

Effect of Ticagrelor versus Clopidogrel on Inflammatory Bio-marker in Patients with Chronic Stable Angina Patients after Percutaneous Coronary Intervention

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Abstract:

Background: Ischemic heart disease remains the leading cause of death in both developed and under developed countries. The use of antiplatelet drugs specifically the thienopyridine has become a standard for the treatment of acute coronary syndrome. These drugs irreversibly inhibit the platelet aggregation by blocking the P2Y12 receptor. But currently this therapeutic choice has become limited due to potential interaction with other drugs, slow hepatic conversion, genetic resistance and narrow therapeutic safety margin. Ticagrelor, a reversible P2Y12 receptor inhibitor may represent a significant advancement over currently available oral antiplatelet drugs. Objectives: The study was intended to compare the effect of Ticagrelor and Clopidogrel on inflammatory and oxidative stress markers in patients of chronic stable angina (CSA) following percutaneous coronary intervention (PCI). Materials & Methods: The present prospective observational study was carried out in the Department of Pharmacology, Cardiology and Microbiology, BSMMU, Dhaka from September 2014 to February 2016. The study included a total of 100 CSA patients. Patients were divided into two groups, Ticagrelor and Clopidogrel treated groups (each having 50 patients). The baseline laboratory parameters-High sensitive C-reactive protein (hs-CRP), bleeding time, clotting time, were measured and then patients of both groups underwent PCI. The same parameters were again assessed at follow up after 4 weeks of intervention. Total 12 patients from Ticagrelor and 14 patients from Clopidogrel groups were dropped out. Comparisons of the laboratory parameters were made between two groups at baseline and at follow up and also within group before and after intervention. Result: In the present study at baseline characteristics of patients treated with Ticagrelor and Clopidogrel were almost identical in terms of age, sex, diabetes and hypertension. The inflammatory marker hs-CRP was also similar in both groups at baseline. At follow up hs-CRP was significantly reduced from baseline 19.7 mg/dl to 1.7 mg/dl (p value- 0.001) in ticagrelor group and 18.4 mg/dl to 2 mg/dl (p value-0.001) in clopidogrel group. There was no significant change in bleeding time and clotting time in both groups of patients. Conclusion: The study concluded that both Ticagrelor and Clopidogrel are similar in improving the status of the inflammatory marker, resulting from inflammatory processes in patients of chronic stable angina.

Introduction:

Coronary heart disease is a major global health problem in European country¹. Low and middle income countries, including South Asian countries like India and Pakistan, contribute significantly to the global burden of cardiovascular disease. A projection made by Murray and Lopez (1997) showed that by 2020, 78% of all deaths and 86.3% of all loss of disability adjusted life years (DALYs) will be attributable to this cause^{2,10}.

Atherosclerotic process as well as inflammatory process undergoing in the coronary arteries may lead to angina pectoris, myocardial infarction (MI) and if untreated may

lead to death. The damage due to athero-thrombotic inception and oxidative stress in such conditions plays pivotal role in the progression of the disease³. High sensitive C-reactive protein (hs-CRP), TNF α and IL-6 are sensitive markers of inflammation⁴ and malondialdehyde and reduced glutathione are sensitive markers of oxidative stress⁵. The hs-CRP exerts a direct role in the expression of cell adhesion molecule, this protein thus may be of great prognostic value as well as those of the oxidants evolved during stressful condition⁶. There is a powerful predictive association between raised serum high sensitive C-reactive protein (hsCRP) values and the outcome of

acute coronary syndrome (ACS)⁴. Baseline values of hs-CRP are indicative of metabolic state associated with athero-thrombotic events. The presence of hs-CRP within most athero-thrombotic plaque suggests that it may contribute to the pathogenesis and complication of cardiovascular disease^{7,8,9}. High sensitive C-reactive protein (hs-CRP) binds to lipoprotein and activates pro-inflammatory complement^{7,8,9}.

