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Early Anti-Inflammatory Effects of Three Different Dosesof Atorvastatin Treatment Before Selective Percutaneous Coronary Intervention

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Abstract:

Background: *Percutaneous coronary intervention (PCI) turn out to be widespread for the treatment of coronary artery disease (CAD). Until now, this treatment strategy remains safe and effective; moreover, an earlier or late procedural related-complications can still occur. We aimed to compare the effects of different atorvastatin loading doses before PCI in CAD patients on PCI-related inflammatory factors, myocardial injury, and the mid-term clinical outcomes.*

Methods:*A total number of 221 patients for elective PCI were randomly assigned into three groups to receive either atorvastatin (20 mg; n=84 group A), (40 mg; n=76 group B) or (80 mg; n=83 group C) 12hours before PCI. The end-point of this study was the changes in the inflammatory factors and myocardial injury, by evaluating the rise of periprocedural serum inflammatory factors and cardiac Troponin T serum levels N3× the upper limit of normal.*

Results: *No significant differences were noted in the baseline clinical data, the coronary angiographic parameters, and medications used before PCI in either group. After PCI Blood levels of homocysteine, highly sensitive C-reactive protein and neutrophils were significantly higher than their levels before PCI in the three groups, changes of their levels before and after PCI in group C (80mg) was statistically lower than 40mg and 20mg groups, (△HCY levels (4.65±2.13 vs. 2.43±1.08 vs. 1.27±0.40) μmol/L，P<0.001; △hs-CRP (6.32 ±2.52 vs. 5.26±2.76 vs. 3.50±1.98) mg/L, P<0.001; and △neutrophil (3.28±0.45 vs. 2.64±0.43 vs. 1.78± 0.41)106/ml, P<0.001), also the elevated homocysteine levels was significantly correlated with the changes of △neutrophil count (r=0.711, P<0．001), △hs-CRP concentrations (R=0.228, P<0.01), and post-PCI cTnI (R=0.183, P<0.05). (3) The incidence of Post-PCI MI at group C (80mg atorvastatin loading dose) was the lowest，and at group A (20mg atorvastatin loading dose) was the highest (0.96±0.39 vs.0.86±0.32 vs.0.75±0.31; P<0.05).*

Conclusion： *Our study concluded that the administration of different loading doses of atorvastatin has various anti-inflammatory and cardiac muscle protective effects, high loading 80mg of atorvastatin pre-PCI within 24 hours has most anti-inflammatory, and myocardial protective effects in patients with CAD.*

Keywords: *atorvastatin, PCI，homocysteine, neutrophil, highly sensitive C-reactive protein, myocardium protection.*

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I. INTRODUCTION:

Percutaneous coronary intervention turns out to be widespread for the treatment of coronary artery disease (CAD) which has been one of the fundamental treatment strategies for either stable CAD or ACS[1]. An injury to the myocardium after PCIprocedure commonly caused by procedural complications such as distal embolization, coronary dissection, side-branch occlusion, or disruption of collateral flow.The incidence of myocardial damage post-PCI which based on the significant elevation of cardiac biomarkers, is 1-30%[2]. A direct injury occurred to the endothelium, the vascular wall, resultingin the activation of the local inflammatory factors such as interleukin 6 (IL-6), homocysteine, C- reactive protein(CRP), macrophage capping protein (MCP)-1, and other inflammatory factors characterized by the adhesion and infiltration of leukocytes at the site of injury[3].

The pleiotropic effects of statins in coronary artery disease are mediated at the level of vascular endothelial cells, platelets, inflammatory cells, and the myocardium itself[4]. Statins are protective when given acutely during any of two phases of myocardial ischemia-reperfusion, the first being before ischemia and the second being at the onset of reperfusion. High homocysteine (HCY) levels considered as a risk factor for the development and evolution of atherosclerosis. C-reactive protein (CRP) is another pro-inflammatory factor that has been occupied in the pathogenesis of CAD. Elevation of both preprocedural or post-procedural CRP is an independent predictor of a higher incidence of MACE[5, 6]. Cardiac troponins T (cTnT) and I (cTnI) are very sensitive and specific cardiac markers to detect myocardial cell injury and necrosis. The predictive value of troponins is now well recognized for patients presenting with acute coronary syndromes (ACS)[7-9] rise of troponin levels after routine PCI has also been known as a prognostic of both short- and long-term major adverse cardiovascular events (MACE)[10].
This study aimed to lookfor the differences in the inflammatory markers post PCI after the early administration of different loading doses of atorvastatin therapy before PCI and the myocardial protective effects.

