The Effect of Tirofiban on ST Segment Resolution in Patients With Non-ST Elevated Myocardial Infarction

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SUMMARY

ST segment resolution in ST elevated myocardial infarction has independent predictive value for congestive heart failure and death at 30 days.1,2) ST segment depression in unstable angina pectoris (UAP) and non-ST elevated myocardial infarction (NSTEMI) predicts high risk of MI and death and may discriminate patients likely to have greater benefit from aggressive antithrombotic and interventional therapy.5-6)

This study assessed the effect of tirofiban added to conventional treatment on ST segment resolution in NSTEMI patients. Sixty-four patients were randomized to one of the two groups: 32 patients received conventional treatment while tirofiban was added in the second group of 32 patients. In the first group, 6 patients refused to participate further after giving initial informed consent while 1 patient in the tirofiban group dropped out. We had 26 patients (mean age, 59 years) in the conventional treatment group and 31 patients (mean age, 59 years) received also tirofiban. Tirofiban was administered by intravenous infusion over a 72 hour period. More than 50% regression of depression was considered to be ST segment resolution.

The characteristics of the two groups were comparable (Table I). The ST segment resolution evolution did not differ at the 4th and 24th hours between the two groups. Significant differences occurred in the 72nd hour ECG (Table III). ST resolution was present in 67.9% of the tirofiban patients and in 32.1% of the conventional treatment group (P < 0.05).

Tirofiban treatment was not associated with an increase in major bleeding even though there was a trend toward an increase in minor bleeding cases and did not influence the occurrence of refractory angina pectoris. (Jpn Heart J 2004; 45: 913-920)

Key words: GP IIb/IIIa inhibitor, Tirofiban, non-ST elevated myocardial infarction, ST resolution

In patients with ST elevated myocardial infarction, ST segment resolution following fibrinolytic therapy has been reported to have an independent predictive value for congestive heart failure and death at 30 days.1,2) In unstable angina pec-
tors and non-ST elevated myocardial infarction (NSTEMI) patients, the presence of ischemic ST-T changes on the basal ECG carries important prognostic value.3,4) It has been reported that ST segment depression is related to a high risk of MI and death in these patients.5,6) Thus ST segment depression is a marker of increased risk but is also useful to discriminate patients likely to have greater benefit from aggressive antithrombotic and interventional therapy.7,8) Recent clinical trials have shown that the addition of GP IIb/IIIa inhibitors consistently reduces the incidence of death and MI in patients with unstable angina or non-ST elevated myocardial infarction (NSTEMI).9,10) This benefit is very significant when these agents are used before or during coronary angioplasty and also to a lesser, but still significant extent, when they are part of medical treatment alone. Meta-analyses involving over 30,000 patients found that treatment with glycoprotein IIb/IIIa inhibitors led to a 21% reduction in death or MI at 30 days.11,12) For glycoprotein IIb/IIIa inhibitors, the greatest benefit has been observed in patients with transient ST segment elevation, followed by ST segment depression, with an absolute benefit two to three times greater compared to patients without ST segment changes.13) ST segment depression is considered as a marker of high risk in patients with UAP and NSTEMI. The prognostic value of resolution of ST segment depression and the effects of glycoprotein IIb/IIIa inhibitors on the resolution remain to be clarified. We investigated the effect of the glycoprotein IIb/IIIa inhibitor tirofiban on depressed ST segment resolution in patients with NSTEMI.

**METHODS**

This randomised controlled trial was performed between 2000 and 2001 at Celal Bayar University Hospital, Manisa, in Western Turkey in 64 patients with NSTEMI. The inclusion criteria included ECG changes > 0.05 mv and elevated troponin T. Exclusion criteria were hepatic or advanced renal failure (creatinine > 2.5 mg/dL), ST elevation on ECG, failure to give informed consent, and age < 18 years.

Thirty-two patients were enrolled in the first group to receive conventional treatment (aspirin, heparin, beta-blocker, nitrate) and tirofiban was added to conventional treatment in the second group of 32 patients. In the conventional treatment group, 6 patients refused to further participate in the study after giving initial informed consent while 1 patient in the tirofiban group dropped out. Therefore, ultimately there were 26 patients (mean age, 59 years) in the conventional treatment group and 31 patients (mean age, 59 years) in the tirofiban group.

In the tirofiban group, tirofiban was administered by continuous intravenous infusion for 72 hours in all patients. Patients had been followed for major and minor cardiac events during their hospital stay (at least the 72 hour inspection
period, except those who died). ST segment depression was the dependent variable of this study and had been measured as millimetres on the ECG obtained at admission. The sum of the ST segment depressions of different ECG derivations was measured by the same investigator using a magnifying glass. Patients with more than 50% regression of ST segment depression were considered as having ST segment resolution according to previous definitions. \(^{14-17}\) Mann-Whitney U and chi square tests were used for the statistical analysis with SPSS 10.0 statistical software.

