Randomized Trial of Statin Administration for Myocardial Injury — Is Intensive Lipid-Lowering More Beneficial Than Moderate Lipid-Lowering Before Percutaneous Coronary Intervention? —

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Background  Minor myocardial damage after percutaneous coronary intervention (PCI) is associated with cardiac risks, which statins seem to reduce. The aim of this study was to examine whether intensive lipid-lowering therapy is more effective in decreasing the risk of cardiac injury after PCI than moderate lipid-lowering therapy.

Methods and Results  Subjects comprised 42 patients with stable angina without previous statin treatment, randomly assigned to either an intensive lipid-lowering group (Group A: target low-density lipoprotein-cholesterol (LDL-C) <70 mg/dl) or a moderate lipid-lowering group (Group B: target LDL-C <100 mg/dl) 2 weeks before PCI. All patients took statins to reach target LDL-C levels. Incidence of periprocedural myocardial injury was assessed by analyzing levels of creatine kinase myocardial isozyme (CK-MB) and cardiac troponin T (TnT) before and 6, 12 and 24 h after PCI. Minor myocardial damage was defined as TnT elevation to >0.01 ng/ml. Frequency of minor myocardial damage was 14.2% in Group A and 47.6% in Group B (p=0.043). CK-MB was above the upper limit of normal (ULN) in 19% of Group A and 33.3% of Group B (p=0.44), and CK-MB was >3×ULN in 9.5% of Group A and 19% of Group B (p=0.66).

Conclusions  Intensive lipid-lowering therapy before PCI reduces minor myocardial damage during PCI with stenting compared with moderate lipid-lowering therapy.  (Circ J 2007; 71: 1225 – 1228)

Key Words: Angioplasty; Cholesterol; Stents

Elevation of cardiac biomarkers has been shown to occur in 5–40% of cases after otherwise successful percutaneous coronary intervention (PCI)1–3 Even mild myocardial damage with elevation of cardiac troponin T (TnT) or creatine kinase myocardial isozyme (CK-MB) is associated with increased risk of subsequent cardiac events3–7 and several strategies have been proposed to address this issue.8–11 Hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors (statins) reportedly reduce myocardial injury during PCI and subsequent cardiovascular events.12–17 With the current wide use of drug-eluting stents to provide full coverage of coronary lesions, longer stents are necessary to prevent restenosis and thus more myocardial injury may occur during PCI with stenting. We performed a randomized controlled study of patients with stable angina to compare periprocedural myocardial damage with intensive or moderate lipid-lowering intervention before PCI with stenting.

Methods

Patient Population  Between January 2004 and June 2005, a total of 42 patients scheduled for elective PCI of a de novo lesion and with no history of statin use were randomly assigned to receive either intensive lipid-lowering therapy (Group A: n=21) or moderate lipid-lowering therapy (Group B: n=21). Patients with stable angina were selected and coronary angiography was performed before the statin therapy. Patients who had a myocardial infarction (MI), or previous PCI, bypass surgery, multivessel disease or renal dysfunction were excluded. All study protocols were approved by the Ethics Committee of Shizuoka Municipal Shimizu Hospital, and all patients gave written informed consent.

Lipid-Lowering Protocols  Group A patients were treated with atorvastatin (5–20 mg) to reach a target low-density lipoprotein-cholesterol (LDL-C) level of <70 mg/dl. Group B patients were treated using the same agent to reach LDL-C <100 mg/dl. Statin therapy was performed for ≥2 weeks before PCI to reach the target LDL-C levels.