II. MATERIALS AND METHODS:

Patients selection: All patients accepted the agreement for the donation of a sample of their blood to be used for scientific purposes. All of the 221 patients were randomly categorized into three groups: group A (20mg/12h before PCI; n=70), group B (40 mg/12h before PCI; n=75) and group C (80 mg/12h before PCI; n=76). Coronary heart disease (CHD): was known as coronary angiography shows of luminal diameter stenosis ⩾75% in at least one of 3 major coronary arteries and indicated for PCI. **Exclusion criteria:** acute ST-elevation myocardial infarction (STEMI); acute non-ST-elevation myocardial infarction (NSTEMI); requiring urgent PCI; aortic aneurism or dissection; Ejection fraction (EF) <30%; acute cerebrovascular accident; hematologic disorders; current trauma; infectious disease within the last 15 days; severe obstructive pulmonary disease; elevated liver enzymes (aspartate-amino- transferases/ alanine aminotransferases), impaired renal function with a serum creatinine level >133umol/L; history of muscle disorders; history of systemic inflammatory disease or cancer.

Treatment and procedures:PCI was performed by standard techniques through radial or femoral artery puncture. The transradial PCI technique was conducted in patients with coronary lesions that required treatment either with single, double or triple stents technique. The atorvastatin loading doses were administered 12hours before PCI. After stenting, all of the patients continued the regimen treatment of dual antiplatelet therapy (DAPT), including aspirin (100 mg/day) indefinitely, clopidogrel (75 mg/day) for ⩾one year, atorvastatin (20 mg/day), β- blockers and angiotensin- converting enzyme (ACE) inhibitors if there were no contraindications, regardless of the primary randomization assignment.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation. We used Kolmogorov–Smirnov test (K–S test or KS test) to estimate the normal distribution of continuous variables, multi-groups were compared by ANOVA, analyzing data was done by using $\chi 2$ test, Correlation analysis was done by linear

regression and Pearson correlation coefficient. The P-value < 0.05 was considered as statistically significant. SPSS 22.0 statistical software (SPSS Inc, Chicago, IL, USA) was applied for all of the analysis.

III. RESULTS:

General Characteristics: Clinical features in the three groups are reported in Table 1. All the groups had the same baseline properties, including age, gender, body mass index (BMI), clinical manifestations, EF and medication used during hospitalization (all P>0.05). Table 1.

Table 1 Main clinical features of patients in the three groups

Variable	Group A(20mg) n=70	GroupB(40mg) n=75	GroupC(80mg) n=76	P
Age(y)	58.47±8.25	58.77±8.00	58.72±7.34	0.943
Gender (male%)	51(72)	55 (73)	59 (77)	0.745
BMI, kg/m2	23.25±4.27	23.87±3.87	22.70±3.82	0.197
Diabetes mellitus	60(14)	66(12)	60(21)	0.312
Hypertension	30 (42)	38 (50)	34 (44)	0.839
Smokers	41 (58)	35 (46)	43 (44)	0.099
Previous PCI	0(0)	0(0)	0(0)	1
Previous CABAG	0(0)	0(0)	0(0)	1
LVEF, %	62±6	59±7	60±7	0.69
RBS, mmol/L	5.82±0.97	6.05±1.53	6.17±1.63	0.321
LDL-C, mmol/L	2.96±0.94	2.64±1.16	2.40±1.09	0.212
TG, mmol/L	3.35±1.51	3.28±1.60	3.54±1.54	0.579
Cholesterol, mmol/L	5.42±1.52	5.35±2.35	5.13±1.40	0.587
HDL-C, mmol/L	1.30±0.42	1.15±0.42	1.28±0.44	0.75
Variable	Group A(20m g) n=70	GroupB(40mg) n=75	GroupC(80mg) n=76	P
Creatinine, mg/L	71.16±19.63	71.93±19.70	73±23.15	0.865
AST, IU/L	37.19±19.74	42.07±33.21	41.10±25.14	0.513
ALT, IU/L	41.54±23.02	37.91±23.66	43.88±25.05	0.306
HCYμmol/L	16.93±5.80	16.81± 6.3	16.09± 5.60	0.659
Hs-CRP mg/L	6.40±2.22	6.66±2.14	6.62±2.56	0.759
Neutrophils 10^9/L	5.89±1.04	5.77±1.06	5.96±1.12	0.561
Other medications				
Aspirin	100%	100%	100%	1
Clopidogrel	100%	100%	100%	1
Beta-blockers	74.2%	77.6%	90.8%	0.432
ACEI/ARB	30.2%	28.4%	38.6%	0.312