**RESULTS**

The two groups in the study were comparable in age, the occurrence of refractory angina pectoris, diabetes mellitus, hypertension, prior aspirin treatment, tobacco smoking, or congestive heart failure (Table I).

Compared to the baseline ECG obtained at admission, the ST segment resolution did not differ significantly on 4\(^{th}\) and 24\(^{th}\) hours between the two groups (Table II). As shown in Table III, the only significant differences occurred in the ECG obtained at 72 hours. A majority of tirofiban patients (67.9\%) had ST reso-

**Table I.** Comparison of the Therapy Groups According to Potential Confounding Variables

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban therapy group</th>
<th>Conventional therapy group</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>31 (54.38%)</td>
<td>26 (45.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>59.77 ± 11.6</td>
<td>59.11 ± 6.3</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>21/10 (51.2%/62.5%)</td>
<td>20/6 (48.8%/37.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (71%)</td>
<td>18 (69.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Tobacco smokers</td>
<td>18 (62.1%)</td>
<td>11 (37.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior ASA therapy</td>
<td>11 (57.9%)</td>
<td>8 (42.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4 (12.9%)</td>
<td>3 (11.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (35.5%)</td>
<td>11 (42.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Refractory angina</td>
<td>8 (25.8%)</td>
<td>7 (26.9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NA = not significant.

**Table II.** Fourth, -24\(^{th}\) and 72\(^{nd}\) Hours ST Segment Resolution Differences of the Two Alternative Therapy Groups (in Milli meters), Compared to Admission ECG

<table>
<thead>
<tr>
<th>ST Resolution difference (mm)</th>
<th>Tirofiban ((n = 31))</th>
<th>Conventional ((n = 26))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4(^{th}) hour ST resolution</td>
<td>0.50 ± 0.63 mm</td>
<td>0.35 ± 0.48 mm</td>
<td>0.442</td>
</tr>
<tr>
<td>24(^{th}) hour ST resolution</td>
<td>0.65 ± 0.69 mm</td>
<td>0.45 ± 0.65 mm</td>
<td>0.171</td>
</tr>
<tr>
<td>72(^{nd}) hour ST resolution</td>
<td>0.84 ± 0.80 mm</td>
<td>0.45 ± 0.66 mm</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Mann-Whitney U test.
Table III. 72nd Hours ST Segment Resolution Differences of the Two Alternative Therapy Groups According to 50% Resolution Cut-off Criterion, Compared to Admission ECG

<table>
<thead>
<tr>
<th>Therapy group</th>
<th>No STR* (&lt;50%)</th>
<th>Positive STR (≥50%)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tirofiban</td>
<td>12 (41.4%)</td>
<td>19 (67.9%)</td>
<td>31 (54.4%)</td>
</tr>
<tr>
<td>Conventional</td>
<td>17 (58.6%)</td>
<td>9 (32.1%)</td>
<td>26 (45.6%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>29 (100%)</td>
<td>28 (100%)</td>
<td>57 (100%)</td>
</tr>
</tbody>
</table>

χ² = 4.03  DF:1  P = 0.045

resolution in their 72 hour ECG, while the conventional treatment group had 32.1% (P < 0.05).

No major bleeding that could be related to tirofiban treatment was observed. The two treatment groups were similar with respect to minor bleeding occurrences, even though we observed a slightly higher tendency to minor bleeding in the tirofiban group that did not reach statistical significance.

Two patients in the control group with persistent ST depression died at 27 and 48 hours following admission. There were no deaths in the tirofiban group, although a patient with refractory angina pectoris and ST depression underwent coronary angiography and urgent surgical revascularisation due to three vessel disease.

There were no differences on the occurrence of major adverse cardiac events, death, or MI between the two groups with a follow-up of one week in the hospital stay, except two deaths in the conventional treatment group in the 12 hour period following admission. We did not observe any differences in the follow-up during a 30 day period after discharge of the patients.

