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Original Research Article

Effect of Ticagrelor Vs. Clopidogrel in STEMI after PTCA

Hansraj Meena

Assistant Professor, Department of Cardiology, Government Medical College, Kota, Rajasthan, India

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Corresponding author: Dr Hansraj Meena
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Abstract

Objective: Acute coronary syndrome patients have an inflammatory response, which is known to have an impact on platelet aggregation. Our goal is to better understand the connection between the intensity of the inflammatory response and the outcomes of antiplatelet medication after percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Method: The 203 STEMI patients who had primary PCI as part of this retrospective, single-center analysis were divided into two groups according to the antiplatelet treatment they were given when they were admitted (clopidogrel vs. ticagrelor). Based on the tertiles of the distribution of high-specificity C-reactive protein levels before to PCI, three categories of inflammation were identified: low, middle, and high. Platelet aggregation function was measured as residual ADP-induced platelet reactivity on light transmittance aggregometry throughout hospitalisation and follow-up. At admission and a year after PCI, inflammation indicators were assessed.

Results: At intermediate and high levels of inflammation, residual ADP-induced platelet aggregation was significantly higher among clopidogrel users than among ticagrelor users. In the clopidogrel group, statistically significant differences in platelet aggregation function were observed among the three levels of inflammation. At 1 year post-PCI, ticagrelor users had significantly lower levels of interleukin-1βand higher levels of interleukin-35 and transforming growth factor-β.

Conclusion: At different inflammation levels, ticagrelor provides more potent platelet inhibition than does clopidogrel, suggesting that ticagrelor might exert a more stable antiplatelet effect at higher levels of systemic inflammation. Furthermore, ticagrelor is associated with reduced indices of inflammation on follow-up after PCI, suggesting that anti-inflammatory effects might play a role in the clinical benefit observed with antiplatelet therapy, which would provide an additional rationale for using ticagrelor in STEMI patients undergoing primary PCI.

Keywords: STEMI, PCI, MEDICATION, Ticagrelor, and Clopidogrel.

Introduction

The inflammatory reaction in the case of ACS patients is defined by elevated levels of C-reactive protein (CRP) [1,2] platelet activation, and platelet aggregation. Adenosine diphosphate (ADP)-induced platelet aggregation [3] is significantly correlated with CRP levels, which are thought to be a sensitive, systemic, acute-phase measure of inflammation [Figure 1].

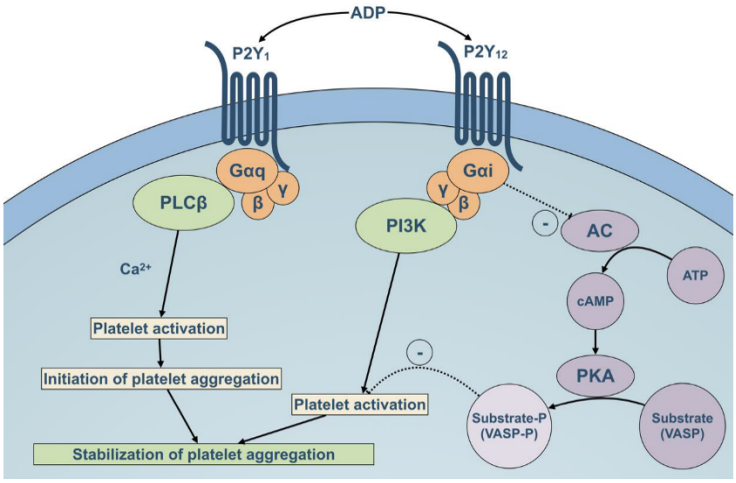

Figure 1: ADP-induced platelet aggregation

Inflammation is known to alter platelet function and increase platelet reactivity, which decreases clopidogrel's effectiveness in patients with coronary heart disease (CHD) who have undergone percutaneous coronary intervention (PCI)4. However, ticagrelor's relationship to inflammation has not yet been studied, and nothing is known about the therapeutic significance of any potential interactions between ticagrelor medication and inflammation. Furthermore, it is yet unknown how the difference between ticagrelor and clopidogrel on the intensity of inflammation, as indicated by high-sensitivity CRP (hs-CRP) levels, affects platelet aggregation in hospitalised patients. There have been claims that ticagrelor offers intensified anti-inflammatory impact and greater platelet inhibition. Initially, it was believed that platelets were only involved in hemostasis and thrombosis;

