Original article

Impact of intensive statin use on the level of inflammation and platelet activation in stable angina after percutaneous coronary intervention: A clinical study

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Abstract

Background and objective: This study was designed to investigate whether high-dose atorvastatin before percutaneous coronary intervention (PCI) can reduce inflammation, platelet activation, and major adverse cardiac events (MACE) in patients with stable angina who are undergoing long-term statin therapy.

Methods: In total, 215 patients with chronic stable angina were randomized to pretreatment with 80 mg of atorvastatin (12 h before PCI; n = 106) or with 20 mg of atorvastatin (12 h before PCI; n = 109). All patients underwent PCI. Serum levels of interleukin-6, high-sensitivity C-reactive protein, tumor necrosis factor-α, GMP-140, and P-selectin were measured 24 h before and after PCI. The 30-day incidence of MACE was determined.

Results: No differences in baseline characteristics were observed between the groups. The levels of inflammation and platelet activation were significantly lower after 24 h in the group that received intensive statin therapy (P < 0.05). The levels of inflammation and platelet activation increased sharply 24 h after PCI in the group that received the lower dose of atorvastatin (P > 0.05). In other words, pretreatment with a high dose of atorvastatin decreased the incidence of MACE sharply within 30 days (P < 0.05).

Conclusions: Pretreatment with a high dose of atorvastatin significantly reduced inflammation, platelet activation, and the incidence of MACE in patients with stable angina.

Estudio clínico del impacto de la utilización intensiva de estatinas sobre los niveles de inflamación y activación plaquetaria en la angina estable después de intervención coronaria percutánea

Resumen

Fundamento y objetivo: El objetivo de este estudio fue diseñado para investigar si dosis altas de atorvastatina antes de la intervención coronaria percutánea (PCI) pueden reducir la inflamación, la activación plaquetaria y episodios cardíacos adversos mayores (MACE) en pacientes con angina estable que se someten a terapia con estatinas a largo plazo.

Métodos: En total, 215 pacientes con angiina estable crónica fueron asignados aleatoriamente a un tratamiento previo con 80mg de atorvastatina (12 h antes de la PCI, n = 106) o con 20mg de atorvastatina (12 h antes de la PCI, n = 109). Todos los pacientes fueron sometidos a PCI. Los niveles séricos de interleucina-6, proteína C reactiva de alta sensibilidad y factor de necrosis tumoral alfa, GMP-140 y P-selectina se midieron 24 h antes y después de la PCI. Se determinó la incidencia a 30 días de MACE.

Resultados: No se observaron diferencias en las características basales entre los grupos. Los niveles de inflamación y activación de las plaquetas fueron significativamente menores a las 24 h en el grupo que recibió terapia intensiva con estatinas (p < 0.05). Los niveles de inflamación y activación de las plaquetas aumentaron considerablemente 24 h después de la PCI en el grupo que recibió la dosis más baja de

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**Introduction**

Percutaneous coronary intervention (PCI) is a useful examination method for patients with stable angina. During PCI, the blood supply to the opened lesions of vessels may cause a ruptured coronary plaque, thrombosis, and damage to vascular endothelial structure and function. Statins have a lipid-lowering effect, limit plaque formation, and reduce inflammation.

The ARMYDA-ACS and ARMYDA-RECAPTURE trials showed that short-term statin therapy can protect myocardial tissue before PCI. The ARMYDA-CAMS trial confirmed that short-term statin use before PCI significantly reduced plasma E- and vascular cell adhesion molecule 1 levels, thereby improving endothelial function. However, limited data are available for platelet activation factors.

Therefore, we conducted a prospective randomized trial to evaluate whether a single loading dose of 80 mg atorvastatin pre-treatment before PCI could affect the levels of inflammation, platelet activation, and incidence of major adverse cardiac events (MACE) within 30 days in patients with stable angina who received long-term statin therapy.

**Methods**

The design of the study was reviewed and approved by the hospital ethics committee. All patients provided written consent.