Note: data shown in this table are presented as n (%) or mean ± SD. HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; TG Triglycerides; PCI percutaneous coronary intervention; CABG Coronary Artery Bypass Grafting; LVEF Left ventricular ejection fraction; RBS Blood

Sugar HCY homocysteine; hs-CRP highly sensitive C-reactive Protein; ALT Alanine Aminotransferase; AST Aspartate Aminotransferase; ACEI/ARB Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

The changes of inflammatory factors and cardiac markers among the three groups: There were no significant differences in the result of HCY, hs-CRP, neutrophils, and cTnI levels before PCIprocedure (all P>0.05). Post PCI HCY, hs-CRP concentrations, neutrophil counts and cTnI levels were significantly higher in group A (20mg loading dose) and lower at group C (80mg loading dose); all P<0.05.

ΔHCY, Δhs-CRP,andΔneutrophilwere defined aschanged HCY levels, hs-CRP concentrations and neutrophils account pre and post PCI. The plasma ΔHCY levels immediately (0.2650 vs. 0.2200 vs. 0.1400)μmol/L, Δhs-CRP (6.32±2.52 vs. 5.26±2.76 vs. 3.50±1.98) mg/L,andΔneutrophil (3.28±0.45 vs. 2.64±0.43 vs. 1.78±0.41) 10^6/ml, for group A (20mg), group B (40mg) and group C (80), respectively; all were significantly lower in the 80mg loading dose group compared with the other two groups; all P≤0.01. Same results were found with the cTnI after PCI, for group A (20mg), group B (40mg) and group C (80), respectively; (0.96±0.39 vs.0.86±0.32 vs.0.75±0.31; P=0.001), all were significantly lower in the 80mg loading dose group compared with the other two groups; (Table 3).

Table3 comparison of the inflammatory and cardiac markers in the three groups

Variable		A(20mg)n=70	B(40mg)n=75	C(80mg)n=76	P
HCY	Before-PCI	16.10±5.61	16.81±6.37	16.93±5.81	0.713
μmol/L	After-PCI	16.42±5.55	17.16±6.25	17.02±5.78	0.748
	ΔHCY	0.2650	0.2200	0.1400	0.040
Hs-CRP	Before-PCI	6.59±2.45	6.67±2.15	6.40±2.22	0.766
mg/L	After-PCI	12.91±2.67	11.93±2.45	9.91±2.43	0.001
	ΔCRP	6.32±2.52	5.26±2.76	3.50±1.98	0.010
NEU	Before-PCI	5.97±1.13	5.78±1.06	5.90±1.04	0.561
$\times 10^9$/L	After-PCI	9.23±1.19	8.41±1.26	7.67±1.17	0.010
	ΔNEU	3.3000	2.7000	1.8000	0.001
CTnI	Before-PCI	0.50±0.28	0.55±0.30	0.52±0.30	0.620
ng/ml	After-PCI	0.96±0.39	0.86±0.32	0.75±0.31	0.001
	ΔCTnI	0.42±0.32	0.31±0.27	0.22±0.25	0.001

Data presented as mean ± SD HCY: homocysteine, hs-CRP highly sensitive C-reactive Protein; cTnI cardiac troponin i.