Ticagrelor, a comparatively recently introduced ADP-receptor inhibitor, is a member of the theienopyridine class of adenosine diphosphate (ADP) receptor inhibitors which reduces platelet aggregation by reversibly binding to ADP receptors on platelet membrane^{7,8,9}. Compared to clopidogrel and prasugrel, ticagrelor inhibit adenosine diphosphate (ADP) induced platelet aggregation more rapidly and more consistently to a greater extent both in the healthy subjects and in patients with coronary artery disease including those undergoing percutaneous coronary intervention (PCI)¹¹ and reduce the risk of death either resulting from vascular cause, myocardial infraction (MI) or stroke¹².

In acute coronary syndrome (ACS) inflammatory processes play active role leading to formation of atheroma. So if the antiplatelet drugs could exert anti-inflammatory effect, might be beneficial for the prevention of morbidity and mortality from cardiovascular diseases¹³.

In patients of ACS following PCI, the chance of thrombotic phenomenon is increased because of inflammatory reaction. In that situation an antiplatelet drug having anti-inflammatory action could be a better option. Therefore the present study has been designed to compare the anti-inflammatory properties of ticagrelor and clopidogrel in CSA patients following PCI.

Discussion and results:

Coronary artery disease is the major cause of mortality and morbidity worldwide¹⁴. Inflammation is a key etiological factor in the development of atherosclerotic disease and acute coronary syndromes (ACS)^{4,15,16}. Many inflammatory biomarkers have been studied as both prognostic indicators and possible intervention targets. Among these are the inflammatory biomarkers interleukin 6 (IL 6), High sensitive C-reactive protein (hs-CRP), myeloperoxidase (MPO), and soluble CD40 ligand (sCD40L), which represent pathophysiological steps in the inflammatory processes that may contribute to the pathogenesis of ACS¹⁷. Ticagrelor and Clopidogrel both groups were almost identical in terms of their demographic characteristics (age and sex). The clinical characteristics

(diabetes and hypertension) were also identically distributed between groups. The inflammatory marker high sensitive C-reactive protein was almost similar between the study groups. As most of the baseline characteristics were almost similar in distribution between groups, the outcome obtained could be considered due to intervention drugs.

Inflammation plays a role in the development of atherosclerosis and coronary heart disease¹⁸. Elevated markers of inflammation, particularly high sensitive CRP are associated with increased risk of cardiovascular events^{19,21,22,23}. Previously, the clinical benefits of antiplatelet therapy with the P2Y₁₂ receptor inhibitor clopidogrel in ACS patients compared with placebo by reducing the cardiovascular deaths and nonfatal MI or stroke²⁰. treatment with ticagrelor, the first reversibly binding oral P2Y₁₂ receptor inhibitor, results in greater inhibition of platelet aggregation than clopidogrel in patients with satable atherosclerotic disease or ACS⁷⁸⁹. Some studies suggest that an anti-inflammatory effect may contribute to the clinical efficacy of P2Y₁₂ inhibitor. In this study we observed that hs-CRP was higher in CSA patients in baseline. After treatment the hs CRP was reduced from baseline to follow-up in ticagrelor group 19.7 mg/dl to 1.7 mg/dl (p value- 0.001) and in clopidogrel group 18.4 mg/dl to 2 mg/dl (p value- 0.001).

After 4 weeks of intervention, both groups showed significant reduction hsCRP indicating that anti-inflammatory effect takes place in patients of CSA. However, summarizing the findings of the study, it is evident that both the antiplatelet drugs are effective in improving the status inflammatory marker but ticagrelor seems to be better than the clopidogrel.

Conclusion:

From the findings of the study, it appears that both ticagrelor and clopidogrel are effective in improving the status of inflammatory marker resulting from inflammatory process caused by chronic stable angina. But in terms of outcome, ticagrelor could be considered better than the clopidogrel.

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