. The other 12 patients had normal serum AST, ALT and CK levels. No additional side effects were noted.

Discussion

Endothelial injury and dysfunction are important contributors in the development of atherosclerosis.[17] Thus, patients in early adulthood with CAAs due to KD are at increased risk because of widespread vascular endothelial damage in the acute phase and persistent coronary artery morphological changes. Our data indicated that systemic endothelial dysfunction and chronic endothelial inflammation existed in patients with CAA due to KD. Furthermore, short-term statin treatment improved chronic vascular inflammation and endothelial dysfunction, as well as reduced lipids,

Table 3. EPC number results in the KD and control groups before treatment

Variables	KD group (n=13)	Healthy controls (n=14)	P value
$D34^+$ (cells/10^5 events)	40.0 (30.0, 70.0)	40.0 (30.0, 70.0)	0.888
KDR^+ (cells/10^5 events)	740.0 (350.0, 1150.0)	340.0 (240.0, 1430.0)	0.318
$CD133^+$ (cells/10^5 events)	30.0 (20.0, 60.0)	40.0 (30.0, 80.0)	0.210
$CD34/KDR^+$ (cells/10^5 events)	8.6 (4.4, 20.0)	8.0 (4.8, 13.5)	0.857
$CD34/CD133^+$ (cells/10^5 events)	13.0 (4.3, 21.2)	10.3 (5.6, 16.2)	0.589
$KDR/CD133^+$ (cells/10^5 events)	20.0 (10.0, 90.0)	20.0 (10.0, 30.0)	0.103
$CD34/KDR/CD133^+$ (cells/10^5 events)	3.4 (0.9, 6.2)	2.2 (1.1, 4.5)	0.849

EPC: endothelial progenitor cell; KD: Kawasaki disease.

Table 4. EPC number in the KD group before and after treatment

Variables	Baseline (n=13)	After treatment (n=13)	P value
$CD34^+$ (cells/10^5 events)	40.0 (30.0, 70.0)	49.0 (34.0, 82.0)	0.622
KDR^+ (cells/10^5 events)	740.0 (350.0, 1150.0)	520.0 (210.0, 1270.0)	0.915
$CD133^+$ (cells/10^5 events)	30.0 (20.0, 60.0)	20.0 (10.0, 60.0)	0.858
$CD34/KDR^+$ (cells/10^5 events)	8.6 (4.4, 20.0)	9.5 (4.0, 19.7)	0.244
$CD34/CD133^+$ (cells/10^5 events)	13.0 (4.3, 21.2)	12.3 (4.7, 19.1)	0.847
$KDR/CD133^+$ (cells/10^5 events)	20.0 (10.0, 90.0)	10.0 (0, 30.0)	0.593
$CD34/KDR/CD133^+$ (cells/10^5 events)	3.4 (0.9, 6.2)	3.9 (1.7, 5.1)	0.685

EPC: endothelial progenitor cell; KD: Kawasaki disease.

without any significant adverse reactions. A previous work by Huang et al[18] showed similar results, however their study subjects were not clearly documented. In their study, 11 children presenting with "coronary artery abnormalities" were treated with simvastatin for three months. They concluded that short-term statin therapy could improve chronic vascular inflammation and endothelial dysfunction with no adverse effects. We specifically evaluated the therapeutic potential of pravastatin in KD patients with coronary aneurysms.

Our patients presented with medium to giant coronary aneurysms due to KD and they were therefore at high risk for ischemic heart disease. They required aggressive anticoagulation treatment and frequent follow-up.[19,20] Vascular stiffness was increased in atherosclerotic vessels, while vascular elasticity was decreased as a consequence of endothelial dysfunction. This resulted in intimal thickening and an increase in the vascular wall extracellular matrix. The loss of vascular elasticity was determined by a poor response to a vasodilator. FMD, a measure of endothelial damage and function was used to determine endothelial NO-dependent vasodilatation. FMD is decreased in adult atherosclerosis,[21] and previous studies[5,6,22] have shown that FMD of the brachial artery is decreased in KD patients, particularly in those with CAAs. Our data showed that FMD significantly decreased in the KD group, indicating systemic endothelial dysfunction after the onset of KD and impaired production of endogenous NO. A limited number of reports failed to show a change in FMD in patients with KD.[7] These discrepancies may be associated with confounding factors such as race, severity of the disease, follow-up time, treatment in the acute phase, lifestyle, dietary habits, etc.

Statins, also known as HMG-CoA reductase inhibitors, are first-line agents used to reduce serum cholesterol concentrations. Statins have been shown to increase endothelial nitric oxide synthase expression and activity in vascular endothelial cells.[23] Recent studies[8-10,24] have shown that statins reduce the rate of progression of coronary atherosclerosis and prevent cardiovascular events in subjects with a wide range of cardiovascular risks. Our study showed that endothelium-dependent FMD of the brachial artery improved after 6 months of statin therapy. These findings support a role for statin therapy in the management of patients with CAAs due to KD and suspected endothelial dysfunction. NMD was not different between the KD and control groups, indicating that endothelial damage contributed to the decreased dilatation of the brachial artery. The carotid artery SI, which is another marker of vascular elasticity, was significantly decreased in the KD group compared with the control group.

Serum TC and HDL-C levels, which are risk factors associated with atherosclerosis, decrease significantly in the acute phase of KD and that lower HDL-C levels persist long after the acute phase.[25] However, a recent study evaluating the lipid profile of adult KD patients, with a mean interval time of more than 20 years from disease onset, found no significant difference compared with healthy adults.[26] Similarly, in our study, the serum lipid levels between the KD and control groups were not different. However, after 6 months of statin therapy, the serum TC and apo-B levels and the apo-B/apo-A1 ratio decreased significantly, suggesting a reduction in cardiovascular risk. Elevated apo-B levels and an increased apo-B/apo-A1 ratio correlate to increased risk and severity of ischemic heart disease.[27,28] Therefore, our data suggested that 6 months of statin therapy reduces the risk of ischemic heart disease. As expected, we did not observe any difference in LDL-C levels after statin treatment between the two groups. This might be due to that apo-B was more sensitive to statin treatment than other lipoproteins. In addition, the HDL-C and LDL-C levels were normal at baseline, and statin therapy is only effective at abnormal levels.

Atherosclerosis is an inflammatory disorder. Patients with persistent CAAs have been shown to have ongoing systemic inflammation years after the initiation of the disease, as indicated by elevated hs-CRP levels.[26,29,30] Our study demonstrated significantly higher baseline levels of hs-CRP in the KD group. hs-CRP levels significantly decreased after 6 months of statin treatment, suggesting a potential role for statins in the management of chronic vascular inflammation.

EPCs are mobilized from bone marrow by inflammatory cytokines such as VEGF, MMP-9 and IL-8, which are up-regulated by tissue ischemia or as a result of ischemic damage to the vascular endothelium. In this study, we did not observe changes in circulating EPC numbers in the convalescent phase of KD. This might be due to the majority of our patients presenting with relatively stable coronary lesions, and thus stimulating or mobilizing factors were insufficient in our patient population. Although colony-forming units, proliferation, migration and apoptosis of the function EPCs were not observed in our study, it is a potential focus for future studies in identifying the role of EPC in the progression of late arterial lesions in KD patients.

In summary, our data suggest that pravastatin improves endothelial function and reduces low-grade chronic inflammation in children with coronary aneurysms after the resolution of KD. Thus, children with coronary aneurysms may benefit from statin therapy. Since the sample size is very small in our study, larger controlled studies are needed to validate these preliminary results.

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