Safety of Tirofiban Therapy in Korean Patients With Acute Coronary Syndrome

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Background Although it has been reported that the glycoprotein IIb/IIIa inhibitor, tirofiban, is beneficial in patients with acute coronary syndrome (ACS) who undergo percutaneous coronary intervention (PCI), there is little data concerning the risks and complications of tirofiban therapy in Korean patients.

Methods and Results The present study reviewed 261 patients who underwent tirofiban administration for ACS between May 2002 and August 2003. The rates of bleeding, transfusion, and thrombocytopenia were analyzed and the rates of complications by age, gender, and PCI vs medical treatment were compared. The rate of minor bleeding was 8.1% (21 patients), major bleeding was 2.3% (6 patients), transfusion was 4.6% (12 patients), and thrombocytopenia was 1.2% (3 patients). Minor bleeding showed a similar rate in both sexes (8% in males vs 8.1% in females) but was higher with older age (12.5% ≥65 vs 2.6% <65 years old, p=0.093). Major bleeding occurred more in older females (5.4% vs 0%, 4.2% vs 0%, p=0.25, 0.093, respectively). The rates of thrombocytopenia and transfusion were higher in old age (2.1% vs 0% by gender, 8.3% vs 0% by age, p=0.052, 0.087 respectively). The rates of complications were similar for groups compared with PCI or medical treatment, and vascular access route.

Conclusions The results suggest that tirofiban is a safe and tolerable therapy for Korean patients with ACS. (Circ J 2005; 69: 650–653)

Key Words: Acute coronary syndrome; Koreans; Safety; Tirofiban

It is estimated that approximately 1 million patients are hospitalized because of unstable angina or non-ST elevation myocardial infarction (NSTEMI) each year in the United States alone and approximately 2–2.5 million people worldwide.1,2 It is known that antithrombotic therapy using aspirin and heparin remarkably improves the prognosis of patients with acute coronary syndrome (ACS)3–10 but these agents are not completely effective, and several studies have shown that events associated with thrombotic closure during percutaneous transluminal coronary angioplasty occur in 4–12.8% of patients.11–13 However, the occurrence of such problems has decreased with the use of strong antiplatelet agents14 and recent studies showed that the additional use of tirofiban and epifibatide, platelet glycoprotein IIb/IIIa receptor inhibitors (GPI), decreased the occurrence of death, myocardial infarction or angina much more, which was a turning point in the treatment of patients with ACS15–18.

The recent ACC/AHA (The American College of Cardiology/American Heart Association) guideline19 recommends that when percutaneous coronary intervention (PCI) is planned in patients with unstable angina or NSTEMI, GPI be administered together with aspirin and heparin, just prior to the procedure (Class I, A), and that tirofiban or epifibatide may be administered in addition to aspirin and low-molecular-weight heparin or heparin to patients with continuing ischemia, an elevated troponin, or with other high-risk features in whom an invasive management strategy is not planned (Class IIa, A).

Tirofiban is a strong and specific non-peptide antagonist for the platelet GP IIb/IIIa receptor, a major platelet surface receptor involved in platelet aggregation. It inhibits platelet aggregation by inhibiting the cross-linking of platelets by interfering with the binding of fibrogen to the GP IIb/IIIa receptor. Platelet aggregation is inhibited by approximately 90% at 30min after administration and continues during the treatment.

Tirofiban is generally used in Korea for high-risk patients with ACS, but there is a paucity of data concerning the risks and complications of tirofiban therapy in oriental patients. Therefore, the aim of our study was to evaluate Korean patients with ACS who were treated with tirofiban.

Methods

This study retrospectively analyzed 261 patients (males: 150, females: 111) treated with tirofiban (Aggrastat®, Merck & Co, Inc, Whitehouse Station, NJ, USA) in hospital because of ACS (unstable angina and NSTEMI) between May 2002 and August 2003.

The diagnosis of unstable angina or NSTEMI was based on the presence of increased chest pain, continued or recurrent chest pain even at rest or at low intensity exercise, myocardial ischemia on ECG, elevated myocardial enzyme or evidence of prior coronary artery disease. Patients with persistent ST elevation, a history of gastrointestinal bleeding, platelet disorder or thrombocytopenia, any history of hemorrhagic or non-hemorrhagic cerebrovascular disease or...
 transient ischemic attack within 1 year, severe heart failure or cardiogenic shock were excluded. All the patients were given aspirin 300 mg, then 100 mg/day (unless contraindicated) and an intravenous bolus of heparin (5,000 units) followed by an initial maintenance infusion of 1,000 units/h, titrated to an activated partial thromboplastin time of approximately 60–85 s. After the patient gave informed consent they were also treated with tirofiban. Patients who refused PCI for financial reasons, wanted conservative treatment, or were not suitable for PCI comprised the medical treatment group.

