ANTIPLATELET ADEQUACY OF CYCLOPENTYL TRIAZOLOPYRIMIDINE VERSUS CLOPIDOGREL IN-PATIENTS WITH CORONARY HEART DISEASE

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Received: 19 September 2018, Revised and Accepted: 22 October 2018

INTRODUCTION

Clopidogrel is a prodrug that required biotransformation into its active metabolite that irreversibly bound to platelet P2Y12 receptor for the platelet's lifespan (7–10) days and inhibit platelets activation and aggregation [1,2]. Inhibition of platelets aggregation using thienopyridine drug in addition to aspirin therapy amended the consequences of patients with acute coronary syndromes and patients with stents insertion as compared to patients with aspirin monotherapy [3].

Some patients after doing percutaneous coronary intervention and using clopidogrel drug with aspirin therapy may have high platelet reactivity (HPR) or may not respond to clopidogrel; those patients may expose to higher rates of ischemic complication events [4].

Ticagrelor, a cyclopentyl triazolopyrimidine compound, is a nonthienopyridine drug and unlike thienopyridine drug is reversibly bound to platelet P2Y12 receptor. Its inhibit platelet activation and aggregation with a rapid onset of action as compared to clopidogrel [5].

Many studies found that ticagrelor possess higher antiplatelet potency than clopidogrel, second-generation thienopyridine, and similar antiplatelet potency as prasugrel, third-generation thienopyridine. Therefore, ticagrelor can be used to reduce the risk of subsequent myocardial infarction and stent thrombosis [6,7].

As expected, due to the reversible binding of Ticagrelor with P2Y12 receptor this may lead to disperse its antiplatelet effect more rapidly with less bleeding [8].

METHODS

A total of 42 patients (27 male and 15 female), their ages ranging (48±8) years completed the designed period of this crossover study. Of 60 patients (43 males and 17 females) their ages ranging (50–60) years with stable angina enrolled from Ibn Albitar Center for Cardiac Surgery for this crossover study. After satisfying, the properties of inclusion criteria they screened for clopidogrel treatment 75 mg daily for 2 weeks than after 2 weeks periods of wash off they treated with ticagrelor 90 mg twice daily for another 2 weeks. Platelet reactivity was tested at baseline (before treatment), after 2 weeks treatment with clopidogrel and after another 2 weeks treatment with ticagrelor. Platelet reactivity measured by light transmittance aggregometry test and by vasodilator-stimulated phosphoprotein (VASP) phosphorylation test.

The purpose of this crossover study was to assay platelets aggregation using two methods: maximal platelet aggregation percent (MPAP) method and platelet reactivity index percent (PRIP) method with two different treatments ticagrelor treatment or clopidogrel treatment in the same patients with stable angina at different times.

RESULTS

The results of MPAP after 2 weeks treatment with clopidogrel or ticagrelor showed high significant reduction in platelet aggregation in patients with ticagrelor treatment as compared to clopidogrel treatment (30±6% vs. 44±8%). As well, the results of PRIP using VASP-phosphorylation after 2 weeks treatment with clopidogrel or ticagrelor showed high significant reduction in platelet aggregation in patients with ticagrelor treatment as compared to clopidogrel treatment (22±5% vs. 36±7%).

CONCLUSION

Treatment with ticagrelor produced a reduction in platelet reactivity consistent with the reduction in major adverse cardiovascular events and improved survival without increasing major bleeding.

Keywords: Clopidogrel, Ticagrelor, Major adverse cardiovascular events, Vasodilator-stimulated phosphoprotein.
inducers, concomitant antithrombotic treatment, hemoglobin (Hb) level <10 g/dl, liver disease, diabetes mellitus, renal failure, heart failure, and patients with neurological disorder such as epilepsy and tumors.

The patients treated with a maintenance dose of clopidogrel (Plavix, France) 75 mg daily for 2 weeks. Then, after a washout period of 2 weeks, the patients treated with a maintenance dose of ticagrelor (Astrazeneca) 90 mg twice daily for another 2 weeks.

