The beneficial effect of high loading dose of rosuvastatin before percutaneous coronary intervention in patients with acute coronary syndrome

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Abstract

Background: Statin therapy prior to percutaneous coronary intervention (PCI) is associated with reduced mortality and periprocedural myocardial injury after PCI. We studied whether single high dose statin loading is beneficial on the outcome of patients with acute coronary syndrome (ACS) underwent PCI.

Methods: Consecutive 445 patients with ACS who underwent PCI were randomly assigned to either the group of no statin treatment before PCI (Control group: \(n=220\), 63±11 years, male 62%) or the group of 40 mg rosuvastatin loading before PCI (Rosuvastatin group: \(n=225\), 64±10 years, male 60%). Incidence of periprocedural myocardial injury was assessed by analysis of creatinine kinase-MB (CK-MB) and cardiac troponin T before PCI, at 6 h and the next morning after PCI.

Result: There were no significant differences in clinical characteristics between the two groups. After PCI, incidence of periprocedural myocardial injury was higher in control than in rosuvastatin group (11.4% versus 5.8%, \(p=0.035\)). Mean preprocedural CK-MB and high sensitivity C-reactive protein were similar between the two groups, whereas after PCI, peak values of both markers were elevated significantly higher in control than in rosuvastatin group. Multivariate analysis revealed that no prior use of statin (OR=2.2; 95% CI =1.1–4.6; \(p=0.029\)), procedural complication (OR=3.1; 95% CI =1.4–6.9; \(p=0.007\)) and multi-vessel disease (OR=2.6; 95% CI =1.0–6.6; \(p=0.039\)) were the independent predictors for periprocedural myocardial infarction.

Conclusion: Single high dose of rosuvastatin prior to PCI reduces periprocedural myocardial injury in patients with ACS.

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1. Introduction

The role of statins in patients undergoing percutaneous coronary intervention (PCI) has been clarified. Some reports suggested that statin therapy prior to PCI is associated with reduced mortality and the reduction of periprocedural myocardial injury after PCI in patients with or without acute myocardial infarction (MI) [1–3]. Moreover, recently reported ARMYDA (Atorvartatin for Reduction of MYocardial Damage during Angioplasty) trial showed that pretreatment with atorvastatin 40 mg/day before PCI in angina patients was associated with 81% risk reduction of periprocedural MI [4].

However, most of these studies were retrospective analysis of patients who underwent chronic statin administration. In real clinical situation, most patients have not been prescribed statins before PCI, especially in emergency setting.
So, the present study purposed to examine whether single high dose statin loading has benefit on PCI in patients without chronic statin administration.

We designed a prospective randomized study, using rosuvastatin. We administered high loading dose of rosuvastatin before PCI to reduce the rate of periprocedural myocardial injury and the rate of major adverse cardiac events (MACE).

2. Methods

2.1. Subjects

From March 2005 to December 2007, we studied 677 consecutive patients who had Non-ST-segment elevation acute coronary syndrome (ACS) and received diagnostic coronary angiography. We excluded cases with previous statin therapy, cardiogenic shock, those in which medical treatment was recommended, those in which coronary artery bypass graft surgery (CABG) was recommended, and those with severe hepatic (history of liver cirrhosis or alanine aminotransferase > 2.5 times upper normal limit) and renal diseases (serum creatinine > 2.0 mg/dL).

107 patients were excluded because of previous or current treatment with statins, 41 for emergency angiography due to cardiogenic shock or ongoing pain, 19 because of renal or hepatic disease. Eligible patients were randomly assigned to the group of no statin pretreatment (Control group) or to the group of 40 mg rosuvastatin loading treatment before PCI (Rosuvastatin group). Randomization was performed by a 1:1 ratio. After coronary angiography, 65 patients who did not receive PCI were excluded from the study; thus, 445 patients with significant coronary artery disease and underwent PCI were enrolled.

All patients gave informed consent according to a protocol approved by the Ethical Committee of Wonkwang University Hospital. The flow chart of this study was described in Fig. 1.