Tirofiban was administered at 0.4 μg·kg⁻¹·min⁻¹ over 30 min followed by a maintenance infusion of 0.11 μg·kg⁻¹·min⁻¹; patients with severe renal disease (creatinine clearance <30 ml/min) received the drug at half of the usual infusion rate. It was administered usually for 48–72 h, and if the patient underwent PCI for at least 12–24 h after the intervention. All the patients were given ß-blocker, nitrates, calcium-channel blocker and lipid-lowering drugs according to the ACC/AHA guideline. The safety of medications used in this study was assessed by the incidence of major and minor bleeding, thrombocytopenia, and the need for transfusion.

Minor bleeding was defined as observed blood loss between 3 and 5 g/dl or if the patients had gross hematuria, hemoptysis and hematemesis. Major bleeding was defined as >5 g/dl decrease in hemoglobin observed or unobserved, intracranial hemorrhage, or pericardial hemorrhage with tamponade by Thrombolysis in Myocardial Infarction (TIMI) II criteria. Thrombocytopenia was defined as normal platelet level before tirofiban treatment followed by decrease to less than 100,000/mm³ and we investigated all blood transfusion cases related to bleeding.

Our investigation included past medical history and family history, smoking, serum concentrations of lipids, lipoprotein(a), peak troponin I, peak creatinine kinase-MB, C-reactive protein (CRP), creatinine and brain natriuretic peptide during hospitalization, hemoglobin A1c in cases of diabetes, and the hospitalization period. To evaluate the efficacy of tirofiban therapy, the incidence of death, re-infarction, re-hospitalization and neovascularization within 30 days after treatment in the medical treatment and PCI groups.

All data are presented as mean ± SD or whether there are applicable diseases or not. Statistical analysis was performed using SPSS-PC 10.0 (SPSS Inc, Chicago, IL, USA) for MS Windows. Frequency comparisons and average comparisons were made with the chi-square test, analysis of variance and unpaired t-test and the correlation between each variable was investigated using Pearson’s correlation test at a significance level of p<0.05.

Results

The subjects of this study totaled 261 (male, dominant) with a mean age of 65 years (144 patients (55%) >65 years old). Risk factors, clinical diagnosis and serum test values are shown in Table 1. Coronary angiography was performed in 195 (75%) patients and their characteristics are shown in Table 2. Bleeding complication was observed in 27 (10.3%), blood transfusion in 12 (4.6%), and thrombocytopenia in 3 (1.1%). Minor bleeding occurred in 21 (8%), among whom 5 cases (1.9%) were caused by melena or gastric ulcer bleeding in 4 (1.5%) and hematuria in 3 (2.3%). Major bleeding occurred in 6 (2.3%), among whom 5 cases (1.9%) were caused by melena or gastric ulcer bleeding and the remaining 1 (0.4%) had subarachnoid hemorrhage and subdural hematoma. No deaths due to

### Table 1 Baseline Clinical Characteristics of the Subjects (n=261) With Acute Coronary Syndrome

<table>
<thead>
<tr>
<th>Risk factors (%)</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Smoking</th>
<th>Dyslipidemia</th>
<th>Family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>150 (57.5)</td>
<td>78 (29.9)</td>
<td>144 (55.2)</td>
<td>192 (74)</td>
<td>18 (6.9)</td>
</tr>
<tr>
<td>265 (%)</td>
<td>144 (55.2)</td>
<td>78 (29.9)</td>
<td>144 (55.2)</td>
<td>192 (74)</td>
<td>18 (6.9)</td>
</tr>
</tbody>
</table>

**Clinical diagnosis (%)**

- Unstable angina: 68 (24.1)
- NSTEMI: 198 (75.9)

**Laboratory findings (mean ± SD)**

- Total cholesterol (mg/dl): 190.9 ± 42.9
- HDL-cholesterol (mg/dl): 46.2 ± 12.5
- LDL-cholesterol (mg/dl): 119.0 ± 37.9
- Triglyceride (mg/dl): 111.3 ± 67.4
- Lipoprotein(a) (mg/dl): 3.1 ± 29.1
- BNP (pg/ml): 470.0 ± 530.1
- CRP (mg/dl): 3.1 ± 3.9
- Peak CK-MB (ng/ml): 588.8 ± 95.0
- Peak TnI (mg/ml): 15.4 ± 24.0
- Creatinine (mg/dl): 1.3 ± 0.5
- HbA1c (%): 7.6 ± 8.0
- In-hospital days (mean ± SD): 13.6 ± 8.0