**Study population**

The study population consisted of 236 patients with stable angina who were admitted to the second affiliated hospital of Chongqing Medical University and who underwent PCI from January 2010 to October 2011. Inclusion criteria were the patients with stable angina and had received long-term regular statin therapy for at least 3 months before the procedure. Exclusion criteria were the patients with acute coronary syndrome (ACS), severe liver and kidney disease, heart failure, cancer, and pregnancy. Twenty-one patients (8.9%) who did not receive angioplasty were excluded from the study because their coronary artery stenosis < 50%. Eligible patients (n = 215) were randomized to receive 80 or 20 mg of atorvastatin. Patients were assigned in a 1:1 ratio with a computer-generated randomization sequence. After coronary angiography, the remaining 215 patients (80-mg atorvastatin group, n = 106; 20-mg atorvastatin group, n = 109) were enrolled in the study.

Hypertension was defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg. Type 2 diabetes mellitus was diagnosed using American Diabetes Association criteria. Kidney disease was defined by an elevated serum creatinine level of >133 mmol/L.

**Treatment**

PCI was performed by experienced interventional cardiologists through a femoral approach using a 7 Fr guiding catheter. Physicians performing the procedure and the follow-up assessments were blinded to the randomization assignment. Patients were allocated to two groups: the intensive statin group (IS group, n = 106) and the standard statin group (SS group, n = 109). Before receiving PCI, the patients in the IS group were administered 80 mg of atorvastatin, whereas those in the SS group were administered 20 mg of atorvastatin. Next, the patients were subjected to PCI. All patients were administered 20 mg of atorvastatin at night after PCI and followed up in the coronary intensive care unit until clinical stabilization was established. The subjects were advised to rest and to consume a low-fat diet with aspirin, beta-blockers, and angiotensin converting enzyme inhibitors.

**Biochemical assessments**

Blood was drawn from an antecubital vein at 24 h pre- and post-PCI. Plasma was isolated and stored at –80° C before analysis. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were assessed using chemiluminescent immunoassay techniques (Access2 Automatic Analyzer; Beckman, Fullerton, CA, USA) and radioimmunoassay (Shanghai Yanyu Chemical Co., Shanghai, China), respectively. Serum glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein (hs-CRP) were also assessed (HITACHI 912 Analyzer; Roche Diagnostics, Mannheim, Germany).

GMP-140 was determined using an enzyme-linked immuno-sorbent assay kit (R&D Systems, Minneapolis, MN, USA). P-selectin (CD62P) was measured by flow cytometry (ELITE; Beckman). CD62P-FITC, CD61-PE, and the same type control for IgG1-FITC/IgG1-PE were provided by Santa Cruz Biotechnology (Santa Cruz, CA, USA). The normal reference value ranged between 2 and 5%.

**Clinical follow-up**

All patients were followed closely in a special outpatient clinic or by telephone for about 30 days after discharge. MACE, including relapse angina, myocardial infarction, cardiac death, and stent thrombosis or target-vessel revascularization by either PCI or coronary artery bypass grafting were recorded. All MACE were reviewed by two experienced cardiologists who were blinded to the angiographic data. Patients received periodic extent-of-disease evaluations. A 30-days clinical follow-up was performed for all patients to evaluate MACE and the evaluations included typical clinical performance and laboratory examinations such as electrocardiograms and myocardial enzymes.

**Statistical analysis**

Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as percentages. Comparisons were made by matching t-tests in each group and t-tests between the groups. Categorical variables were compared using chi-square or Fisher’s exact tests, as indicated. All variables with P-values < 0.05 in a univariate analysis (age, hypertension, current smoking, diabetes mellitus, statin pretreatment, and stenting) were included in the model. A P-value < 0.05 was considered significant. SPSS version 13.0 (Chicago, IL, USA) was used for all statistical analyses.
Table 1
Baseline demographic and clinical properties in all patients with stable angina.