The production of cytokines that are pro-inflammatory and interactions with endothelial cells, however, show their role in the inflammatory and immunological responses in recent research. Platelet activation causes the surface manifestation of P-selectin (CD62), which links to P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes, encouraging the development of platelet-leukocyte complexes [6, 7], and platelet-leukocyte complexes [8]. Another receptor for the platelet-leukocyte interaction, 2 integrin Mac-1, is expressed on the surface of activated leukocytes9. P-selectin expression also causes tissue factor, a key mediator of the coagulation cascade, to be expressed on monocytes, which in turn triggers the release of a variety of inflammatory cytokines [10]. According to reports, luminal platelet deposition in the heart has been demonstrated to be induced by myocardial infarction and pressure overload [11,12]. Additionally, there is proof that clopidogrel, which targets the platelet-activating receptor P2Y12, prevents the production of inflammatory mediators that are known to encourage myocardial remodeling [12]. There is a lack of clinical evidence supporting P2Y12 receptor inhibitors' immunomodulatory effects. Inhibitors of P2Y12 have anti-inflammatory properties. A single dosage of ticagrelor reduced ex vivo cytokine production by lipopolysaccharide-stimulated leukocytes in healthy individuals [13].

Similar results were shown when human endotoxemia was treated with ticagrelor or clopidogrel, which reduced levels of the pro-inflammatory mediators tumour necrosis factor-, IL-6, and chemokine (C-C motif) ligand 2 in the blood.

For patients having PCI, clopidogrel and ticagrelor are now considered routine dual-antiplatelet treatments [15, 16]. However,

some individuals do not respond well to clopidogrel medication or do not respond well at all, and these patients have a greater residual risk of serious adverse cardiovascular events [17]. Ticagrelor is a direct-acting medication that blocks P2Y12 receptor signalling without obstructing ADP binding and does not need metabolic activation. Contrarily, clopidogrel is a pro-drug that activates metabolism in the liver in two steps, and its active metabolite binds permanently and covalently to the P2Y12 receptor to prevent ADP binding [18]. In the meanwhile, it has been hypothesised that inflammation alters platelet function, increasing platelet reactivity and decreasing the effectiveness of clopidogrel in CHD patients after PCI(4). As a result, ticagrelor is advised for the therapy of ACS patients who are at moderate to high risk [19]. Adenosine-mediated platelet actions such cardioprotection, vasodilation, inflammatory control, and platelet function inhibition are blocked by ticagrelor [20]. The equilibrative nucleoside transporter 1 (ENT1) and other adenosine transporters, which are present on erythrocytes and other cell types, contribute to adenosine's longer half-life and higher local extracellular concentration. Ticagrelor was demonstrated to enhance adenosine-induced increase in coronary blood flow in a canine model and in healthy volunteers (Figure 1; 21, 22]). It reduces the cellular absorption of adenosine, probably via inhibiting ENT1 [21].

Therefore, the purpose of the current study is to assess the anti-inflammatory activity of antiplatelet agents following primary PCI for ST-elevation myocardial infarction (STEMI), as well as to investigate the relationship between inflammation severity and the effect of clopidogrel vs. ticagrelor therapy on platelet aggregation.

Methods

Study Design:

This was a cross-sectional study carried out at Government Medical College, Kota over 3 year.

Methodology

By methodically going through the medical records kept by our hospital, we were able to gather information on baseline demographics, angiographic features, complications, and laboratory and physical examination outcomes on hospitalisation. The femoral method was utilised to administer an intra-aortic balloon pump when necessary, but the percutaneous radial artery technique was often employed for primary PCI. The catheterization laboratory records were used to get the angiographic data, which was then evaluated using a traditional technique. If the vascular stenosis was greater than 70%, the culprit artery was considered to be clinically important. The thrombolysis in myocardial infarction (TIMI) score was used to rate the blood flow in the infarct-related artery receiving initial PCI.