### Table 2 Characteristics of the Subjects Undergoing Coronary Angiography and Revascularization Therapy (n=195)

<table>
<thead>
<tr>
<th>Coronary angiography result (%)</th>
<th>Normal</th>
<th>1-vessel disease</th>
<th>2-vessel disease</th>
<th>3-vessel disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>114 (58)</td>
<td>66 (33.8)</td>
<td>42 (21.5)</td>
<td>72 (36.9)</td>
</tr>
</tbody>
</table>

### Table 3 Incidence of Complication in Subjects (n=261) Given Tirofiban

<table>
<thead>
<tr>
<th>Bleeding (%)</th>
<th>Minor (TIMI criteria)</th>
<th>Hemoglobin drop &gt;3 g/dl, &lt;5 g/dl</th>
<th>Gross hematuria</th>
<th>Melena</th>
<th>Gastric ulcer bleeding</th>
<th>Major (TIMI criteria)</th>
<th>Melena, gastric ulcer bleeding</th>
<th>SAH, SDH</th>
<th>Transfusion (%)</th>
<th>Thrombocytopenia (%)</th>
<th>Death due to complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 (10.3)</td>
<td>21 (8)</td>
<td>12 (4.6)</td>
<td>2 (0.8)</td>
<td>3 (1.1)</td>
<td>4 (1.5)</td>
<td>6 (2.3)</td>
<td>5 (1.9)</td>
<td>1 (0.4)</td>
<td>12 (4.6)</td>
<td>3 (1.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

TIMI, thrombolysis in myocardial infarction; SAH, subarachnoidal hemorrhage; SDH, subdural hemorrhage.
complications occurred (Table 3).

When the frequency of complications by age was investigated, minor bleeding occurred in 3 (2.6%) of the patients under 65 years old and in 18 (12.5%) of those over 65, with no statistical significance, and the incidence of major bleeding was 0% in patients under 65 and 6 (4.2%) in patients over 65 with no statistical significance (p=0.093). The incidence of blood transfusion was 0% in the under 65 group and 12 (8.3%) in the over 65 group with no statistical significance (p=0.087). Thrombocytopenia occurred in 0% of patients under 65 and in 3 (2.1%) of patients over 65, without statistical significance (p=0.052). Hospitalization periods by age were 11.9±4.4 days in the under 65 group and 14.7±9.5 days in the over 65 group; although the period was somewhat long in the older age group there was no statistical significance (p=0.065).

In the analysis of bleeding frequency by gender, minor bleeding was observed in 12 males (8%) and 9 females (8.1%) with similar frequency and all the cases of major bleeding were in 6 females (5.4%) without statistical significance (p=0.250). Transfusion occurred in 3 males (2%) and 9 females (8.1%) with no statistical significance (p=0.204). Thrombocytopenia was detected in 3 males (2%) and no females (0%).

Among the 195 patients who underwent coronary angiography, it was performed with a transradial approach in 105 patients (54%) and a transfemoral approach in 90 patients (46%) and the frequency of minor bleeding, transfusion and thrombocytopenia did not differ between the 2 approaches. The incidence of minor bleeding, major bleeding, transfusion and thrombocytopenia also did not differ between the medical treatment group (141 patients, 54%) and the PCI group (120 patients, 46%) (Table 4). In the comparison of each variable among the no bleeding, minor bleeding and major bleeding groups, the 3.3±1.4 mg/dl of creatinine of the major bleeding group was statistically significantly higher than the 1.2±0.4 and 1.5±0.5 mg/dl, respectively, of the no bleeding and minor bleeding groups (p<0.001). Also, the hospitalization period of the major bleeding group was 37±41 days, which was statistically significantly longer than the 12.5±4.9 days and 18.6±8.9 days, respectively, of the no bleeding and minor bleeding groups (p=0.004). In the comparison of the blood transfusion and no blood transfusion groups, the age and hospitalization period of the blood transfusion group was 76.5±5.6 years old and 21.6±10.3 days, respectively, which were statistically significantly more or longer than the 64±11 years old and 13.2±7.6 days of the no blood transfusion group (p=0.026, p=0.033). Also, variables related to hospitalization period and high density lipoprotein cholesterol concentration showed negative correlations (r=0.303, p=0.004) and CRP and creatinine concentrations showed positive correlations (r=0.328, p=0.002) (r=0.485, p<0.001), respectively. Within the 30 days after tirofiban treatment, there were no cases of death or myocardial infarction, and 1 case (0.8%) of revascularization in the PCI group. However, there were 2 cases (1.4%) of death, 4 cases (2.8%) of myocardial infarction and 2 cases (3.4%) of revascularization in the medical treatment group.