2.2. Percutaneous coronary intervention

PCI was performed according to current clinical practice at physician’s discretion. PCI was performed immediately after diagnostic angiography. On diagnostic coronary angiography, the patency of the treated artery was evaluated by the Thrombolysis In Myocardial Infarction (TIMI) score. Angiographic success of PCI was defined as TIMI III flow with residual stenosis below 20%.

In all patients, aspirin (300 mg/day) and clopidogrel (300 mg/day) were loaded before procedure. An intravenous bolus of 5000 U of unfractionated heparin was given, and then additional heparin boluses were given to maintain activated clotting time > 300 s during procedure. Platelet glycoprotein IIb/IIIa inhibitors (GPI) were administered according to operator preference.

The occurrence of angiographic complications during PCI was recorded. These included failed PCI such as wire or balloon passage failure, side branch occlusion, slow or no reflow, major dissection, and distal embolization.

2.3. Post-procedural management

Aspirin (200 mg/day), clopidogrel (75 mg/day) and rosuvastatin (10 mg/day) were prescribed to all patients after the procedure. CK-MB and troponin T were measured before (at admission, mean 20 ± 4 h before PCI), at 6 h and next morning after PCI. Additional samples were obtained if the patients showed signs or symptoms of myocardial ischemia. High-sensitivity C-reactive protein (hsCRP) levels were also assessed before PCI and next morning after PCI.

2.4. Primary and secondary end points

The primary end point was the occurrence of periprocedural MI, defined as a post-procedural increase of CK-MB over 2 times higher the normal upper limit in patients with normal baseline enzyme level. In patients with elevated baseline levels of CK-MB, MI was defined as a subsequent increase of more than 2-fold in CK-MB from baseline value and an additional increase in second sample [5]. Secondary end points included (1) any post-procedural increase of markers of myocardial injury above upper limit of normal or ≥ 20% increase of elevated baseline value [6], (2) peak values of hsCRP after PCI; (3) occurrence of MACE during 1 month (death, Q wave MI, target vessel revascularization, ischemic stroke).

2.5. Statistical analysis

The sample size was selected to demonstrate a reduction in the primary end point from a 12% in the control group to 6% in the statin group [2,7]. Minimal sample size of 390 randomized patients would provide 80% power with two-sided alpha of 0.05. All measurements were represented as mean ± standard deviation. Inter-group analysis was done using independent
t-test and $\chi^2$ test, which were conducted using SPSS 11.0 for Window (SPSS inc., Chicago, IL). To compare the change of cardiac enzymes before and after PCI, we used paired t-test. A multivariable logistic regression model was constructed for the prediction of CK-MB elevation $>2$ times upper normal limit after PCI. The following variables, selected according to the literature data [7] and significant univariate analysis, were inserted into the logistic regression analysis; no prior use of statin, procedural complication, age, multi-vessel disease, long stent length, and complex lesion. For continuous variables, the median value was used as a cut-off point to define the two subgroups in logistic regression analysis. Statistical significance was set at $p<0.05$.

3. Results

3.1. Baseline characteristics

Clinical and procedural data were described in Tables 1 and 2, respectively. Rosuvastatin 40 mg loading was performed for $16\pm 5$ h (range 7–25 h) prior to the index procedure. There was no significant difference in the most relevant clinical characteristics between the two groups (Table 1).

We used drug-eluting stents in most cases (96.2%), and over 32% of patients were received multi-vessel stenting. All angiographic and procedural characteristics were similar between the two groups (Table 2). Angiographic complications during the procedure occurred in 28 patients (12.7%) in control group and 24 patients (10.7%) in rosuvastatin group ($p=0.499$, Table 3).