Before PCI, a chewable loading dose of either 180 mg ticagrelor and 600 mg of clopidogrel or 300 mg of aspirin was given. An infarct-related artery with less than 20% stenosis and TIMI 3 blood flow was considered to have been successfully treated. Following the surgery, the patients were sent to our cardiac care unit where they received the recommended course of therapy for STEMI, which included either 90 mg of ticagrelor twice a day or 75 mg of aspirin, 40 mg of rosuvastatin, and 75 mg of clopidogrel once a day.

Collecting blood samples and calculating cytokine levels

All patients had venous blood drawn after being admitted. Platelet function was assessed at admission and 72 hours later using light transmittance aggregometry to measure ADP-induced residual platelet reactivity. Induced platelet aggregation was measured as a percentage of aggregated cells at a final ADP concentration of 20 mol/L. Hs-CRP levels, which were

determined using a readily accessible immunonephelometric kinetic assay using Cardiophase hs-CRP reagents, were used to represent the severity of the inflammation. Using established techniques, the 12-hour fasting serum concentrations of blood sugar, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were determined. Enzyme-linked immunosorbent assay was used to measure the amounts of plasma and supernatant cytokines using cytokine-specific kits.

Sample Size

Inclusion criteria:

Admission within 12 hours of the onset of symptoms, which are defined as a characteristic chest pain lasting greater than 30 minutes, ST-segment elevation more than 1 millimetre in two consecutive electrocardiogram leads, or a new onset of complete left bundle-branch block, as well as primary PCI, which includes balloon angioplasty, thrombus aspiration, and/or stent implantation.

Exclusion criteria:

Tirofiban use during surgery, history of hemorrhagic disorders, long-term oral dipyridamole, warfarin, abciximab, anti-inflammatory drugs, glucocorticoids, or a strong cytochrome P-450 3A modulator use, and concurrent influenza are all contraindications to taking clopidogrel or ticagrelor.

Statistical analysis:

While qualitative data were reported as frequency (%), quantitative data were expressed as mean value standard deviation or median (interquartile range) if not normally distributed. To compare groups, the independent two-sample t-test was applied. The Fisher's exact test or the chi-square test, as applicable, was used to compare categorical variables. Mann-Whitney to compare sets of non-normally distributed data, U tests were utilised. In order to undertake a multivariable study of platelet function in clopidogrel vs. ticagrelor users with various degrees of in-hospital inflammation, linear regression was performed. Two-sided p-values below >0.05 were considered statistically significant. SPSS version 19.0 was used for all statistical calculations.

Results

Baseline characteristics

The study enrolled 203 patients (133 men and 70 women) categorized into the clopidogrel group (n=125) or ticagrelor group (n=78) based on the antiplatelet therapy at hospitalization. There were no differences between the groups regarding baseline demographics, angiographic characteristics, or medication use. Additionally, there were no significant differences between the groups regarding laboratory characteristics or regular medications

Platelet function and inflammation severity during hospitalization

Residual ADP-induced platelet aggregation was found to be associated with hs-CRP levels in the clopidogrel group ($p<0.0001$). Based on data from a large clinical trial, inflammation severity was defined according to the tertiles of the distribution of hs-CRP levels as low, intermediate, and high for hs-CRP levels <2, 2–10, and >10 mg/L, respectively. At intermediate and high-level inflammation, clopidogrel had significantly lower antiplatelet effect than noted at low-level inflammation.

Anti-inflammatory effect during follow-up after PCI

During the follow-up period of 1 year, the levels of the pro-inflammatory cytokine interleukin (IL)-1β (256.90±70.92 vs 201.94±54.88 ng/L, $p<0.001$) and tumor necrosis factor (TNF)-α (86.54±26.75 vs 77.22±19.66 µg/L, $p=0.005$) were significantly lower, whereas the levels of the anti-inflammatory cytokines IL-35 (21.43±6.31 vs 27.34±9.86 ng/L, $p<0.001$) and transforming growth factor (TGF)-β

(9.79±4.89 vs 13.01±5.15 ng/L, p<0.001) were significantly higher among ticagrelor users than among clopidogrel users. Interleukin (IL)-6 and hs-CRP had no significant differences between clopidogrel and ticagrelor groups [Table 1].

