ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 5, Issue 2, February: 2017, 26-35

Short Review Article

COMPARING THE EFFECT OF DUAL AND TRIPLE ANTIPLATELET THERAPY ON HIGH SENSITIVITY C-REACTIVE PROTEIN LEVELS IN PATIENTS WITH CORONARY ARTERY DISEASE.

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Received 01 Feb. 2017; Accepted 25 Feb. 2017

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.

KEY WORDS: Coronary Artery Disease, Dual antiplatelet therapy, Triple antiplatelet therapy, High sensitivity C-Reactive Protein.

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 (CRP) is a substance produced by the liver in response to inflammation. High CRP levels can indicate that there is inflammation in the arteries of the heart, which can mean a higher risk for myocardial infarction. C-reactive protein is measured in milligrams of CRP per litre of blood(mg/L).CRP is traditionally measured down to concentration of 3-5mg/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.

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.

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.

CAD starts when certain factors damage the inner layer of the coronary artery. These factors include

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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.

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.

REVIEW OF LITERATURE

1. Neeraj K Agarwal *et al.,* (2007); **"CILOSTAZOL REDUCES INFLAMMATORY BURDEN AND OXIDATIVE STRESS IN HYPERTENSIVE TYPE 2 DIABETES MELLITUS PATIENTS"**

It was a randomized open controlled clinical trial. Patients were randomly assigned into cilostazol group and control group (placebo). Cilostazol group received the drug at a dose of 100 mg twice daily orally for 1 month as add-on therapy to the standard therapeutic regimen metformin + sulfonylureas and anti-hypertensive drugs. After 1-month, clinical parameters were re-evaluated.The study concluded that cilostazol showed a significant reduction in hs C-reactive protein, ESR, total leukocyte count, plasma malondialdehyde, HbA1c and increase in serum albumin and blood reduced glutathione than the control group.

2. Chen YU-guo *et al.,* (2005;) **"EFFECT OF ASPIRIN PLUS CLOPIDOGREL ON INFLAMMATORY MARKERS IN PATIENTS WITH NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME".**

Patients were randomly assigned to group A(Aspirin) and group B(Aspirin+Clopidogrel). The patients of group A received a loading dose of 300 mg aspirin, then 100 mg aspirin per day. The patients of group B took a loading dose of 300 mg aspirin and 300 mg clopidogrel, then 100 mg aspirin and 75 mg clopidogrel per day. All patients were treated with similar medications without intervention therapy during the observation period.The study concluded that aspirin plus clopidogrel reduced serum hs-CRP and TNF-α more than aspirin alone.

3. Ching-Jung Hsieh *et al.,* (2009;)"EFFECT OF CILOSTAZOL TREATMENT ON ADIPONECTIN AND SOLUBLE CD40 LIGAND LEVELS IN DIABETIC PATIENTS WITH PERIPHERAL ARTERIAL OCCLUSION DISEASE"

92 Type 2 diabetics with PAOD and 100 non- PAOD diabetics were enrolled and randomly assigned to a group receiving either cilostazol or placebo for 6 months. The atherogenic cytokines were measured at the beginning and completion of the study.The study concluded that cilostazol can decrease hs-CRP and soluble CD40 Ligand levels and increase that of adiponectin and delay the progression of atherogenesis and chronic inflammation in type 2 diabetics, especially with PAOD.

4. Seung-Whan Lee *et al.,* (2011;) **"A RANDOMIZED, DOUBLE BLIND, MULTICENTRE COMPARISON STUDY OF TRIPLE ANTIPLATELET THERAPY WITH DUAL ANTIPLATELET THERAPY TO REDUCE RESTENOSIS AFTER DRUG ELUTING STENT IMPLANTATION IN LONG CORONARY LESIONS".**

Patients were assigned randomly to triple (aspirin, clopidogrel and cilostazol) or dual (aspirin, clopidogrel and placebo) for 8 months after long zotarolimus- eluting stent implantation. The study concluded that patients receiving triple antiplatelet therapy had decreased extent of late luminal loss,percent intimal hyperplasia volume and restenosis than patients who received dual antiplatelet therapy.

5. Ignatios Ikonomidis et *al*.,(1999;)**"INCREASED PROINFLAMMATORY CYTOKINES IN PATIENTS WITH CHRONIC STABLE ANGINA AND THEIR REDUCTION BY ASPIRIN"**

Plasma macrophage colony stimulating factor (MCSF), IL-1, IL-6 and CRP were measured in 60 chronic stable angina patients after Aspirin treatment and also in 24 matched controls. The study was a 6 week, randomized, double blind, crossover trial. The study concluded that patients receiving aspirin had decreased cytokines and CRP levels than patients receiving placebo.

CONCLUSION

From the above review it is understood that Aspirin, Clopidogrel and Cilostazol exhibit both antiplatelet and anti inflammatory effects. Coronary Artery Disease patients are often prescribed with Dual (Aspirin+Clopidogrel) and Triple (Aspirin+Clopidogrel+Cilostazol) antiplatelet therapy. Hence comparing the effect of Dual and Triple antiplatelet therapy on High sensitivity C-reactive protein levels in Coronary Artery Disease patients is important to predict the risk of future cardiovascular events.

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