



Comparing the Effect of Dual and Triple Antiplatelet Therapy on High Sensitivity C-reactive Protein Levels in Patients with Coronary Artery Disease

Dr. Mathew George¹, Dr. Lincy Joseph², Deepthi Mathew³, Agnus Elsa Francis⁴, Nevin Sam⁵, Princy Abraham⁶, Rosemary Jose⁷
Principle¹, HOD&PG Incharge², Assistant Professor³, Pharm D Student^{4,5,6,7}
Department of Pharmacology¹, Department of Pharmaceutical Chemistry², Department of Pharmaceutics³
Pushpagiri College of Pharmacy, Thiruvalla, Kerala, India

Abstract:

Inflammation is widely considered to be an important contributing factor of the pathophysiology of Coronary Artery Disease (CAD), and the inflammatory cascade is particularly important in the atherosclerotic process. Hence High Sensitivity C-Reactive Protein (hs-CRP) is considered as the most valuable inflammatory biomarker, for they take part in the formation and progression of atherosclerotic plaque and can predict outcomes of patients with Coronary Artery Disease. Coronary artery disease patients are often prescribed with Dual (Aspirin+Clopidogrel) or Triple (Aspirin+Clopidogrel+Cilostazol) anti-platelet therapy. Several research suggest that Aspirin, Clopidogrel and Cilostazol have anti-inflammatory effect by reducing the inflammatory biomarkers such as hs-CRP, TNF- α , Interleukin-1,6. The present review is aimed to compare the effect of dual and triple antiplatelet therapy in reducing hs-CRP levels in patients with Coronary Artery Disease and thereby reducing the risk of future cardiovascular events.

Keywords: Coronary Artery Disease, Dual antiplatelet therapy, Triple antiplatelet therapy, High sensitivity C - reactive protein.

I. INTRODUCTION

C-reactive protein (CRP) is a specific biomarker for inflammation. Elevated serum levels of CRP using a high sensitive assay (hs-CRP) reflect subclinical inflammatory states such as vascular inflammation. CRP is believed to be both the marker and mediator of atherosclerosis and Coronary Artery Disease. CRP levels can strongly and independently predict adverse cardiovascular events including myocardial Infarction, ischaemic stroke, and sudden cardiac death in individuals both with and without overt CAD. C-reactive protein is measured in milligrams of CRP per litre of blood (mg/L). CRP is traditionally measured down to concentration of 35mg/L, whereas hs-CRP measures down to concentrations around 0.3mg/L. This improved sensitivity allows hs-CRP to be used to detect low levels of chronic inflammation. However, a desirable value is probably less than 1mg/L. Coronary Artery Disease (CAD) is also known as Coronary Heart Disease or simply Heart Disease. It is a narrowing or blockage of the coronary arteries that provide oxygen and nutrients to the heart. It includes stable angina, unstable angina, myocardial infarction and sudden cardiac death. Aspirin induces a permanent functional defect in platelets. Low doses of aspirin are sufficient to irreversibly acetylate serine 530 of cyclooxygenase (COX-1). This effect inhibits platelet generation of thromboxane A₂, resulting in an anti-thrombotic effect. The active metabolite of Clopidogrel selectively inhibits the binding of adenosine diphosphate to its platelet P2Y₁₂ receptor and subsequent ADP mediated activation of Glycoprotein GP IIB/IIIa complex thereby inhibiting platelet aggregation.

Cilostazol is a reversible type III phosphodiesterase inhibitor, with vasodilator and antiplatelet effects. It increases intraplatelet cAMP, reduces cellular adenosine uptake and inhibits vascular smooth muscle cell proliferation.

II. METHODS

A prospective, experimental study was conducted in Department of Cardiology at Pushpagiri Medical College Hospital, Kerala from January 2017 to June 2017. The entire study was carried out only after getting approval from Institutional Ethics Committee.

The selection of patients was based upon the inclusion and exclusion criteria. A total of 60 coronary artery disease patients (30 on dual and 30 on triple antiplatelet therapy) were selected. A brief introduction regarding the study was provided to the subjects. A written Informed Consent was obtained from the patient or authorized care-giver. Demographic details of the patients were collected and recorded and the confidentiality of the data was assured. Patients with ischemic manifestations suspected to represent Coronary Artery Disease, patients with acute ST segment elevation or non ST segment elevation myocardial infarction, stable angina and unstable angina, both male and female patients, patients who are willing to sign the informed consent and patients of age >18 yrs was selected. The study objectives were described to patients and they entered consciously and voluntarily. Pregnant and breast feeding women, patients who are not willing to sign informed consent, patients who are already on antiplatelet therapy and patients with any inflammatory or auto immune diseases were excluded from the study.

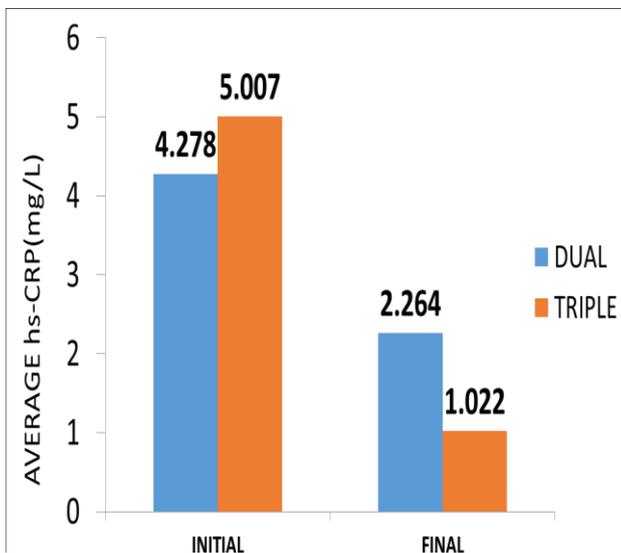
Each patient was followed at the time of admission and after 1 month. The residual blood of the participants involved in the study were collected from the laboratory and analyzed for serum hs C-reactive protein using semi-auto analyzer at Pushpagiri College of Pharmacy. The data was analysed using SPSS and independent t-test was used for comparing means and Chi-square test for multiple comparisons among populations. Level of significance was considered as $p \leq 0.05$.

