Comparison of ticagrelor with clopidogrel in Chinese ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention

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Abstract: Background: Ticagrelor has shown better efficacy and safety in comparison with clopidogrel in acute coronary syndrome patients. However, there is a paucity of evidence supporting the use of ticagrelor in Chinese ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PCI). Materials and methods: This is a prospective, randomized, parallel design, investigator initiated, pharmacodynamic study carried out at our hospital from June 2014 to May 2015. Patients were randomized in a 1:1 ratio to receive a loading dose (LD) of clopidogrel 600 mg and aspirin 300 mg (n = 94) or ticagrelor 180 mg and aspirin 300 mg (n = 94). The adenosine diphosphate (ADP) inhibition rate and the maximum amplitude were measured using the thrombelastography at various time points post LD. Results: The ADP inhibition rates at 0.5 h, 1 h, 2 h, and 4 h were significantly higher for ticagrelor in comparison with clopidogrel (P < 0.05). The maximum amplitude at 0.5 h, 1 h, 2 h, and 4 h were significantly lower for ticagrelor in comparison with clopidogrel (P < 0.05). Conclusion: Ticagrelor is more potent with faster onset in comparison with clopidogrel in Chinese STEMI patients treated with primary PCI.

Keywords: Acute myocardial infarction, percutaneous coronary intervention, ticagrelor, clopidogrel

Introduction

The advances in the treatments of ST-segment elevation myocardial infarction (STEMI) have significantly decreased the mortality of patients with acute MI [1]. Thrombosis in the coronary artery is one of the most important causes of acute MI. Platelets play a crucial role in the development of thrombosis. Atherosclerotic plaque rupture damages the vascular endothelium and platelets adhere to the matrix beneath the damaged endothelium. The platelet aggregation leads to the thrombosis and blocks the vessel. The platelet activation can be inhibited by targeting the synthesis of thromboxane A2, the adenosine diphosphate (ADP) signaling pathway, and the glycoprotein IIb/IIIa signaling pathway [2]. The most commonly used antiplatelet agents include aspirin, clopidogrel, and tirofiban. Conclusive evidences show that antiplatelet therapy can significantly decrease the mortality and risk of cardiovascular events in MI patients. For acute MI patients treated with primary PCI, dual antiplatelet therapy post procedure is an important method for the prevention of stent thrombosis and in-stent restenosis. The CURE study and the CREDO trial established the treatment basis using aspirin and clopidogrel as post-PCI medications [3, 4]. However, despite the use of dual antiplatelet therapy, cardiovascular events still occur in approximately 20% of acute MI patients, such as subacute thrombosis and sudden death [5-7].

Interindividual variability in the responsiveness to antiplatelet agents have well been documented. The low platelet reactivity to clopidogrel is of great clinical interest in the treatment of coronary diseases and has been intensively investigated. Ticagrelor is a third-generation P2Y12 inhibitor with faster onset and higher potency [8-10]. In comparison with clopidogrel, ticagrelor does not require the metabolite oxi-
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Dative activation in the liver and is associated with lower platelet reactivity. Many clinical studies have shown that ticagrelor is superior to clopidogrel with better efficacy and lower rate of clinical events. However, there is a paucity of evidences supporting the efficacy and safety of ticagrelor in Chinese STEMI patients.

The present study was designed to investigate the platelet inhibition ability of ticagrelor in comparison with clopidogrel in Chinese STEMI patients treated with primary PCI.

Materials and methods

Patients

This is a prospective, randomized, parallel design, investigator initiated, pharmacodynamic study carried out at our hospital from June 2014 to May 2015. Patients were included if they presented with STEMI within 12 h and planned to receive primary PCI. Patients with the following conditions were excluded from this study: contraindications to clopidogrel or ticagrelor; had thrombolysis within 24 h; was on glycoprotein IIb/IIIa inhibitors prior to the PCI; was already on oral anticoagulants and needed to continue the medications after the procedure; severe bradycardia or conduction block; severe liver or kidney impairment; active bleeding or coagulation disorder; age > 75 years.

