ORIGINAL ARTICLE

ELECTIVE PERCUTANEOUS CORONARY INTERVENTIONS-A COMPARISION OF EFFICACY OF CLOPIDOGREL AND PRASUGREL

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Background: Percutaneous coronary interventions are almost always preceded by the loading dose of platelets inhibiter drugs such as clopidogrel or prasugrel and followed by maintenance therapy to decrease the mortality and morbidity due to stent thrombosis. This study was conducted to compare the efficacy of clopidogrel and prasugrel for inhibiting platelet aggregation among patients undergoing elective percutaneous coronary intervention. **Methods:** This randomized controlled trial study was done in Department of Cardiology, Postgraduate Medical Institute Govt. Lady Reading Hospital Peshawar. A total of 148 patients were randomly allocated to either group-A containing 74 patients using clopidogrel or group-B containing 74 patients using prasugrel **Results:**. Group-A had 55 (74.3%) male and 19 (25.7%) females while group-B had 56(75.7%) males and 18(24.3%) females (p=0.85). Mean age was 54.9±11.2 years in group-A and was 57.7±8.7 years in group-B (p=0.09). Mean body weight was 71.8±6.4 Kg in group-A and 70.8±6.3 Kg in group-B (p=0.35). Mean Baseline platelet aggregation before drug administration was 10.43±1.9 ohm in group-A while 10.12±2.2 ohm in group-B (p=0.36). Mean Follow up platelet aggregation 6 hours after drug administration was 5.88±2.9 in group-A while it was 3.47±1.8 ohm in group-B (p=0.001). Mean Difference between basal and follow up platelet aggregation ±SD was 52.9649±24.77 in group-A while it was 82.25±14.34 in group-B (p=0.001). 63(85.15%) of group-A had inhibition of platelets aggregation >10% as compare to 72(97.3%) of group-B had inhibition of platelets aggregation >10% (p=0.009). **Conclusion:** Prasugrel is more efficacious than clopidogrel in term of inhibition of platelets aggregation.

Keywords: Clopidogrel, prasugrel, platelets aggregation

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INTRODUCTION

The 20th century saw the unparalleled increases in life expectancy and a major shift in the causes of illness and death throughout the world. During this transition, cardiovascular disease became the most common cause of death worldwide. A century ago, cardiovascular disease (CVDs) accounted for less than 10 percent of all death.[1] An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke. Low- and middle-income countries are dis-proportionally affected. Over 80% of CVD deaths take place in low- and middle-income countries and occur almost equally in men and women.[1]

Coronary thrombolysis and mechanical revascularization have revolutionized the primary treatment of acute myocardial infarction and coronary artery disease, largely because they allow salvage of the myocardium when implemented early after the onset of ischemia.

One of the major complications of percutaneous coronary interventions (PCI) is acute stent thrombosis for which various antiplatelet drugs like clopidogrel, prasugrel, ticlopidine and aspirin are used. So PCI should almost always be preceded by the loading dose of platelets inhibiter drugs such as clopidogrel or prasugrel followed by maintenance therapy to decrease the mortality and morbidity due to stent thrombosis.[2]

The action of both clopidogrel and prasugrel is related to an adenosine diphosphate (ADP) receptor on platelet cell membranes. Both of these drugs specifically and irreversibly inhibit the $P2Y_{12}$ subtype of ADP receptor, which is important in aggregation of platelets and cross-linking by the protein fibrin. But clopidogrel is a pro-drug requires sequential activation in liver through cytochrome 450 system. Its metabolism is affected by CYP 2C19 gene.[3] This gene has a polymorphism of about 2–14% in United States.[4] In the presence of loss of this gene function, clopidogrel metabolism is not optimal which may lead to decrease antiplatelet effect with its associated mortality and morbidity.[2,5] Unlike clopidogrel, prasugrel is not a prodrug so does not require extensive metabolism in liver and is not affected by CYP 2C19 gene. So its antiplatelet effect is more optimal and consistent which is associated with improvement in mortality and morbidity.[2,3] The responders rate in coronary arteries disease patients ranges from 79%,

83% and 94% for clopidogrel as compared to 95% for prasugrel in various studies.[6–8]

The aim of this study was to compare of efficacy of clopidogrel and prasugrel among patients undergoing elective percutaneous coronary interventions for a demonstrable lesion on diagnostic coronary angiography instable angina patients.