3.2. Periprocedural myocardial injury

Myocardial infarction by CK-MB elevation $>2$ times upper normal limit was detected after PCI in 11.4% of the patients in control group and in 5.8% of those in rosuvastatin group ($p=0.035$, Fig. 2). Moreover, incidence of post-procedural elevation of troponin T was higher in control group than in rosuvastatin group (Fig. 3). In the two groups, mean baseline

<table>
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<tr>
<th>Table 2</th>
<th>Coronary angiographic and procedural characteristics.</th>
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<tbody>
<tr>
<td></td>
<td>Control $(n=220)$</td>
</tr>
<tr>
<td>Multi-vessel disease (%)</td>
<td>118 (54)</td>
</tr>
<tr>
<td>Mean time to angiography (h)</td>
<td>24±7</td>
</tr>
<tr>
<td>Target vessel (%)</td>
<td>0.328</td>
</tr>
<tr>
<td>LAD</td>
<td>111 (51)</td>
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<tr>
<td>LCX</td>
<td>52 (24)</td>
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<tr>
<td>RCA</td>
<td>49 (22)</td>
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<tr>
<td>LM</td>
<td>8 (3)</td>
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<tr>
<td>ACC/AHA B2/C lesion (%)</td>
<td>165 (75)</td>
</tr>
<tr>
<td>Bifurcation (%)</td>
<td>77 (35)</td>
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<tr>
<td>Thrombus (%)</td>
<td>12 (5)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Table 3</th>
<th>Procedural complications.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control $(n=220)$</td>
</tr>
<tr>
<td>Failed PCI</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Slow or no reflow</td>
<td>17 (7.7)</td>
</tr>
<tr>
<td>Distal embolization</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Side branch occlusion</td>
<td>6 (2.8)</td>
</tr>
<tr>
<td>Major dissection</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Any of above</td>
<td>28 (12.7)</td>
</tr>
</tbody>
</table>

PCI: percutaneous coronary intervention; EF: ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; LMWH: low molecular weight heparin; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.
CK-MB and troponin T were similar, whereas after PCI, the peak value of all markers were elevated significantly higher in control group. That is, CK-MB changed from 28±30 to 35±27 IU/L in control group (\(p=0.005\) by paired \(t\)-test), from 27±27 to 30±25 IU/L in rosuvastatin group (\(p=0.051\)). Troponin T changed from 0.2±0.6 to 0.5±1.0 ng/mL in control group (\(p<0.001\)), from 0.2±0.7 to 0.3±0.5 ng/mL in rosuvastatin group (\(p=0.050\)). After rosuvastatin 40 mg loading, hsCRP levels were less elevated than in patients without rosuvastatin loading from 4.8±8.5 mg/dL to 16.2±28.1 mg/dL on the next morning after PCI (\(p<0.001\)). Whereas, hsCRP levels were changed from 4.7±8.9 to 9.4±12.6 mg/dL in patients with rosuvastatin loading (\(p<0.001\)) (\(p=0.001\) compared to control group). After medication, LDL cholesterol levels were more reduced in rosuvastatin group than in control group. LDL cholesterol changed from 122±38 mg/dL to 104±28 mg/dL in rosuvastatin group (\(p<0.001\)), from 124±40 mg/dL to 117±33 mg/dL in control group (\(p=0.001\) compared to rosuvastatin group). Multivariate analysis revealed that no prior use of statin (OR=2.2; 95% CI=1.1–4.6; \(p=0.029\)), procedural complication (OR=3.1; 95% CI=1.4–6.9; \(p=0.007\)) and multi-vessel disease (OR=2.6; 95% CI=1.0–6.6; \(p=0.039\)) were the independent predictors for periprocedural MI (Table 4).

### 3.3. Adverse cardiovascular events

The patients who were received rosuvastatin loading prior to PCI had a lower incidence of 30 day MACE compared to the patients who have not taken statin before PCI (15.9% vs. 6.7%, \(p=0.002\)). The different outcomes mainly resulted from the higher incidence of periprocedural MI in control group (Table 5).

There are no serious side effects on rosuvastatin loading. Myalgia without elevation of muscle enzyme occurred in only 1 patients. Any other side effects were not developed during study period.