DISCUSSION

In the last decade, several observations have led to a reappraisal of the clinical predictive value of ST segment monitoring after ST elevated MI. Schroder and colleagues first reported that ST segment resolution can predict accurately the risk of death and congestive heart failure in myocardial infarction patients treated with fibrinolytic agents. Several publications highlighted the prognostic value of ST segment depression in acute coronary syndromes (ACS). ST segment depression is considered as one of the most important predictors of recurrent angina pectoris, reinfarction, and death in ACS. Nyman and colleagues reported that patients with unstable angina and NSTEMI having ST segment depression on baseline admission ECG were at highest risk for cardiac death, MI, and severe angina pectoris with a follow-up of one year.
Patients with ST segment changes benefit 2-3 times more with GP IIb/IIIa inhibitors compared to patients with stable ST segments. Therefore, ST segment depression helps to discriminate patients likely to benefit most from aggressive antithrombotic and invasive therapeutic strategies. There is no study on the evolution of ST segment depression resolution even though the clinical value of ST depression is often accepted. To the best of our knowledge, there are no publications about the clinical significance of depressed ST segment resolution in unstable angina pectoris and non-ST elevated myocardial infarction patients. Our study is the first one evaluating the effect of GP IIb/IIIa inhibitors on ST segment resolution in NSTEMI patients. All of our patients had positive troponin T values and ST segment depression. Both treatment groups were found to be similar with respect to the occurrence of congestive heart failure, hypertension, age, sex, diabetes mellitus, and previous use of aspirin. When the ECGs were compared for ST segment resolution, only the 72nd hour ECGs were found to be different compared to initial ECG ($P < 0.05$).

The influences of sex, hypertension, diabetes mellitus, tobacco smoking, and previous use of aspirin on ST segment resolution have also been investigated. No significant relation could be found between ST segment resolution and these 5 factors. A possible clinical benefit of the appearance of ST segment resolution at the 72nd hour can be speculated using the findings of the PRISM-PLUS trial, which reported better outcomes compared to PRISM study where the tirofiban infusion was maintained during 72 hours in ACS compared to 48 hours in PRISM.

Patients who have invasive procedures seem to gain the most benefit from GP IIb/IIIa inhibitor treatment. Boersma, et al reported in a meta-analysis that the GP IIb/IIIa inhibitor treatment was associated with a significant reduction in mortality and recurrent MI in the early period of medical treatment before percutaneous coronary intervention (PCI) in unstable angina and NSTEMI.

Two patients in the conventional treatment group died in the first 12 hours. We cannot speculate about better outcome with tirofiban in NSTEMI due to the limited number of patients admitted in our study. We did not observe any significant difference in mortality the between two groups in a 30 day follow-up even though the 72 hour ST resolution was significantly better in the tirofiban group. This may be related to our small sample size.

We initiated the GP IIb/IIIa inhibitor treatment during the initial 72 hours after admission during a medical follow-up period of 30 days without PCI.

Our results are in general agreement with previous studies, but also reveal some differences. We found the best ST segment resolution after 72 hour perfusion of tirofiban, while others found a better clinical outcome with 72 hour tirofiban infusion.
We followed all patients included in the study for refractory angina pectoris for one week. We did not observe any difference in the occurrence of refractory angina between patients receiving tirofiban and the control group even though an improvement in ST segment resolution was evident at 72 hours. One could then expect a lower occurrence of refractory angina in patients treated with tirofiban as seen in previous clinical studies. The reason for this unexpected result in our study may be explained in the following way: Patients receiving tirofiban were often followed with invasive strategy in previous clinical studies. It should be emphasized that the major benefit observed with tirofiban was seen in patients undergoing invasive treatment with PTCA or stent implantation. The beneficial effect of additional tirofiban was attributed to the antiaggregant action of tirofiban in non-ST elevated myocardial infarction patients. This action should improve the microcirculation in patients treated with a conservative strategy and should reduce the occurrence of thrombosis following percutaneous interventions in such patients.

Our patients had not been subjected to invasive procedures and were followed with a conservative strategy. Refractory angina appeared in some of our patients when the tirofiban treatment was stopped as they were not subjected to invasive treatments. Our results support the benefit of an invasive strategy in non-ST elevated myocardial infarction patients treated with tirofiban.

One may then speculate that ST segment resolution may be a predictor of a better clinical outcome. The number of patients was too low to verify that relation. No significant difference could be observed between the two groups for refractory angina pectoris.

Patients with previous aspirin treatment or diabetes mellitus did not obtain more benefit from GP IIb/IIIa inhibitor treatment compared to the others. To the best of our knowledge, our study is the first publication reporting the effect of GP IIb/IIIa inhibitor treatment on ST segment resolution in patients with NSTEMI.

Larger scale trials are necessary to further clarify the clinical significance and possible prognostic use of ST segment depression resolution in NSTEMI patients.

**Conclusion:** After eliminating the potential effects of variables by randomisation, the significant improvement in ST segment resolution found at the 72nd hour in the tirofiban treated group can be attributed to the addition of tirofiban to conventional treatment. Tirofiban treatment was not associated with an increase in major bleeding even though there was a slight increase in minor bleeding cases. Tirofiban treatment did not influence the occurrence of refractory angina pectoris. Since the occurrence of refractory angina pectoris was comparable to the control group, this result supports the benefit of early intervention and encourages
the use of an early invasive strategy in patients with NSTEMI treated with tirofiban rather than a conservative option.

REFERENCES