Study protocol

The finally included patients were randomized in a 1:1 ratio to receive a loading dose (LD) of clopidogrel 600 mg and aspirin 300 mg (n = 94) or ticagrelor 180 mg and aspirin 300 mg (n = 94). After the primary PCI, a maintenance dose of clopidogrel 75 mg daily or ticagrelor 90 mg daily was used for each group for at least 12 months, respectively. Aspirin 100 mg daily was used indefinitely. Peripheral blood was collected from each patient at 0.5 h, 1 h, 2 h, 4 h, 6 h, 12 h, 24 h, 48 h, and 72 h after the LD. The ADP inhibition rate and the maximum amplitude were measured using the thrombelastography (Hemostasis Analyzer Model 5000, Haemoscope, IL, USA). A flow chat diagram of the study is shown in Figure 1.

The study protocol was approved by the Ethics Committee of TEDA International Cardiovascular Hospital. Informed consent was obtained from each patient before the enrollment.

Table 1. Patients’ demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel 600 mg (n = 94)</th>
<th>Ticagrelor 180 mg (n = 94)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n)</td>
<td>58</td>
<td>54</td>
<td>0.94</td>
</tr>
<tr>
<td>Age (year)</td>
<td>55±16</td>
<td>59±21</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>23</td>
<td>26</td>
<td>0.99</td>
</tr>
<tr>
<td>Smoking (n)</td>
<td>36</td>
<td>33</td>
<td>0.88</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.13±2.61</td>
<td>24.08±4.14</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51</td>
<td>56</td>
<td>0.83</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>42</td>
<td>36</td>
<td>0.54</td>
</tr>
<tr>
<td>Prior MI</td>
<td>14</td>
<td>10</td>
<td>0.66</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>18</td>
<td>22</td>
<td>0.70</td>
</tr>
</tbody>
</table>

BMI, Body mass index; MI, Myocardial infarction; PCI, Percutaneous coronary intervention.

Table 2. Adenosine diphosphate inhibition rate (%) in patients treated with clopidogrel or ticagrelor

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel 600 mg (n = 94)</th>
<th>Ticagrelor 180 mg (n = 94)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>8.3±1.2</td>
<td>41.1±10.1</td>
<td>0.008</td>
</tr>
<tr>
<td>1 h</td>
<td>21.0±4.1</td>
<td>70.2±20.1</td>
<td>0.013</td>
</tr>
<tr>
<td>2 h</td>
<td>38.4±10.2</td>
<td>88.6±19.9</td>
<td>0.047</td>
</tr>
<tr>
<td>4 h</td>
<td>51.7±9.8</td>
<td>86.1±24.4</td>
<td>0.032</td>
</tr>
<tr>
<td>6 h</td>
<td>62.1±11.4</td>
<td>87.2±20.8</td>
<td>0.097</td>
</tr>
<tr>
<td>12 h</td>
<td>66.5±20.4</td>
<td>80.4±30.4</td>
<td>0.184</td>
</tr>
<tr>
<td>24 h</td>
<td>73.4±19.3</td>
<td>82.0±27.5</td>
<td>0.331</td>
</tr>
<tr>
<td>48 h</td>
<td>72.0±27.2</td>
<td>84.7±20.8</td>
<td>1.13</td>
</tr>
<tr>
<td>72 h</td>
<td>74.3±15.3</td>
<td>81.9±17.9</td>
<td>1.102</td>
</tr>
</tbody>
</table>

Basis
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Continuous data were presented as mean ± standard deviation and categorical data were presented as frequencies. Comparisons were made using the independent t-test for the continuous data and using the Fisher’s exact test for the categorical data. All statistical analyses were performed using the SPSS 19.0 software (SPSS, Chicago, IL, USA). P < 0.05 was considered statistically significant.

Results

A total of 221 patients were considered for inclusion in this study and 33 were excluded (Figure 1). Demographic and clinical characteristics of the randomized patients are shown in Table 1. No significant differences were noticed the demographic and clinic information between the two groups.