MATERIAL AND METHODS

This randomized control trial was conducted in Department of Cardiology, Lady Reading Hospital, Peshawar from 1st June 31st December 2012. Sample size was 74 in each group using 95%[9] proportion of efficacy of prasugrel and 79%[10] proportion of efficacy of clopidogrel for platelet aggregation inhibition for elective PCI cases[11], 95% confidence interval and 80% power of the test under WHO sample size calculations. Patients were included in the study by Consecutive non probability sampling.

All patients undergoing elective PCI for demonstrable significant lesions on coronary angiography with stable angina patients from age 35–75 years of both genders having weight ≥60 Kg and baseline platelets aggregation inhibition of ≥5 ohm.

While Patients already taking clopidogrel, prasugrel or glycoprotein IIb/IIIa fibrinogen receptors inhibitors beforehand were excluded. Also patients with chronic liver diseases, chronic renal failure and bleeding disorders were excluded.

The study was approved by the Hospital Ethical Committee. Patients who were admitted to Cardiology unit Lady Reading Hospital Peshawar through Outpatient Department diagnosed as having demonstrable lesion on diagnostic coronary angiography with stable angina were included in the study. A detailed informed consent was obtained and all the pros and cons of the study were explained in detail. Patients undergoing elective PCI with demonstrable lesion on previous diagnostic coronary angiography were randomly allocated in two groups by lottery method. There baseline platelet activity was checked using Chronolog Whole-blood aggregometer model 591.Group A was given clopidogrel 600 mg loading dose 06 hours before PCI orally. Group B was given 60mg of loading dose of prasugrel 6 hours before PCI orally.

Venous blood sample of 2 cc was taken using 21gauge standard needle syringe after 6 hours of loading dose just before PCI. Platelets activity was checked again by the same operator and same chronolog aggregometer model 591. If the drug caused the inhibition of platelets aggregation by ≥20% at 20 micromole ADP (Agonist) from baseline it was considered efficacious. Confounding variables like patients with age less than 35 or above 75 years, weight less than 60 kg, history of transient cerebrovascular events/stroke, chronic liver disease, chronic renal disease , bleeding disorders, platelets less than one 100,000/uL or already taking clopidogrel, prasugrel or glycoprotein IIb/IIIa inhibitors were excluded by following strict exclusion criteria. Bias in the study was controlled by using same brand of drugs, administration of drugs 06 hours before PCI, using same device for platelets reactivity measurement and same operator. All the detailed information was collected through a specially designed *Pro forma*.

All the data collected with the help of *pro forma* was entered and analysed using Statistical package for social sciences; SPSS version 16. Mean±SD was calculated for numerical variables like age, baseline platelets activity, follow up platelets activity and percentage inhibition of platelets activity. Frequency and Percentage was calculated for categorical variables like gender and efficacy. Comparison of efficacy was done using chi-square test. *p*-value <0.05 was consider significant. Efficacy in both the groups was stratified among age, gender and baseline platelet aggregation to see the effect modifications. All the results were presented as tables and graphs wherever needed.

RESULTS

A total of 148 patients were included in the study. Group-A (using clopidogrel) and group-B (using Prasugrel) had similar number of 74 patients. Group-A had 55 (74.3%) males and 19 (25.7%) females while group-B had 56 (75.7%) males and 18 (24.3%) females; *p*=0.85. Mean age±SD was 54.9±11 years in group-A and 57.7±8.7 years in group-B (*p*=0.09). Mean body weight was 71.8±6.4 Kg in group-A and 70.8±6.3Kg in group-B; (*p*=0.35).

Mean baseline platelet aggregation before drug administration was 10.43±1.9 ohm in group-A while 10.12±2.2 ohm in group-B (*p*=0.36). Mean follow up platelet aggregation 6 hours after drug administration was 5.88±2.9 in group-A while it was 3.47±1.8 ohm in group-B (*p*=0.001). Mean difference between basal and follow up platelet aggregation±SD was 52.97±24.8 group-A while it was 82.25±14.3 in group-B (*p*=0.001). Sixty-three (85.15%) of group-A had inhibition of platelets aggregation >10% as compare to 72(97.3%) of group-B; (*p*=0.009).

Table-1: Baseline characteristics of patients in group-A&B.