Correlation between ΔHCY with Δhs-CRP, Δneutrophil, and cTnI, after PCI.

There was positively correlation between ΔHCY with Δneutrophils (r=0.711, P<0.001)，Δhs-CRP (r=0.228 ,P<0．001) and post-PCI cTnI levels (r=0.183,P<0.05). But the correlation between ΔHcy and age, blood sugar, TC,LDL-C, HDL-C, TG, BMI was not statistically significant(P>0.05) (Table 3).

Table 2 The relationship between ΔHCY levels，Δhs-CRP，Δneutrophil count，cTn I and cardiovascular risk

factors

Item	r	P
Age	0.036	0.593
BMI	-0.008	0.907
TC (mmol/L)	0.089	0.189
LDL-C (mmol/L)	0.056	0.405
HDL-C (mmol/L)	0.031	0.650
TG (mmol/L)	-0.034	0.610
Pri-operative blood sugar	-0.046	0.494
Post-PCI cTnI (μg/L)	0.183	0.007
∆neutrophil (10^9)	0.711	0.000
∆hs-CRP(mg/L)	0.228	0.000
Pri-operative neutrophils (10^9)	-0.032	0.637
Pri-operative hs-CRP(mg/L)	0.086	0.202

Note BMI: body mass index, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, PCI: percutaneous coronary artery intervention, cTnI: cardiac troponin I, hs-CRP highly sensitive C-reactive Protein.

IV. DISCUSSIONS:

In our current study, the results demonstrated a single dose of atorvastatin (80, 40, or 20 mg) within 24 hours before to electivePCI can effectively reduce the incidence of peri-procedural MI in CAD patients. Moreover, the cTNI elevations after PCI were significantly the lowest at 80mg atorvastatin group. This finding isconsistent with previous studies, demonstrating that statinscan reduce the rate of MI following PCI as well as othermajor cardiac adverse events[11-13].Nevertheless, it should be noted that other trails used different methods of statin administration. Therefore, our study result is valuablebecause a large number of patients who undergo electivePCI every year are using statins, and it might be decidedthat extra administration of statins may not be beneficial.

Evidence that aggressive lipid reduction is of particularadvantage in the prevention of CAD either primarily or secondarily, itsmost effective with statins such as Atorvastatin. Indirect evidence from WOSCOPS, ASCOT, and the CARE trials, in terms of subgroup analysis, has revealed that the relative risk reduction in cardiovascular mortality and morbidity in individuals in the statins group was still significant despite comparable serum cholesterol levels with the placebo group. This brought to the front position of the importance of the non-lipid lowering actions of statins in cardiovascular protection[4].

Pleiotropic actions of statins are defined as extrahepatic beneficial effects, that are dependent on mechanisms not related to its ability to lower cholesterol[4]. Mevalonic acid levels are minimized as a result of the effect of statins on the enzyme. However, mevalonic acid is also a precursor for non-cholesterol compounds such as isoprenoids, which have various actions in cell signaling and cell survival. Inhibition of this isoprenoid synthesis has been the focus of much of the pleiotropic actions of statins. while the pleiotropic actions may vary to some extent depending on the lipophilicity of the specific statins, the actions principally remain similar. The pleiotropic actions of statins in coronary artery disease are mediated at the level of vascular endothelial cells, platelets, inflammatory cells and the myocardium itself[4]. Statins can improve endothelial dysfunction by increasing the expression of eNOS,causing an increase of NO synthesis, and by reducing endothelin1 production[14].In-vivo rat modeldemonstrated that Atorvastatin could enhance endothelial function by hindering the expression of the p22phox subunit of NADPH oxidase which is the main resource of ROS also reduces oxidative stress. The associated reduction in reactive oxygen species (ROS) will decrease the cleansing of NO and consequently enhancing the availability of NO[15]. Statins have also been demonstrated to inhibit platelet