The thrombelastography showed that the ADP inhibition rates at 0.5 h, 1 h, 2 h, and 4 h were significantly higher for ticagrelor in comparison with clopidogrel (P < 0.05). There was a non-significant trend toward higher ADP inhibition rates at 6 h, 12 h, 24 h, 48 h, and 72 h for ticagrelor in comparison with clopidogrel (Table 2; Figure 2).

The maximum amplitude at 0.5 h, 1 h, 2 h, and 4 h were significantly lower for ticagrelor in comparison with clopidogrel (P < 0.05). There was a non-significant trend toward lower maximum amplitude at 6 h, 12 h, 24 h, 48 h, and 72 h for ticagrelor compared with clopidogrel (Table 3; Figure 2).

There were two cases of in-hospital death due to cardiac rupture, one in the clopidogrel and another one in the ticagrelor group. Mild bleeding occurred in 17 patients treated with clopidogrel, including gingival bleeding in 6 patients, skin bruise in 7 patients, nosebleed in 1 patient, and hemorrhoidal bleeding in 3 patients. Mild bleeding occurred in 23 patients treated with ticagrelor, including gingival bleeding in 4 patients, skin bruise in 15 patients, conjunctival bleeding in 2 patients, nosebleed in 1 patient, and hemorrhoidal bleeding in 1 patient. There was no significantly difference in the rate of mild bleeding between the two groups (P = 0.37). No life-threatening bleeding
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Discussion

Our study found that ticagrelor 180 mg is associated with significantly higher ADP inhibition rate and significantly lower maximum amplitude in comparison with clopidogrel 600 mg in the first 4 hours after the loading dose in STEMI patients treated with primary PCI. Ticagrelor inhibits the P2Y12 receptor in a reversible manner and does not require the oxidative activation in the liver. The platelet inhibition of ticagrelor is more potent and faster in comparison with other antiplatelet agents [11, 12]. The PLATO trial compared the efficacy and safety of ticagrelor in comparison with clopidogrel in 18,624 acute coronary syndrome (ACS) patients recruited from 862 centers of 43 countries [13]. This study found that ticagrelor significantly reduced the risk of the composite endpoint of cardiovascular death, MI, and stroke in comparison with clopidogrel without increasing the overall bleeding rate in ACS patients. The RESPOND study showed that ticagrelor is effective in both clopidogrel responders and nonresponders [14].

Although ticagrelor has shown better efficacy and safety in comparison with clopidogrel, these evidences are obtained from patients with stable coronary artery disease or broad ACS. There is a paucity of data of ticagrelor in STEMI patients. In addition, STEMI patients often need dual or triple antiplatelet agents or heparin-based anticoagulation therapy, which is associated increased risk of bleeding. The safety of ticagrelor in the STEMI patients should be further evaluated. The difference in antiplatelet agent efficacy between different regions and races is also a concern [15]. However, the use of ticagrelor in Chinese STEMI patients is still not adequately supported. Our study compared the platelet inhibition rate and the maximum amplitude of ticagrelor with clopidogrel in Chinese STEMI patients treated with primary PCI using the thrombelastography. Thrombelastography is a well-established method for measuring platelet inhibition. In thrombelastography, an ADP inhibition rate > 70% and a maximum amplitude < 47 suggest satisfactory platelet inhibition. Our results showed that ticagrelor is more potent with faster onset in comparison with clopidogrel in STEMI patients treated with primary PCI. Ticagrelor onset was 1 h after the LD, while clopidogrel onset was 6 h after the LD. It took 24 h that clopidogrel reached the same inhibition rate of platelets as ticagrelor. Therefore, the advantages of higher potent and faster onset of ticagrelor also exist in Chinese patients.

In conclusion, ticagrelor is more potent with faster onset in comparison with clopidogrel in Chinese STEMI patients treated with primary PCI.

Disclosure of conflict of interest

None.

Abbreviations

STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; LD, loading dose; ADP, adenosine diphosphate; ACS, acute coronary syndrome; BMI, body mass index.

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