Clinical Research

Safety and efficacy of dalteparin in percutaneous coronary intervention in Chinese patients with non-ST-elevation acute coronary artery syndromes: comparison with unfractionated heparin

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Objective To prospectively evaluate the safety and therapeutic efficacy of dalteparin in patients with high risk non-ST-elevation acute coronary syndromes (ACS) during percutaneous coronary intervention (PCI). Methods A total of 175 patients with high risk non-ST-elevation ACS were randomly assigned to 2 groups [dalteparin group and unfractionated heparin (UFH) group]. The patients in dalteparin group were given dalteparin at a dose of 5,000U subcutaneously soon after diagnosis and then an additional 60U/kg intravenous bolus of dalteparin before emergent PCI. Vascular access sheaths were removed immediately after PCI or coronary artery angiography; the patients in UFH group were given UFH intravenously at a dose of 25mg just before PCI and an additional 65mg bolus was administered if angiographic findings showed that the patients were suitable for percutaneous transluminal coronary angioplasty (PTCA). Sheaths were removed at 4-6 hours after PCI; Results Eighty-three patients in dalteparin group underwent PCI while 82 patients in UFH group underwent PCI; anti-Xa activities of 52 patients in dalteparin group were measured. The average anti-Xa activity was (0.83 ± 0.26) U/ml at 15 minutes after intravenous injection of dalteparin and anti-Xa>0.5U/ml was obtained in 96.1% of the patients; hematomas at puncture sites were significantly fewer in dalteparin group as compared with UFH group (2.3% vs 9.2% , P < 0.05); none of the patients in 2 groups suffered major bleeding events. No death, acute arterial reocclusion or emergent revascularization events occurred at 30 days after PCI. Conclusions Our study demonstrated that early subcutaneous injection of dalteparin at a dose 5,000U after diagnosis and an additional 60U/kg intravenous bolus of dalteparin before PCI is safe and efficacious for patients with high risk non-ST-elevation ACS undergoing emergent PCI (J Geriatr Cardiol 2009; 6:98-98)

Key words Coronary artery disease; dalteparin; angioplasty, percutaneous transluminal coronary

Recent studies1-3 have demonstrated that low-molecular-weight heparins (LMWH) are at least as good as, if not better than unfractionated heparin (UFH) in reducing the incidence of cardiac events in patients with acute coronary syndromes (ACS). Based on the available evidence, the 2005 American College of Cardiology/American Heart Association (ACC/AHA) guidelines prefer the use of LMWH over UFH in percutaneous coronary intervention (PCI) therapy of unstable angina/non-ST-elevation Myocardial infarction(MI). However, there have been no studies in China on the safety and therapeutic efficacy of LMWH in patients with high risk non-ST-elevation ACS during PCI.

Patients and methods

Patients

Enrollment criteria: according to Thrombolysis in Myocardial Infarction (TIMI) risk stratification system, non-ST-elevation ACS patients with risk score of 5-7 (high risk stratification) were enrolled into this study. Diagnosis criteria: chest pain with concommitant electrocardiographic changes such as ST-segment depression or T-wave inversions, an increase in myocardial damage marker [troponin I (Tnl) or creatine kinase(CK-MB)], a positive result of previous exercise tolerance test, or definite coronary heart disease history with a non-ST-elevation ACS initial diagnosis. Exclusion criteria: age >80 years, plasma creatinine > 176. 8 μ mol/L; contraindication for antiocoagulation therapy such as active peptic ulcer, organ active hemorrhage, infective endocarditis, hypertension not controlled, a cerebrovascular accident within 3 months and other diseases with high risk of hemorrhage; allergic to heparin. A total of 175 patients with high risk non-ST-elevation ACS were randomly assigned to dalteparin group and UFH group.

PCI procedure

After performance of coronary artery angiography
through femoral artery according to standard Judkins method, balloon pre-dilation and stent implantation in coronary artery were carried out to cope with culprit arteries. Endocardium temporary cardiac pacemakers were implanted through veins in advance in patients with concomitant III atrioventricular block or severe bradycardia, while intra-aortic balloon pump was performed in patients with unstable hemodynamics that defined medications. Thrombus-aspirating catheter was used to aspirate thrombus in patients with heavy thrombotic burden and no blood flow after PTCA. Stent implantation was performed after improvement in blood flow was achieved. Successful PCI was defined as a residual diameter narrowing of <30% with TIMI flow II - III without complications such as acute arterial reocclusion, emergent bypass surgery or cardiac death.