Blood samples were collected in vacutainer tubes containing 3.2% sodium citrate, after discarding first 3 ml of free-flowing blood, at baseline (day 0 of treatment), after 2 weeks treatment with clopidogrel and after 2 weeks treatment with ticagrelor in the morning after 2 h of the last dose of the drug intake to measure the MPAP and the PRI.

The MPAP was assay by measuring the inhibition of ADP (20 μmol/L)-induced platelet aggregation of platelet-rich plasma which expressed as change in light transmittance from baseline, with platelet-poor plasma used as a reference and quantitated by light transmission aggregometry [8].

Whereas the PRI was assay by using vasodilator-stimulated phosphoprotein (VASP), platelet VASP-kit, which measured platelet P2Y12 receptor reactivity, and quantified by flow cytometry [9].

Platelet reactivity was expressed as a PRI and calculated as:

\[ \text{PRI} = \left( \frac{\text{MFI (PGE1)}}{\text{MFI (PGE1 + ADP)}} / \frac{\text{MFI (PGE1)}}{\text{MFI (PGE1)}} \right) \times 100. \]

Where MFI is mean fluorescence intensity, PGE1 is prostaglandin E1, and ADP is adenosine diphosphate. The (PRI) ratio expressed as mean percentage of platelet reactivity and it is inversely correlated with antiplatelet drugs efficiency.

We used the following previously defined cut points of HPR associated with long-term ischemic event occurrence: >55% (20 μmol/L) ADP-induced maximal platelet aggregation [6] and >50% PRI based on the VASP phosphorylation assay [9].

The primary safety endpoint was defined major bleeding as bleeding with clinically overt evidence or non, associated with a decrease in Hb 5 g/dl, and minor bleeding as bleeding associated with a decrease in Hb of <3 g/dl [7].

All numerical data stratified as mean±standard deviation with 95% confidence interval. Comparisons of continuous variables were assessed by Student’s t-test, p values of 0 <0.05 were regarded to be statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 18.0 for windows.

RESULTS

Baseline clinical data and demographic characteristics of the studied participants displayed in Table 1. The platelet responsiveness to ADP stimulation, MPAP, after 2 weeks treatment with clopidogrel 75 mg daily was highly appreciably lower as compared with its value at the baseline (before treatment).

Whereas the MPAP in the same patients after 2 weeks washout and after another 2 weeks treatment with ticagrelor 90 mg twice daily was highly significantly decrease as compared with its value at the baseline or after 2 weeks treatment with clopidogrel 75 mg daily (Table 2 and Fig. 1).

As noted in Fig. 2, the bar graph revealed the variations of MPAP and PRI versus baseline after 2 weeks treatments, high variation achieved

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>Number (n)</td>
<td>42</td>
</tr>
<tr>
<td>Gender (males, females)</td>
<td>(27,15)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48±8</td>
</tr>
<tr>
<td>WBC count (1000/mm)</td>
<td>6.5±1.5</td>
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<tr>
<td>Platelet count (1000/mm)</td>
<td>220±55</td>
</tr>
<tr>
<td>S. Creatinine (μmol/L)</td>
<td>91.05±20.33</td>
</tr>
<tr>
<td>S. Uric acid (μ mol/L)</td>
<td>348±82.8</td>
</tr>
<tr>
<td>S.LDL-C (mmol/L)</td>
<td>2.978±0.388</td>
</tr>
<tr>
<td>S.HDL-C (m mol/L)</td>
<td>1.114±0.259</td>
</tr>
</tbody>
</table>

Data are presented as means±SD (standard deviation) for continuous variables, μ mol/L: Micromole per liter; mmol/L: Millimole per liter. 1000/mm: Multiply by thousand cell per millimeter; Number (n): Sample size of the participants, S.LDL-C: Serum low-density lipoprotein cholesterol, S.HDL-C: Serum high-density lipoprotein cholesterol. SD: Standard deviation, WBC: White blood cell

Fig. 1: Line chart demonstrates the effect of Clopidogrel 75 mg daily treatment or ticagrelor 90 mg twice daily treatment on the mean maximal platelet aggregation percent or the mean platelet reactivity index percent versus baseline (before treatment) and after 2 weeks treatments, sample size (n)=42.

