Comparison on the Effects of Clopidogrel Versus Tirofiban in Treating High-Risk Non-ST-Segment-Elevation Acute Coronary Syndromes: Risk-Adjusted Prospective Data Analysis

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ABSTRACT

AIM: To compare the outcomes of clopidogrel versus tirofiban in treating non-ST-segment elevation acute coronary syndromes among patients before percutaneous coronary intervention.

METHODS: This was a prospective data bank analysis study with 342 patients (216 in the clopidogrel group and 126 in the tirofiban group) with high risk unstable angina (Braunwald/TIMI risk stratification) and/or non-ST acute myocardial infarction included between May 2010 and November 2012 who were receiving clopidogrel or tirofiban within the first 24 hours of admission and before percutaneous coronary intervention. The following data were obtained: age, sex, diabetes, systemic arterial hypertension, smoke, dyslipidemia, previous coronary artery disease (percutaneous coronary intervention or coronary artery bypass graft), hemoglobin, creatinine, higher troponin, left ventricle ejection fraction and medication used at hospital. The primary endpoint was all cause of in hospital death and major adverse cardiac events (MACE) (death, non-fatal unstable angina or myocardial infarction/ targeted vessel revascularization, Killip III/IV, bleeding and stroke). Comparison between groups was made by Anova and Q-square. Multivariative analysis were determined by logistic regression and was considered significative when \( p<0.05 \).

RESULTS: The median age was 64 years and 60.5% were male. In the tirofiban group were observed higher troponin levels \( (p=0.02) \), higher prevalence in previous coronary artery disease \( (p=0.02) \) and differences between use of enoxaparin \( (92\% \text{ in the tirofiban group} \times 85\% \text{ in the clopidogrel group}, p=0.02) \). No significant difference was observed between the tirofiban versus clopidogrel groups in deaths \( (15.8\% \times 8.3\%, p=0.14) \) and MACE \( (29.4\% \times 20.4\%, p=0.72) \).

CONCLUSIONS: In patients with high risk non-ST acute coronary syndromes, the use of clopidogrel or tirofiban in the first 24 hours of admission were similar and the result did not show statistical significance difference between groups regarding mortality and MACE, despite higher tendency of that in tirofiban group.

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Key words: Acute coronary syndromes; Tirofiban; Clopidogrel

INTRODUCTION

The knowledge of the mechanisms of platelet-mediated thrombosis has increased dramatically over the last 40 years. This increased understanding has identified treatment strategies for acute coronary syndromes (ACS) by targeting key mediators of platelet activation and aggregation processes [1].

Several randomized trials have convincingly demonstrated the usefulness of glycoprotein IIb/IIIa receptor antagonists and clopidogrel. The most recent guidelines for the management of patients presenting with a non-ST-segment-elevation (NSTE-ACS) strongly recommend the use of glycoprotein IIb/IIIa receptor antagonists and clopidogrel for high-risk patients when percutaneous coronary intervention (PCI) is planned [2-4].

The thienopyridine clopidogrel has been the standard of care, but is limited by variable response and treatment failure. Glycoprotein IIb/IIIa targeted agents (tirofiban and abciximab) are also used in ACS patients undergoing PCI. These inhibitors utilize a different
mechanism of action by preventing fibrinogen-mediated platelet aggregation, with short initial time of action\(^2\). So, a large number of studies have been discussed which agent should be used and the most appropriate timing for that\(^3\).

There isn’t any study comparing clinical events in patients with ACS that received clopidogrel versus tirofiban. In this context, we developed a prospective study comparing clinical events related to use of clopidogrel or tirofiban within the first 24 hours of admission and before PCI in patients with high-risk NSTE-ACS.

**METHODS**

**Study population**

This was an observational prospective data bank analysis study performed in a tertiary health center with 342 patients (216 in the clopidogrel group and 126 in the tirofiban group) with high-risk unstable angina (Braunwald/TIMI risk stratification)\(^4\)\(^5\) and/or non-ST acute myocardial infarction (AMI) included between May 2010 and November 2012 who were receiving clopidogrel or tirofiban within the first 24 hours of admission and before PCI. Exclusion criteria included contraindications against clopidogrel or tirofiban, ST-ACS, active bleeding, a history of a major operation/external injury within three months, history of a stroke within six months and low/moderate-risk unstable angina.