III. RESULTS

Of the 60 subjects in study, there were 30 patients on dual antiplatelet therapy and 30 patients on triple antiplatelet therapy. Among the patients on dual therapy, 66.7% were males and 33.33% were females. Among the patients on triple antiplatelet therapy, 80% were males and 20% were females. Majority of the patients were in the age group between 55 to 70. Among the 60 subjects, in both males and females, the triple antiplatelet therapy caused a greater reduction of hs-CRP levels than the dual antiplatelet therapy. In the case of dual antiplatelet therapy, the mean hs-CRP level on admission and on review (after 1 month) was found to be 4.278 and 2.264 respectively. In case of triple antiplatelet therapy the mean hs-CRP level on admission and on review (after 1 month) was found to be 5.007 and 1.022 respectively. This indicated that triple antiplatelet therapy had more efficiency in reducing hs-CRP levels than dual antiplatelet therapy ($p < 0.001$)

Antiplatelet Therapy	Initial mean hs-CRP value	Final mean hs-CRP value	Mean difference hs-CRP levels
Dual (aspirin+clopidogrel)	4.278	2.264	2.014
Triple (aspirin+clopidogrel+cilostazol)	5.007	1.022	3.985

IV. BASED ON CLINICAL VALUE



V. DISCUSSION

The study investigated the effect of dual (aspirin+clopidogrel) and triple (aspirin +cloidogrel+cilostazol) antiplatelet therapy on hs-CRP levels. From our results it can be said that both dual and triple antiplatelet therapy caused a reduction in hs-CRP levels having an anti-inflammatory effect. It was also seen that triple antiplatelet therapy caused greater reduction in hs-CRP levels than dual antiplatelet therapy. Inflammation is widely considered to be an important contributing factor of the pathophysiology of Coronary Heart Disease (CHD), and the inflammatory cascade is particularly important in the atherosclerotic process. Hence hs-CRP is considered as the most valuable inflammatory biomarker, for they take part in

the formation and progression of atherosclerotic plaque and can predict outcomes of patients with Coronary Artery Disease. CAD starts when certain factors damage the inner layer of the coronary artery. These factors include smoking, high blood pressure, high cholesterol, diabetes or insulin resistance and blood vessel inflammation. Once the inner wall of a coronary artery is damaged, fatty deposits (plaque) and other cellular waste products tend to accumulate at the site of injury in a process called atherosclerosis. Over time, plaque can harden or rupture. Hardened plaque narrows the coronary arteries and reduces the flow of oxygen rich blood to heart, this can cause angina. If the plaque ruptures, platelets stick to the site of injury and clump together to form a blood clot. If the blood clot becomes large enough, it can mostly or completely block a coronary artery and cause a heart attack. C-reactive protein (CRP) is a liver-derived pattern recognition molecule that is increased in inflammatory states. It rapidly increases within hours after tissue injury, and it is suggested that it is part of the innate immune system and contributes to host defense. Since cardiovascular disease is at least in part an inflammatory process, CRP has been investigated in the context of arteriosclerosis and subsequent vascular disorders. Based on multiple epidemiological and intervention studies, minor CRP elevation [high-sensitivity CRP (hsCRP)] has been shown to be associated with future major cardiovascular risk (hsCRP: $<1\text{mg/L}$ =lowrisk; $1\text{-}3\text{mg/L}$ =intermediate risk; $3\text{-}5\text{mg/L}$ =high risk; $>5\text{mg/L}$ =unspecific elevation). The patients at intermediate or high risk of coronary heart disease may benefit from measurement of hsCRP with regard to their individual risk prediction. Hence reduction of CRP levels using the dual and triple antiplatelet therapy reduces the risk of future cardiovascular events. Based on the risk of the patients (hsCRP: $<1\text{mg/L}$ =lowrisk; $1\text{-}3\text{mg/L}$ =intermediate risk; $3\text{-}5\text{mg/L}$ =high risk) and their Prothrombin time (PT), Activated plasma thromboplastin time (APTT) and international normalised ratio (INR) values, patients may be prescribed with dual and triple antiplatelet therapy. The patients have a low to moderate cardiovascular risk maybe be prescribed with dual antiplatelet therapy and patients with a moderate to severe cardiovascular risk maybe be prescribed with triple antiplatelet therapy.

VI. CONCLUSION

Cardiovascular diseases have a high prevalence and results in increased morbidity and mortality. Measurement of inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) may provide a novel method for detecting individuals at high risk of cardiovascular disease. The study concluded that both dual and triple antiplatelet therapy have anti-inflammatory effect causing a reduction in hs-CRP levels and thus reducing the cardiovascular risk. A total of 60 patients were included in the study. This study also determined that the triple antiplatelet therapy has more effectively reduced hs-CRP levels than dual antiplatelet therapy. Thus, dual antiplatelet therapy (aspirin+clopidogrel) may be regarded as the therapy of choice in low to moderate cardiovascular risk patients and triple therapy maybe prescribed in patients with moderate to high cardiovascular risk.

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