<table>
<thead>
<tr>
<th>% Variation</th>
<th>MPAP%</th>
<th>PRI%</th>
</tr>
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<tbody>
<tr>
<td>55</td>
<td>55</td>
<td>-55</td>
</tr>
<tr>
<td>56</td>
<td>-56</td>
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<tr>
<td>40</td>
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<td>42</td>
<td>42</td>
<td>-42</td>
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</tbody>
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Fig. 2: Bar graph elucidated the percent variation of the mean maximal platelet aggregation percent and the mean platelet reactivity index percent versus baseline after 2 weeks treatment with clopidogrel or with ticagrelor, sample size (n)=42.
in patients on ticagrelor treatment 90 mg twice daily as compared to clopidogrel treatment 75 mg daily.

Analysis of adverse events showed that two minor bleeding occurred during ticagrelor treatment, and no bleeding occurred during clopidogrel treatment. As well, dyspnea episodes testified in five patients on ticagrelor therapy and three patients on clopidogrel therapy. On continuous treatment, dyspnea commonly ameliorated, especially when its intensity was mild to moderate.

Power analysis for the minimum detectable effect of clopidogrel treatment 75 mg daily or ticagrelor treatment 90 mg twice daily on MPAP and PRIP after 2 weeks of treatments are elucidated in Fig. 3.

There is 80% probability that a decrease of MPAP by 4.96% with clopidogrel treatment 75 mg daily can be described and by 4.33% with ticagrelor treatment 90 mg twice daily can also be described. As well, there is 80% probability that a decrease of PRIP by 4.74% with clopidogrel treatment 75 mg daily can be sensed and by 4.07% with ticagrelor treatment 90 mg twice daily can also be sensed.

DISCUSSION

The results of this study elucidated that treatment with the reversibly binding platelet P12Y12, ticagrelor, was greater inhibitor of platelet aggregation than clopidogrel and thereafter reduced major ischemic events by reducing cardiovascular death, myocardial infarction, and stroke without significantly increasing major bleeding, these results are consistent with the PLATO overall results [10,11].

Likewise, to the other study [12,13], the current study showed that ticagrelor treatment may associate with adverse events such as bradycardia and dyspnea, which may be related to the inhibitory effect of ticagrelor on adenosine reuptake by red blood cells.

Cannon et al. reported that the patients intended for non-invasive management and non-ST elevation coronary artery syndrome, exhibit higher rate of long-term adverse events than did those intended for invasive management [14]. As well, the patients who managed without revascularization usually have more comorbidity, higher risk of bleeding, and inferior outcome than patients who are revascularized [15].

Cannon et al. revealed that in contrast to clopidogrel treatment, ticagrelor treatment throughout the 1 st week produced an additional ventricular gap that detected by Holter instrument [13]. Many studies reported a link between patients’ resistance to clopidogrel and major adverse cardiovascular events (MACCE) [16-18].

VASP is a critical protein that is involved in the remodeling of the actin cytoskeleton, while in platelets it plays a role in regulating adhesive events that are associated with platelet aggregation [19].

Flow cytometric assessment of VASP phosphorylation and the Verify Now P12Y12 assay has the advantage of measuring P12Y12 function directly, whereas ADP-induced platelet aggregation (light transmission) is influenced by P12Y12 receptor and other receptor (P1Y2 receptor) which activate platelet and promoting platelet aggregation [20].

![Fig. 3: Power analysis for the minimum detectable effect of clopidogrel treatment (75 mg daily) or ticagrelor treatment (90 mg twice daily) on maximal platelet aggregation percent and on platelet reactivity index percent after 2 weeks treatments. Assuming alpha=0.05, beta =0.2, power (1-beta)=0.8 (80 %), and sample size=42.](image)