The study was approved by the ethics and research committee and in all cases was obtained informed consent by patient or a family member.

**Study protocol and medication**

All 342 patients were treated according by AHA/ESC Task Force Myocardial Infarction Guidelines\(^6\)\(^7\). The decision regarding the administration of clopidogrel or tirofiban was made by clinical cardiologist in the admission, according by individual experience. All patients were included in a data bank and followed prospectively until discharge.

Patients in clopidogrel group received an oral loading dose of 300 mg immediately after admission. Clopidogrel were continued with daily maintenance dose of 75 mg. In the tirofiban group, patients received after admission bolus of 0.4 mg/kg/min about 30 minutes, followed by 0.1 mg/kg/min for 48 hours. All coronary angioplasty used bare-metal stent. The number of stents used were left at the discretion of the operator. The patients were submitted to PCI within 24 and 48 hours of admission.

**Analytical methods**

Blood was sampled immediately after admission prior to administration of medications (baseline) and daily according by institution protocol. Cardiac markers like troponin-T was measured using standard clinical chemistry. Laboratory upper limits of normal were 0.03 ng/mL for troponin-T measured by 4th generation immunoassay for the Elecsys 2010 automated analyzer (Roche Diagnostics GmbH, Germany).

In addition, the following data were obtained: age, sex, diabetes, systemic arterial hypertension, smoke, dyslipidemia, previous coronary artery disease (percutaneous coronary intervention or coronary artery bypass graft), hemoglobin, creatinine, higher troponin, left ventricle ejection fraction and medication used at hospital.

Definitive treatment (coronary artery bypass bypass graft surgery (CABG), coronary angioplasty or clinical treatment) and the number of stents used in each group was compared too.

Patients were followed during internation after the index event. Long term follow-up was not adquired. Major adverse cardiac events (MACE) included all causes of death, non-fatal unstable angina or AMI/targed vessel revascularization, Killip III/IV, bleeding (major and minor) and stroke. New electrocardiographic signs and/or the typical rise and fall in troponin were required to document a new unstable angina/AMI during follow-up. Major bleeding events were scored if haemoglobin dropped by \(\geq 50\) g/L or intracranial bleeding was noted. Minor bleeding complications included macrohaematuria, haematemesis, or a drop in haemoglobin ranging from 30 to 50 g/L.

**Statistical Analysis**

Descriptive analysis of data collected included median, minimum and maximum values. Comparison between groups was made by Anova and Q-square. If Komolgorov-Smirnov tests confirmed normal distribution, continuous variables were summarized using mean+standard deviation and were compared using the student t-test for independent samples. The Mann-Whitney U test was used to compare continuous variables if they were not normally distributed.

In multivariate analysis, the primary endpoint was all cause of in hospital death and MACE. Multivariate analysis were determined by logistic regression and was considered significative when \(p < 0.05\). The variables included all baseline characteristics as showed in table 1. All statistical procedures were performed using the Statistical software SPSS v10.0.

**RESULTS**

**Characteristics of treatment groups**

The median age was 64 years and 60.5% were male. In the tirofiban group were observed higher troponin levels \((p=0.02)\), higher prevalence in previous coronary artery disease \((p=0.02)\) and differences between use of enoxaparin (92% in the tirofiban group \(\times\) 85% in the clopidogrel group, \(p=0.02)\). All baseline characteristics of both groups were showed in table 1.

Significative difference was obtained in number of CABG between groups, with higher prevalence in tirofiban group (18.3%\(\times\)10.6%, \(p=0.04)\). Treatment data was showed in table 2. All MACE were described in table 3.

Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Tirofiban group</th>
<th>Clopidogrel group</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>63.58±11.72</td>
<td>64.25±12.05</td>
<td>0.68</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60.5%</td>
<td>61.1%</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>64.1%</td>
<td>64.3%</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>77.7%</td>
<td>77.00%</td>
<td>0.87</td>
</tr>
<tr>
<td>Tabasipim (%)</td>
<td>58.6%</td>
<td>60.7%</td>
<td>0.14</td>
</tr>
<tr>
<td>FH of CAD (%)</td>
<td>12.1%</td>
<td>13.1%</td>
<td>0.74</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>48.4%</td>
<td>48.4%</td>
<td>0.99</td>
</tr>
<tr>
<td>Stable Angina (%)</td>
<td>13.6%</td>
<td>17.3%</td>
<td>0.38</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>7.00%</td>
<td>4.5%</td>
<td>0.25</td>
</tr>
<tr>
<td>Previous AMI (%)</td>
<td>42.5%</td>
<td>31.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>CAGB (%)</td>
<td>20.5%</td>
<td>17.6%</td>
<td>0.43</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>28.4%</td>
<td>32.00%</td>
<td>0.4</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>138.61±28.27</td>
<td>138.32±31.30</td>
<td>0.46</td>
</tr>
<tr>
<td>FB (g/dL)</td>
<td>13.80±1.80</td>
<td>13.77±2.0</td>
<td>0.39</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>1.21±1.16</td>
<td>1.21±1.08</td>
<td>0.86</td>
</tr>
<tr>
<td>Troponin (higher) (ng/L)</td>
<td>24.41±26.21</td>
<td>20.29±22.13</td>
<td>0.002</td>
</tr>
<tr>
<td>EF (%)</td>
<td>51.73±12.41</td>
<td>51.44±11.85</td>
<td>0.56</td>
</tr>
<tr>
<td>AAS (%)</td>
<td>99.4%</td>
<td>97.9%</td>
<td>0.38</td>
</tr>
<tr>
<td>B-blocker (%)</td>
<td>83.7%</td>
<td>79%</td>
<td>0.07</td>
</tr>
<tr>
<td>Enoxaparin (%)</td>
<td>92.1%</td>
<td>84.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>74.4%</td>
<td>66.4%</td>
<td>0.12</td>
</tr>
<tr>
<td>Statin (%)</td>
<td>90.2%</td>
<td>87.3%</td>
<td>0.32</td>
</tr>
</tbody>
</table>

FH: family history; CAD: coronary artery disease; AMI: acute myocardial infarction; CABG: coronary artery bypass bypass graft surgery; PCI: percutaneous coronary intervention; SAP: systolic arterial pressure; FB: haemoglobin; Cr: creatinine; EF: ejection fraction; ACE: angiotensin-converting-enzyme.
Multivariate analysis and clinical outcomes

No significant difference was observed between the tirofiban versus clopidogrel groups in deaths (15.8% vs. 8.3%, p=0.14) and MACE (29.4% vs. 20.4%, p=0.72) as observed in table 3.

DISCUSSION

We didn’t find any similar study comparing clopidogrel versus tirofiban and evaluating clinical outcomes. Besides the molecular differences between clopidogrel and tirofiban, in our study no significant difference was observed between the tirofiban versus clopidogrel groups in deaths and MACE. However, this study was made at the major tertiary center of cardiology in Latin America and all patients considered were high-risk, so the patients are more severe than usual, justifying the great mortality and prevalence of diabetes. How PCI’s were conducted after 24 hours, we considered that was made at the major tertiary center of cardiology in Latin America and CABG and PCI, higher troponin levels and higher total action of clopidogrel at the time of catheterization. There were differences between clopidogrel and tirofiban, in our study no significant difference was observed between the tirofiban groups and the placebo.

Solinas et al.[8], randomized patients with NTSE-ACS undergoing PCI to be treated with clopidogrel 600 mg, tirofiban and tirofiban plus clopidogrel 300 mg. The authors analysed P-selectin expression and platelet aggregation. Treatment with clopidogrel 600 mg significantly reduced P-selectin expression in comparison with tirofiban alone. However tirofiban inhibited platelet aggregation significantly more than clopidogrel during the first 6 hours, and the addition of clopidogrel 300 mg did not inhibit platelet aggregation any more than tirofiban alone throughout the 24 hours. Clinical outcomes were not observed.

CONCLUSION

In patients with high-risk NSTE-ACS, the use of clopidogrel or tirofiban in the first 24 hours of admission were similar and the result did not show statistical significance difference between groups regarding mortality and MACE, despite higher tendency of that in tirofiban group.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES


**Peer reviewer:** Javier Mariani, Coordinator of Coronary Unit, Department of Cardiology, Hospital El Cruce, Florencio Varela, Buenos Aires, Argentina.