stimulation, therefore, have an effect on thrombogenicity. In a normocholesterolemic mouse model, atorvastatin has been shown to increase nitric oxide synthase-3 in platelets and this was accompanied by decreased platelet stimulation[16]. Statins have a protective effect when given acutely during any of two phases of myocardial ischemia-reperfusion, the first being before ischemia and the second being at the start of reperfusion. This study designed to compare the acute effects of different loading doses administered orally of 20mg, 40mg, and 80mg atorvastatin 12 hours before PCI procedure, in patients with CAD, on PCI-related inflammatory and cardiac injury. The study showedthat the increased levels of HCY, hs-CRP, and neutrophil count in 80mg atorvastatin loading dose (group C) significantly lower than that in 40mg and 20mg atorvastatin loading dose (group B and A respectively), also at the 40mg group was significantly lower than that in 20mgatorvastatin loading dosegroup.In this study we also have found that the peak average of postoperative cTnI at 80mg loading dose group was significantly less than that in 40mg and 20mgatorvastatin loading dose groups, as well in 40mggroup was significantly less than 20mgatorvastatin loading dose group, this indicating perioperative myocardial protective effects of 80mg atorvastatin, that can significantly improve myocardial perfusion in patients with CAD undergoing PCI.

Many studies showed that the applying of concentrated statins drugs before coronary intervention therapy could improve myocardial perfusion diminished major adverse cardiac events(MACEs) and have been demonstrated to be relatively safe[17-20]. Atorvastatin for Reduction of Myocardial Damage during Angioplasty (ARMYDA) trialwas the first investigation of patients who never used statins before PCI, atorvastatin dose of 40mg/day was administratedfor seven days prior PCI inpatients with stable coronary disease[21]. In ARMYDA-Acute Coronary Syndromes (ACS)[22] and ARMYDA -REC APTURE[17], atorvastatin dose schedule was 80mg 12 h pre-PCI and an additional 40 mg was given just before PCI procedure. In the Novel Approaches for Preventing or Limiting Events (NAPLES) II trial[11], a loading dose of 80mg atorvastatin was administered the day before elective PCI. In both of these four trials, atorvastatin has been shown a significant reduction in the levels of markers of myocardial injury compared with placebopost-PCI. The endpoint was the incidence of perioperative MI (which defined as greater than the upper limit of normal CK-MB 2 times); MI patients in the experimental group rate were reduced from 18% to 5% ($P = 0.05$)[22].

PCI-related inflammation is an important concept in cardiovascular medicine. There were studies that showed the range of inflammatory aggravation following PCI related to post-PCI clinical outcome[23]. Homocysteine (HCY) is a sulfur-containing amino acid; its synthesized reveals during the metabolic transformation of methionine to cysteine (Cys). As the physiological role of HCY in methyl transfer reactions, elevated plasma levels of HCY (>15 μmol/l) can cause endothelial damage in humans and are related to increased cardiovascular risk[24]. Different studies[25-28] showed that moderately elevated concentrations of HCY are expected modifiable risk factors for coronary heart disease, which may contribute to the development of atherosclerosis. High levels of plasma HCY was considered as a predictor of major accident cardiac event in patients with ACSand represents an independent risk factor for recurrent ACS[29]. several years ago, homocysteine has been regularly more debated as a risk factor for coronary heart disease. Several mechanisms have been recommended for homocysteine in the pathogenesis of atherosclerosis, a number of those mechanisms could also be involved in restenosis after coronary interventions[30]. In this study, we have found that the blood levels of HCY after PCI was significantly higher than HCY levels before PCI among the three groups, and it was significantly highest in group A(20mg), while in group C(80mg) was the lowest with ($P<0.05$). This is the same resultasVerdoia, Monica et al[31] study. suggesting that the presence of neutrophil mobilization and activation after PCI Due to HCY which is maybe a sign of instability of plaque and the poor prognosis, therefore the detection of HCY levels to identify, guide and manage MACE Highly-risk patients after PCI have a clinical significance. Recent studies have shown that HCY accelerates the onset of EPC apoptosis and leads to cellular dysfunction[32, 33]. Atorvastatin may inhibit HCY-induced activation of NADPH oxidase and exert cellular antioxidant effects by declining the mRNA expression of the necessary NADPH oxidase subunit Nox1[34] and inhibiting endothelial Nox4 overexpression and formatting an active complex with p22-phox, which enhances superoxide anion formation and phosphorylation of p38MAPK[35]. a study shows that atorvastatin (10 μmol/L) significantly suppressed HCY(1mmol/L for 30 min) induced ROS accumulation (3.17 ± 0.33 vs. 4.34 ± 0.31,$P<0.05$)[36]. also,hs-CRP and neutrophil counts were significantly lower in groupC(80mg loading dose), and significantly highest at group A(20mg), both ($P<0.05$). Recently, an indication of the existence of TNFa, IL-6, and IL-8 in atherosclerotic lesions has been obtained[37, 38]. In reality, during the response to tissue inflammation or infection, IL-6, IL-1, and TNFa stimulate the production of CRP. so the IL-6 is a regulator of CRP and has an explanation in the initiation of inflammation. CRP attracts monocytes, activates complement and stimulate a reducing in endothelial function[39]. hs-CRP[40] and IL-6 are considered as new biomarkers of cardiovascular disease[26] and elevated IL-6 and hs-CRP levels are strongly related to the inflammatory system and the course of clinical andhemodynamically significant CAD[41].