Coronary Intervention  Sirolimus-eluting Cypher stents (Johnson & Johnson...
Cordis, Miami Lakes, FL, USA) were implanted in all patients according to standard techniques. All patients received aspirin 100 mg/day and ticlopidine 200 mg/day for ≥3 days before stenting. All patients received a 70 IU/kg intravenous bolus of unfractionated heparin just before PCI. Additional heparin boluses were given to maintain activating clotting time (ACT) >300 s. Angiographic measurements were performed using an automated ACOM PC v3.1 computer-based system (Siemens Medical Systems, Tokyo, Japan). All TnT and CK-MB levels before PCI were 0 ng/ml and baseline CK-MB was measured by electrochemiluminescent immunoassay (ECLIA) (Roche, Tokyo, Japan). All TnT values of p<0.05.

Cardiac Enzyme Measurements

CK-MB and TnT levels were assessed serially before and 6, 12 and 24 h after PCI using an electrochemiluminescent immunoassay (ECLIA) (Roche, Tokyo, Japan). All TnT levels before PCI were 0 ng/ml and baseline CK-MB was within normal limit at ≤7.5 ng/ml.

Definitions

Late loss was considered as the difference between minimum lumen diameter (MLD) after PCI and MLD at 6 months. Restenosis was defined as ≥50% stenosis (by diameter) at follow-up. Frequency of major adverse cardiac events (MACEs) was determined as the cumulative frequency of death, MI, emergency coronary artery bypass graft surgery and ischemia-driven target lesion revascularization (TLR).

Study Endpoints

The primary endpoint of this study was the rate of small myocardial injury during PCI with stenting, defined as a postprocedural increase in TnT to >0.1 ng/ml. The secondary endpoint was CK-MB above the upper limit of normal (ULN) or >3×ULN, and occurrence of all MACE (death, MI or need for unplanned revascularization), restenosis, TLR from time of PCI until follow-up after 6 months.

Statistical Analysis

We enrolled 42 patients and divided them into 2 groups (Group A: n=21, Group B: n=21). Continuous variables are presented as a mean value ± standard deviation, with subgroup differences assessed using Student’s t-test. Categorical variables are presented as counts and/or percentages, with differences between subgroups assessed using Fisher’s exact test. Statistical significance was assumed for 2-sided values of p<0.05.

Results

Baseline Characteristics

Demographic data are summarized in Table 1. No significant differences in background data were identified between the groups. Total cholesterol was reduced by 32% in Group A and 20% in Group B (p<0.05). LDL-C was reduced by 43% in Group A and 20% in Group B (p<0.05). Duration of statin treatment did not differ significantly between groups, and no adverse effects of statin therapy were observed. All patients took aspirin and ticlopidine for 6 months.

Angiographic Outcome and IVUS Analysis

QCA and IVUS data are presented in Table 2. No significant differences in lesion location or lesion type were noted between groups. IVUS analysis detected no lipid-rich images, dissections or intramural hematomas during PCI.

Table 1 Baseline Characteristics of Patients Undergoing PCI

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=21)</th>
<th>Group B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±10</td>
<td>67±10</td>
</tr>
<tr>
<td>Male</td>
<td>16 (76%)</td>
<td>15 (71%)</td>
</tr>
<tr>
<td>Hemoglobin A₅ (%)</td>
<td>5.7±0.39</td>
<td>5.4±0.55</td>
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<tr>
<td>Systemic hypertension</td>
<td>11 (52%)</td>
<td>12 (57%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>14 (67%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>Family history of MI</td>
<td>6 (28%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Pre-statin TC (mg/dl)</td>
<td>229±29</td>
<td>222±28</td>
</tr>
<tr>
<td>Pre-statin LDL-C (mg/dl)</td>
<td>129±11</td>
<td>125±13</td>
</tr>
<tr>
<td>Pre-statin TG (mg/dl)</td>
<td>124±21</td>
<td>120±28</td>
</tr>
<tr>
<td>Pre-statin HDL-C (mg/dl)</td>
<td>52±14</td>
<td>51±16</td>
</tr>
<tr>
<td>Pre-PCI TC (mg/dl)</td>
<td>158±14</td>
<td>179±19*</td>
</tr>
<tr>
<td>Pre-PCI LDL-C (mg/dl)</td>
<td>73±5</td>
<td>101±*</td>
</tr>
<tr>
<td>Pre-PCI HLD-C (mg/dl)</td>
<td>51±11</td>
<td>53±14</td>
</tr>
<tr>
<td>Pre-PCI TG (mg/dl)</td>
<td>108±23</td>
<td>119±34</td>
</tr>
<tr>
<td>△-blocker</td>
<td>16 (76%)</td>
<td>17 (80%)</td>
</tr>
<tr>
<td>ACE inhibitor or ATII antagonist</td>
<td>20 (95%)</td>
<td>20 (95%)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>2 (10%)</td>
<td>2 (10%)</td>
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</tbody>
</table>