**Adjunctive medications**

All the patients were administered chewable aspirin (300mg) and oral clopidogrel (300mg) before PCI. Statins drugs, β-receptor blockers, angiotensin converting enzyme inhibitors (ACEI) and nitrate esters drugs were administered. The patients in dalteparin group were given dalteparin at a dose of 5,000U subcutaneously soon after diagnosis and were given an additional 60U/kg intravenous bolus of dalteparin before emergent PCI. Vascular access sheaths were removed immediately after PCI or coronary artery angiography. No additional UFH was administered during PCI. The patients in UFH group were given UFH intravenously at a dose of 25mg just before PCI and an additional 65mg bolus was administered if angiographic findings showed that the patients were suitable for percutaneous transluminal coronary angioplasty (PTCA). Sheaths were removed at 4-6 hours after PCI. All the patients were given dalteparin at a dose of 5,000U subcutaneously twice daily for 8 days. Enteric coated aspirin at a dose of 100mg/d was administered continuously if there was no contraindication and clopidogrel (75mg) was given daily (the course of treatment was 12 months including drug eluting stent implantation after a successful PCI).

**Plasma anti-Xa activity measurement**

Blood samples of 52 patients in dalteparin group were obtained 15 minutes after intravenous injection of dalteparin. Serum anti-Xa activity was determined by using chromogenic substrate method on SysmexCAI 1500 automatic coagulation analyzer (Dade Behring Company).

**Follow-up**

A follow-up of 30 days was made by telephone interview with the patients and by a review of medical records in out-patient department to confirm adverse events.

**Statistical analysis**

Continuous variables are expressed as the mean value ± standard deviation (±s±); statistical analyses were performed using SPSS for Windows 10.0. Group comparisons were assessed using the unpaired sample t test and categorical variables were compared using chi-square test. P value less than 0.05 was considered to be statistically significant.

**Results**

**Basic characteristics of patients**

The basic characteristics of patients were shown in Table 1. There were no statistically significant differences between the 2 groups regarding age, sex distribution, cardiac function and co-morbidities.

**Coronary angiography and PCI results**

Eighty-three patients in dalteparin group underwent PCI; one patient with left main coronary artery lesion and 4 patients with triple vessel lesion underwent coronary artery bypass surgery (5.7 %). Eighty-two patients in UFH group underwent PCI; 2 patients with left main coronary artery lesion and 3 patients with triple vessel lesion underwent coronary artery bypass surgery (5.7 %). Time interval between admittance and emergent PCI in the 2 groups: (2.9 ± 1.2) h vs (3.0 ± 1.1) h ( t = 0.572 , P > 0.05). Table 2 showed coronary artery angiographic findings in the 2 groups.

**Plasma anti-Xa activity**

The average anti-Xa activity in dalteparin group was (0.83 ± 0.26) U/ml and anti-Xa>0.5U/ml was obtained in 96.1% of the patients (the predefined target range is ≥ 0.5U/ml).

**Clinical outcomes**

During PCI therapy, heavy thrombotic burden and no blood flow phenomena occurred after PTCA in 2 patients in dalteparin group and one patient in UFH group. We used thrombus-aspirating catheter to aspirate thrombus and successfully implanted stent after improvement in blood flow was achieved. In dalteparin group, sheaths were removed immediately after PCI and hematomas at puncture site occurred in 2 patients (2.3%); in UFH group, sheaths were removed at 4-6 hours after PCI and hematomas at puncture site occurred in 8 patients (9.2%). Hematomas at puncture sites were significantly fewer in dalteparin group as compared with UFH group (x² = 3.891 , P = 0.049); none of the patients in 2 groups suffered major bleeding events and neither intraductal thrombus nor acute or sub-acute thrombosis occurred during and after PCI as well as hospitalization. There was no acute arterial reocclusion, emergent percutaneous revascularization or cardiac death during follow-up period. There was no major bleeding event either.
Table 1  Basic characteristics of patients