Table 1: Anti-Inflammatory Effect

Anti-Inflammatory	Initial Value	Value after 1-year	P-Value
(IL)-1β)	256.90±70.92 ng/L,	201.94±54.88	p<0.001
(TNF)-α	86.54±26.75	77.22±19.66	p=0.005
TGF-β	9.79±4.89	13.01±5.15	p<0.001

Discussion

Over the past decade, it has become well-established that inflammation is a component of ACS[23] [24]. From a pathological point of view, the initiation, growth, and complications of atherosclerotic plaque might be considered inflammatory responses to vessel wall injury [25]. Both the pathophysiology of ACS and the mechanisms underlying vessel repair involve local and systemic inflammation [26]. Inflammatory stimuli induce hepatic effects reflected in the levels of CRP and various other acute-phase reactants [27]. The elevated levels of inflammatory markers might be incorrectly attributed to atherosclerotic cardiovascular disease. High levels of hs-CRP represent a well-known predictor of cardiovascular events and thus are widely performed for screening. While new assays may become available in the future for other inflammatory markers that provide higher accuracy, standardization, and other characteristics superior to those of hs-CRP, the hs-CRP assay currently serves as the best marker of inflammation [27].

Compared to clopidogrel, ticagrelor showed superior efficacy in reducing the rate of cardiovascular events and mortality in the Platelet Inhibition and Patient Outcomes (PLATO) study [28].

In our clinical study, we confirmed that, compared to clopidogrel, ticagrelor did achieve greater inhibition of platelet aggregation and exerted a more stable antiplatelet effect at higher hs-CRP levels. Our present results suggest that ticagrelor is associated with a higher degree of platelet inhibition as well as with significantly better anti-inflammatory effects. Thus, ticagrelor use is expected to provide superior antiplatelet action after primary PCI for STEMI even in patients with higher systemic inflammation. Further studies are necessary to clarify whether anti-inflammatory agents can decrease platelet reactivity and thus help improve the efficacy of antiplatelet drugs.

Inflammation is of cardinal importance among the pathologic mechanisms of atherosclerosis, and interventions focused on reducing inflammatory signaling might attenuate atherosclerosis after stenting [29]. The number of monocytes adhering to the luminal surface of stented arteries was shown to be linearly correlated with the degree of neointimal hyperplasia [30]. Compared to patients with chest pain syndrome, acute myocardial infarction is triggered by an imbalance of inflammatory cytokines such as IL-12, IL-27, TGF-β, and IL-3531. There is evidence that patients with CHD who have elevated CRP after PCI is proposed to benefit from anti-inflammatory medications (as seen in data with aspirin, clopidogrel, etc.) [5]. Meanwhile, it must be pointed out that the use of anti-inflammatory medication in ACS is entirely speculative, as chronic inflammatory disease preceding CHD is a different entity than that covered by the population of this study.

It is likely that platelet-mediated inflammation is involved in the initiation and propagation of atherosclerosis and the development of a vulnerable plaque, which suggests that drugs downregulating the

biomarkers of inflammation may provide a clinical benefit in ACS [32]. Furthermore, beneficial effects of clopidogrel on inflammatory markers have been demonstrated across a wide spectrum of atherothrombotic diseases including ACS, acute ischemic stroke, and peripheral arterial disease [33,34]. Thus, there is reason to believe that the anti-inflammatory effect of antiplatelet drugs will be applicable to other hypercoagulable and vascular conditions caused by atherosclerosis.

Conclusion

At different levels of inflammation severity, ticagrelor provided more potent platelet inhibition than did clopidogrel, which suggests that ticagrelor might exert a more stable antiplatelet effect at higher levels of systemic inflammation. Furthermore, ticagrelor was associated with reduced indices of inflammation on follow-up after PCI, suggesting that anti-inflammatory effects might play a role in the clinical benefit observed with antiplatelet therapy, which would provide an additional rationale for using ticagrelor in STEMI patients undergoing primary PCI.

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