Values are mean±SD or number (percentages). *p<0.05.

PCI, percutaneous coronary intervention; MI, myocardial infarction; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; ACE, angiotensin-converting enzyme; ATII, angiotensin II.

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Angiographic success was reached in 100% of patients in each group, and side branch occlusion, thrombus, or slow-flow after PCI did not occur in either group. Results of PCI, stent length and maximum balloon pressure were also similar between groups. There were also no statistical differences in balloon inflation time and balloon-to-artery ratio (data not shown). Anticoagulant therapy was continued as described previously without side-effect and the ACT level were maintained >300 ms during procedure.

Periprocedural Increases in Cardiac Markers
CK-MB and TnT changes during PCI are presented in Table 3. CK-MB elevation to >ULN occurred in 4 patients in Group A (19%) and 7 patients in Group B (33.3%; p=0.484). CK-MB elevation to >3×ULN occurred in 2 patients in Group A (9.5%) and 4 patients in Group B (19%; p=0.66). TnT >0.01 ng/ml was identified in 3 patients in Group A (14.2%) and 10 patients in Group B (47.6%; p=0.043). There was no statistical correlation between LDL-C level (14.2%) and 10 patients in Group B (47.6%; p=0.043).

Table 3. CK-MB elevation to >ULN occurred in 4 patients in Group A (19%) and 7 patients in Group B (33.3%; p=0.484).

Table 4. Follow-up 6 Months After PCI

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In conclusion, the present study shows that intensive lipid-lowering therapy decreases the risk of cardiac damage during elective PCI, but the presen results are the first from a prospective, randomized trial to indicate that compared with moderate lipid-lowering therapy intensive lipid-lowering therapy decreases the frequency of myocardial injury during PCI. TnT has better sensitivity and specificity for detecting minor myocardial damage than changes in CK-MB, so in the present study TnT >0.01 ng/ml was defined as minor myocardial damage. CK-MB elevation >3×ULN was also used as the generally accepted cut-off to signify periprocedural MI. Furthermore, CK-MB elevation above ULN was used to indicate minor myocardial damage. Elucidating the mechanisms of the effects of statin therapy is difficult. According to previous reports, statins exert antiinflammatory effects, anti-thrombogenic effects and beneficial effects on endothelial function beyond merely decreasing cholesterol levels.

The pleiotropic effects of statins are supported by numerous in vitro and in vivo studies, and such effects are obviously beneficial in limiting myocardial damage during PCI15–20. In our study, given that both groups received statin pharmacotherapy, we could not find a difference between the dose of statin and cardiac damage. Only intensive lipid-lowering was statically correlated with reducing myocardial damage during PCI, which may indicate that lipid lowering is more important than the pleiotropic effect of the clinical dose of statin.

As for the 6-month follow-up after PCI, no clinical or angiographic differences were apparent between groups. Sirolimus-eluting stent deployment decreased the risk of coronary events. However, evaluating the effects of statins in this small study was difficult and further studies are required to precisely elucidate the mechanisms of statins in the short- and long-term beneficial effects.

In conclusion, the present study shows that intensive lipid-lowering therapy rather than moderate lipid-lowering therapy before PCI may reduce periprocedural myocardial damage.

References
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