<table>
<thead>
<tr>
<th>Variable</th>
<th>ISG (n = 106)</th>
<th>SSG (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.2 ± 11.1</td>
<td>58.4 ± 9.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67 (63)</td>
<td>66 (61)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>58 (55)</td>
<td>73 (67)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>64 (60)</td>
<td>67 (62)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>53 (50)</td>
<td>57 (52)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.3 ± 1.1</td>
<td>4.2 ± 1.5</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.6 ± 1.2</td>
<td>2.6 ± 1.5</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.7 ± 0.4</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.3 ± 0.1</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>69 (65)</td>
<td>62 (57)</td>
</tr>
<tr>
<td>Beta-blockers (%)</td>
<td>74 (70)</td>
<td>71 (65)</td>
</tr>
<tr>
<td>ACEI (%)</td>
<td>42 (40)</td>
<td>41 (38)</td>
</tr>
<tr>
<td>Atorvastatin (%)</td>
<td>58 (55)</td>
<td>49 (45)</td>
</tr>
<tr>
<td>Simvastatin (%)</td>
<td>21 (20)</td>
<td>30 (28)</td>
</tr>
<tr>
<td>Pravastatin (%)</td>
<td>27 (25)</td>
<td>30 (27)</td>
</tr>
<tr>
<td>Stent numbers</td>
<td>1.3 ± 0.2</td>
<td>1.4 ± 0.4</td>
</tr>
<tr>
<td>DES</td>
<td>85 (80)</td>
<td>82 (75.2)</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or number (%).
ISG, intensive statin group; SSG, standard statin group; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitor; DES: drug-eluting stents. All P > 0.05.

Results

Baseline clinical and procedural characteristics

PCI was performed successfully in all patients. The clinical data of the 216 patients are shown in Table 1. No significant differences were observed in the baseline clinical and procedural characteristics, including mean age, sex ratio, stent placement, or coronary risk profiles such as diabetes mellitus, smoking, hypertension, and hyperlipidemia between the two groups. All patients were treated with stents, and drug-eluting stents were used in 167 cases (77.8%). Mean number of stents per patient was 1.4, which were not significantly different between the two groups.

Serum levels of the inflammatory factors IL-6, TNF-α, and hs-CRP

No significant differences in levels were observed between the two groups for IL-6, TNF-α, and hs-CRP before PCI (Table 2). Compared with the SS group at 24 h after PCI, the serum levels of IL-6 (95% CI: 11.2–11.8 vs. 14.1–16.5; 11.5 ± 0.3 ng/L vs. 15.3 ± 1.2 ng/L, P = 0.04), TNF-α (95% CI: 0.3–0.9 vs. 0.3–3.3; 0.6 ± 0.3 ng/L vs. 1.8 ± 1.5 ng/L, P = 0.03), and hs-CRP (95% CI: 2.6–2.8 vs. 2.9–5.3; 2.7 ± 0.1 mg/L vs. 4.1 ± 1.2 mg/L, P = 0.04) decreased consistently in the IS group, and these values were lower in the IS group than before PCI. Additionally, similar parameters were higher at 24 h after PCI than before PCI in the SS group (P < 0.05).

Serum levels of the platelet activation factors GMP-140 and CD62P

Changes in the platelet activation factors GMP-140 and CD62P are given in Table 3 and Fig. 1. No significant differences in levels were observed between the two groups for GMP-140 and CD62P before PCI. The serum levels of GMP-140 (95% CI: 3.24–11.08 vs. 8.90–14.94; 7.25 ± 3.83 µg/L vs. 11.92 ± 3.02 µg/L, P = 0.03) and CD62P (95% CI: 2.97–5.07 vs. 5.89–9.49; 4.02 ± 1.05% vs. 7.69 ± 1.80%, P = 0.04) were much lower in the IS group than in the SS group at 24 h after PCI. These data were lower at 24 h after PCI than before PCI in the IS group. Moreover, the serum levels of GMP-140 and CD62P did not differ in the SS group at 24 h after PCI compared to those before PCI (P > 0.05).

MACE

Total MACE occurred in 2.8% of patients (3 of 106) in the IS group compared with that of 8.3% (9 of 109) in the SS group (RR = 0.34; Table 4). The incidence of MACE at 1 month was mostly driven by angina pectoris (2.8% vs. 6.4%, P = 0.04). Stent thrombosis occurred in two patients (1.8%) in the SS group and was successfully treated with re-intervention and stent implantation. These patients did not have elevated myocardial enzymes to fulfill the criteria for myocardial infarction. The findings in electrocardiograms and myocardial enzymes showed better event-free survival at 30 days in the IS group.