Furthermore, In this study, we also have found that the elevated levels of homocysteine were positively correlated with the elevated neutrophil counts before and after PCI ($r=0.711$，$p<0.05$), same with the elevated hs-CRP concentrations before and after PCI ($r=0.228$，$p<0.05$). This may be an indication of HCY activation which leads to the relevant process of the neutrophils to the bloodstream. Bryushkova, E. A., et al[41] study have shown that HCY does not affect the function of intact cells but stimulates ROS generation and degranulation in in-vivo then activated neutrophils isolated from the inflammatory area, so these facts indicate that HCY is able to modify neutrophil function by stimulating their cytotoxicity. Also, there was a study showed that after PCI blood levels of CRP, IL.6, MCP.1, JPG and other inflammatory factors increased, suggesting that after PCI accompanied by systemic or local Inflammation[42]. Increased hs-CRP levels are strongly associated with the inflammatory system and the course of clinical and hemodynamically changes in CAD[43]. In recent studies[44], elevated hs-CRP was significantly correlated with clinical symptoms in patients with ACS and perform an effective advantage for CRP in risk stratification[45].

Our results demonstrate that early administration of different loading-dose of atorvastatin before PCI may enhance the declaration of the inflammatory response marked by hs-CRP, so in this study, the plasma level of hs-CRP in group C (80mg loading dose) was significantly lower than those in groups A(20mg loading dose) and B(40mg loading dose) at each sampling point (group C vs. group B; group C vs. group A) ($P<0.05$), which indicated the anti-inflammatory effects of loading-dose atorvastatin therapy. Basic research also supports the confidence that atorvastatin was the most potent statin, which could exert acute and rapid response to the inflammation within 5 minutes after administration[46].

V. CONCLUSIONS

Our study discovered that acute pre-PCI loading with statins may reduce the degree of PCI-related inflammatory factors, and the incidence of PCI-induced myocardial injury, also these beneficial acute effects of statins on the myocardium increased with increasing dose of statin loading before PCI. This early loading dose treatment might be related to mild adverse reactions and be well tolerated. The present study proposes that different loading protocols before PCI procedure may be used clinically relying on the individual conditions of the patient.

Limitations

Our study has limitations. This study is a small sample single-center observational study and a small sample of cases, so some necessary information between groups is not balanced enough. In this study, the time taking of atorvastatin pre-treatment in each group was not similar, did not separate stable angina patients from unstable angina patients, so this study has certain limitations. The patient follow-up was also not enough, not fully understanding the impact of statin pretreatment prognostic because the safety of statins must be confirmed by most of the other tests, so this experiment did not observe the side effects of statins.

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