### 4. Discussion

In this study, we showed that high dose of rosuvastatin loading therapy before PCI for the patients with ACS is associated with the reduction of periprocedural myonecrosis and inflammatory response.

Relatively low-level release of cardiac enzymes after PCI occurred in about 25% of the patients treated with stent [8–10]. It was demonstrated that periprocedural myocardial injury is associated with a worse long-term clinical outcomes [11–13]. Ellis et al. [14] reported that CK-MB elevation to any level...
above the normal limit appears to heighten the risk of death after PCI, and there is an early risk period apparently limited to 3 to 4 months after PCI. Therefore, strategies to decrease myonecrosis may translate into a decrease in mortality. Different strategies such as platelet GP IIb/IIIa inhibitors, high dose clopidogrel, and statin have been proposed and tested to prevent periprocedural myocardial infarction [15–17]. However, we noted the efficacy of statin.

Briguori et al. [2] reported randomized study supporting the cardioprotective effect of statins in PCI. They reported that the incidence of CK-MB elevation >5 times upper normal limit was approximately 50% lower in the statin treated patients. In addition, the CK-MB peak after stenting was significantly lower in the statin group than in the control. Recent ARMYDA-ACS trial, using 80 mg loading of atorvastatin and 600 mg loading of clopidogrel, revealed that even short-term pretreatment with high dose atorvastatin improve outcomes and prevent myonecrosis [5]. In our randomized study, using rosuvastatin 40 mg loading dose, the CK-MB and troponin T peak after PCI were significantly lower in patients treated with statin loading before PCI, and 30 day outcomes were more favorable in statin loading patients.

The benefits of statin in cardiovascular diseases can be explained not only by their lipid-lowering potential but also by non-lipid-related mechanisms, so called pleiotropic effects [18]. The pleiotropic effects encompass non-lipid mechanisms that modify endothelial function, inflammatory responses, plaque stability and thrombus formation [19]. These pleiotropic effects may potentially improve outcome after PCI. Many studies were demonstrated that early statin therapy among PCI patients is associated with significant mortality and morbidity advantages in different patient subsets [1–4,20–25].

Vascular injury during PCI is associated with a systemically measurable inflammatory response, and the degree of inflammation has been shown to correlate with cardiovascular risk [24,26]. The increase in serum CRP concentration follows the increase in serum IL-6 concentration by 12–36 h, reaching its peak value by 24 h after the procedure [27,28]. Bonz et al. [28] found the increase in the serum concentrations of both IL-6 and CRP to be more obvious in patients with concomitant post-procedural troponin T elevation. Additionally, Gaspardone et al. [22] reported that 80 mg/day of atorvastatin given at the time of coronary stenting reduces the acute inflammatory response and the incidence of clinical events at 6 months. Hong et al. [29] demonstrated that elevated preprocedural CRP levels are associated with neointimal hyperplasia and restenosis after PCI. Therefore, survival benefit with statin pretreatment is dependent on periprocedural inflammatory status, and periprocedural myocardial injury is correlated with vascular inflammation. In our study, the hSCRP peak after stenting was significantly lower in the statin loading group than in the control group, and these results support the important role of inflammation in periprocedural myocardial injury. Also, the patients received high dose rosuvastatin revealed lower LDL cholesterol level after 24 h and it could account for some benefit of high dose statin therapy.

Our study has several limitations. The study was not blinded, and the sample size was small. However, we revealed the significant difference in periprocedural myocardial injury between the two groups. Further study was needed to generalize our result. Furthermore, the optimal dose of loading and time of onset before stent implantation were not identified. Use of platelet GP IIb/IIIa inhibitors was not randomized, but it had little influence on the results because only 7.2% patients received platelet GP IIb/IIIa inhibitors.

In conclusion, high dose of rosuvastatin loading therapy before PCI may reduce periprocedural myonecrosis resulting from the inhibition of inflammation. These results emphasized the need of potent anti-inflammatory therapy during the peri-PCI period.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [30].

References