<table>
<thead>
<tr>
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<th>Dalteparin group (n=88)</th>
<th>Unfractionated heparin group (n=87)</th>
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<tbody>
<tr>
<td>Age</td>
<td>67.9 ± 8.1</td>
<td>(68.7 ± 8.6)</td>
</tr>
<tr>
<td>Double vessel lesion</td>
<td>50/38</td>
<td>48/39</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>51 (58.0 %)</td>
<td>53 (60.9 %)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68 (77.3 %)</td>
<td>66 (75.9 %)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>19 (21.6 %)</td>
<td>18 (20.7 %)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>46(52.3 %)</td>
<td>45 (51.7 %)</td>
</tr>
<tr>
<td>Non-Q-wave myocardial infarction</td>
<td>64 (72.7 %)</td>
<td>61 (70.1 %)</td>
</tr>
<tr>
<td>Cardiac function Killip ≥ 2</td>
<td>21 (23.9 %)</td>
<td>61 (70.1 %)</td>
</tr>
<tr>
<td>Increase in myocardial enzyme</td>
<td>64 (72.7 %)</td>
<td>61 (70.1 %)</td>
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Table 2  Results of coronary angiography in the 2 groups (n, %)

<table>
<thead>
<tr>
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<th>Dalteparin group (n=88)</th>
<th>Unfractionated heparin group (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single vessel lesion</td>
<td>18 (20.5)</td>
<td>19 (21.8)</td>
</tr>
<tr>
<td>Double vessel lesion</td>
<td>32 (36.4)</td>
<td>30 (34.5)</td>
</tr>
<tr>
<td>Triple vessel lesion</td>
<td>33 (37.5)</td>
<td>35 (40.2)</td>
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</table>

Discussion

Large-scale clinical trials have demonstrated that invasive intervention at early phase can significantly reduce the incidence of death, myocardial infarction or refractory heart failure. The ESSENCE5-10 and TIMI21B2,11-14 studies, by administering LMWH before catheterization and during PCI, have demonstrated the superiority of LMWH over UFH for the treatment of unstable angina/non-Q-wave MI (UA/NQMI). Hong et al.7-8 demonstrated that there is no difference in the incidence of acute MI, target vessel revascularization and death rate between dalteparin group and UFH group during hospitalization. However, a 6-month follow-up after PCI showed that dalteparin was superior to UFH in reducing restenosis and target vessel revascularization without increasing bleeding complications. As to patients with high risk non-ST-elevation ACS undergoing emergent PCI, whether LMWH can substitute for heparin sodium and an appropriate therapeutic modality of LMWH still remain uncertain at present. Although some foreign experts8 recommended that LMWH should substitute for UFH in PCI therapy for patients with coronary artery diseases, one suggestion limited the application of LMWH in PCI: LMWH should be administered for more than 2 days before PCI and sheaths can not be removed immediately after PCI. Therefore, during emergent PCI therapy for patients with high risk non-ST-elevation ACS, besides a subcutaneous injection of LMWH, an additional intravenous bolus of UFH was given before cardiac catheterization to strengthen anticoagulation. However, this procedure not only lacked the support of evidence-based medicine, but also could increase the risk of bleeding. This study showed that if patients with high risk non-ST-elevation ACS were given dalteparin at a dose of 5,000U subcutaneously soon after diagnosis and were given an additional 60U/kg intravenous bolus of dalteparin before emergent PCI, acute or sub-acute thrombosis during and after PCI could be prevented, and the incidence of bleeding events was found to be significantly fewer than UFH. Moreover, sheaths can be removed immediately after PCI, which is of great clinical significance to the reduction of bed rest time.

In addition, we measured anti-Xa activity of some patients in dalteparin group to reflect anticoagulation intensity and anti-Xa>0.5U/ml was obtained in 96.1% of the patients after intravenous injection of dalteparin during PCI. This level satisfied the demand on the anticoagulation effect and demonstrated the feasibility of not monitoring coagulation during PCI.

In summary, this study investigated the best anticoagulation strategies in emergent PCI therapy for patients with high risk non-ST-elevation ACS, but because the number of cases enrolled was limited, larger series of patients are needed to carry out further studies.
References