### Discussion

The incidence of complications in patients treated with tirofiban for ACS in the present study was similar to that observed in other Western studies. The treatment did not increase the rate of complications including bleeding because of age, gender, whether or not intervention was performed, the vascular access route chosen, or a prolonged hospitalization.

Three intravenous GP IIb/IIIa inhibitors (abciximab, tirofiban, and eptifibatide) are currently available for high-risk patients with ACS; each of them has a different structure, receptor affinity, and pharmacodynamics. Although a recent study demonstrated limited effects of anti-GP IIb/IIIa receptor antagonists in low- to intermediate-risk patients receiving a high loading dose of clopidogrel, PCI with an intravenous GP IIb/IIIa receptor inhibitors has become the standard of care within the high-risk population of patients with ACS. The additional beneficial effect of GP IIb/IIIa inhibitors of dissolution of platelet thrombi formed on the collagen surface under blood flow conditions has been demonstrated. Recent studies have shown that the use of tirofiban or eptifibatide greatly reduced the incidence of death, acute myocardial infarction or recurrent angina compared with standard therapy, thus providing a major advance in the treatment of unstable angina and NSTEMI.

The PRISM-PLUS study concluded that GP IIb/IIIa inhibitor significantly decreased the incidence of major cardiac events without increasing complications based on the finding that major bleeding was observed in 1.4% of the tirofiban and heparin combination group and in 0.8% of the heparin and aspirin therapy group with no difference shown between the 2 groups; blood transfusion occurred in 4.0% and 2.8% of each group and severe thrombocytopenia (< 50,000/mm³) in 0.5% of the treatment group compared with 0.3% of the control group.

The PRISM study showed that tirofiban decreased the incidence of major cardiac events by 32% at 48h and the death rate by 38% at 30 days. The incidence of major bleeding was 0.4% in the tirofiban and heparin combination therapy group and 0.4% in the heparin only group. Minor bleeding occurred in 2.0% and 1.9%, respectively, and blood transfusion in 2.4% and 1.4% of each group with no difference shown. The incidence of severe thrombocytopenia (<50,000/mm³) was 0.4% in the tirofiban group, which was higher than the 0.1% of the control group.

The RESTORE study reported that major bleeding...
occurred in 2.4% of the tirofiban group and 2.1% of the control group with no significant difference shown and that blood transfusion and thrombocytopenia occurred in 3.5% and 1.1%, respectively. The PURSUIT study\(^8\) showed that minor bleeding and major bleeding were observed in 12.9% and 10.6%, respectively, of the epistabilate group compared with 7.6% and 9.1% of the control group with a statistically significant increase shown; however, the incidence of hemorrhagic stoke was not increased with the treatment.

In the present study, bleeding complications were observed in 10.3%, blood transfusion was required in 4.6%, thrombocytopenia occurred in 1.1%, minor bleeding according to TIMI II criteria in 8% and major bleeding in 2.3%. These results are similar to those of 2 of the previous trials\(^15,17\) which showed an incidence of minor bleeding of 10.5% and 12%, respectively, and 2.4% incidence of major bleeding and 4% and 3.5% incidence of blood transfusion. Therefore, we suggest there is not a genetic difference between Asians and Caucasians with regard to hemorrhagic complications of tirofiban therapy.

In our investigation of the frequency of complications by age, minor and major bleeding, blood transfusion and thrombocytopenia, all these occurred with high incidence in the over 65 years old group, but no statistical significance was shown. The frequencies of minor and major bleeding, transfusion and thrombocytopenia by gender did not different between the males and females. The concentration of creatinine in the major bleeding group was statistically significantly higher than in the no and minor bleeding groups, so tirofiban should be carefully administered to patients with decreased renal function.

The major limitation with our study is that it was non-randomized, non-controlled, and retrospective. However, the overall incidence of major hemorrhage and significant thrombocytopenia with tirofiban administration was low and not significantly different from the results of Western studies. Therefore, we consider that tirofiban can be relatively safely administered even to patients older than 65 years.

References