Discussion

The results of the present study demonstrate that pretreatment with a high dose of atorvastatin significantly reduced inflammation, platelet activation, and the incidence of MACE in patients with stable angina who underwent long-term statin therapy. Earlier studies suggested that statins have pleiotropic effects, which are independent of their lipid-lowering properties, including
improvements in nitric oxide bio-availability and endothelial function, anti-inflammatory activity, plaque stability, and anticoagulant activity. In the NAPLES II and ARMYDA-RECAPTURE trials, patients were administered 80 mg of atorvastatin prior to undergoing PCI. The administration of atorvastatin significantly reduced the incidence of MACE within 30 days; however, the beneficial outcomes in patients with stable angina who underwent long-term statin therapy could be attributed to a reduction in the inflammatory response and platelet activation.

These results indicate that intensive atorvastatin therapy further reduced the levels of serum IL-6, TNF-α, and hs-CRP. Hs-CRP, which is caused by the IL-6, plays a central role in the inflammatory process as a predictor of vascular inflammation and cardiovascular events. Apart from reflecting the degree of systematic inflammation, hs-CRP could be considered a surrogate of atherosclerotic burden, as it plays a direct role in atherosclerotic plaque rupture and thrombosis. In other words, serum levels of IL-6, TNF-α, and hs-CRP may be used to predict severe cardiovascular risk. A large dose of atorvastatin reduces inflammation in patients diagnosed with ACS. However, as reported earlier, these are critical patients who receive greater benefit from intensive statin therapy. Hence, a single loading dose of 80 mg of atorvastatin before PCI efficiently reduced inflammation in patients with stable angina. The main mechanism includes preventing the formation of inflammatory cells and inhibiting macrophages and metal protease expression. This reduces the number of macrophages and IL-6 synthesis.

Platelet activation is an important stage in the treatment of coronary heart disease. In this study, we found that an intensive dose (80 mg) of atorvastatin before PCI restrained platelet activation. GMP-140 and CD62 are specific markers of platelet activation that play an important role in rehabilitating patients suffering from thromboembolic accidents. The thromboxane 2 (TXA2) content is maintained in the blood under normal physiological conditions; however, TXA2 synthesis increases when endothelial vessels are injured, leading to greater platelet aggregation and thrombosis. We confirmed that PCI triggered increased coronary inflammation and platelet activation, thereby increasing the risk of stenosis. Simvastatin reduces platelet activation in patients with ACS; however, the effect of high-dose statin pretreatment on the level of platelet activation is not completely understood, as very few studies have been conducted.

Table 4
The outcome measures of 30-day incidence of MACE in the ISG and SSG.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ISG (n=106)</th>
<th>SSG (n=109)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina pectoris</td>
<td>3 (2.8)</td>
<td>7 (6.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>-</td>
<td>2 (1.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Total MACE</td>
<td>3 (2.8)</td>
<td>9 (8.3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are given as number of patients (%).
ISG, intensive statin group; SSG, standard statin group; MACE, major adverse cardiac events.
* RR < 0.34, P < 0.05, the incidence of MACE in the ISG was lower than the SSG.
Thus, we found that intensive atorvastatin pretreatment reduced platelet activation in patients with stable angina who underwent long-term statin therapy. We did not uncover any significantly different outcomes in the SS group; this was attributed to the fact that patients received long-term statin therapy along with routine treatment for coronary heart disease. The statin anti-platelet mechanism may be reduced through lipid deposition, thereby preventing endothelial injury and thrombosis.

The 30 days after PCI comprise the main period of thrombosis. Pretreatment with a high dose of atorvastatin reduced the risk of MACE at 30 days. This beneficial outcome may be attributed to IS pretreatment in patients with stable angina. Statins also cause a significant decrease in cardiovascular mortality when initiated early in ACS. In other words, statin therapy before PCI can reduce myonecrosis. A meta-analysis by Afflalo et al. indicated that a loading dose of statin reduced the incidence of death in patients with ACS. Our results suggest that intensive statin use before PCI reduced the incidence of MACE to a greater extent in patients suffering from stable angina.

Our study has several limitations. The sample size was small, and patients with non-specific symptoms such as chest pain required further investigation. We could not determine the clinical outcome according to the dose of statin or the exact duration of therapy given the small sample size. Thus, a large registry study is needed to generalize our results.

Conclusions

In conclusion, our results show that a single loading dose of 80 mg of atorvastatin as pretreatment reduced inflammation, platelet activation, and the incidence of MACE in patients with stable angina who underwent long-term statin therapy.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

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References