Baseline characteristics	Group-A, n=74(%)	Group-B, n=74(%)	*p*-value
Age±SD	54.9±11.2	57.7±8.7	0.09
Male	55 (74.3)	56 (75.7)	0.85
Female	19 (25.7)	18 (24.3)	0.85
Weight(Kg)	71.8±6.4	70.8±6.3	0.35

Table-2: Platelets aggregation inhibition in group-A & B.

Characteristics	Group-A	Group-B	*p*-value
Baseline platelet aggregation before drug administration±SD	10.43±1.9	10.12±2.2	0.36
Follow up platelet aggregation 6 hours after drug administration±SD	5.00±3.04	1.83±1.7	0.001
Percentage inhibition of platelet aggregation	52.9649±24.77	82.25±14.34	0.001
Efficacy (%)	63 (85.1)	72 (97.3)	0.009

DISCUSSION

This study demonstrated that prasugrel is a more effective antiplatelet agent as compared to clopidogrel in patients with stable coronary artery disease (CAD) undergoing elective percutaneous coronary intervention (PCI). In our study, the efficacy of prasugrel as an antiplatelet agent in patients with stable CAD undergoing elective PCI was 97% as compared to clopidogrel whose efficacy was 87% with a statistically significant p- value of 0.009.This study is in accordance with published literature. An evaluation of prasugrel vs. clopidogrel was done in the ThePrasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE-TIMI 44) study.[12] It was carried in patient with stable coronary disease undergoing elective PCI in which prasugrel was more efficacious antiplatelet agent as compared to clopidogrel; 74.8±13.0% Vs 31.8±21.1%; $p<0.0001$. In this study, 201 subjects were randomized to prasugrel and clopidogrel groups respectively. Baseline characteristics of patients were similar in both groups. Platelet aggregation inhibition was measured by light-transmission aggregometry (LTA) and vasodilator-stimulated phosphoprotein (VASP) in that study as against in our study in which chronolog whole blood aggregometry was used. In another study by Jernberg T *et al*., the response rate to prasugrel was 68.4% as compared to clopidogrel in which response rate was 30% with a p-value of $p<0.0001$.[13]This study also enrolled patients with stable coronary artery disease in which baseline characteristics were similar in both groups of patients. In another study by Dasbiswas A et al. the response rate to prasugrel loading dose in term of platelet aggregation inhibition was higher as compared to clopidogrel loading dose, 97.4% vs 87.6% respectively with a *p*-value=0.05.[11] However this study enrolled patients with acute coronary syndrome as against to our study in which patients with stable coronary artery disease was studied. In a sub study of TRITON-TIMI 38 trial, it was shown that that increased inhibition of platelets aggregation is associated with low incidence of adverse cardiovascular events.[10] in this study mean platelet aggregation (MPA) with ADP 20 mM was significantly lower in prasugrel- than in clopidogrel-treated subjects at both 1 and 2 h post-loading dose (46.5+7.7 vs. 73.7+1.5%, mean+SE, $p=0.004$). At 1 and 2 h post-loading dose, prasugrel also resulted in significantly lower follow up platelet aggregation (FPA) in response to ADP 20 mM and lower MPA and FPA in response to ADP 5 mM. These findings support our study in term of mean decrease in platelets aggregation after 6 hours of loading dose administration. The mean decrease in platelets aggregation inhibition was 52.97±24.8 for clopidogrel and 82.3± 14.3 for prasugrel in our study. This increase inhibition of platelet in our study may be because of that we have checked platelets inhibition after 6 hours as compared to that study in which they checked it just after 1–2 hours.

In our study percentage inhibition of platelet aggregation for prasugrel and clopidogrel were 82.3±14 and 52.9±24 respectively with a *p*-value of 0.001. The net difference of platelet inhibition between the two groups was 30%.This is also similar to other published studies. In a study by Wiviott SD *et al*. percentage inhibition of platelet aggregation for prasugrel and clopidogrel were 74.8±13.0% and 31.8±21.1% respectively with a net difference of 31.8±21.1% and p-value of $p<0.0001$.[14] In another study by Jernberg T *et al*. percentage inhibition of platelet aggregation for prasugrel and clopidogrel were 68.4 vs. 30.0%, respectively; $p<0.0001$.[13] However this study enrolled patients with acute coronary syndrome contrary to our study which consisted of patients with stable coronary artery disease. In a study done in India by Dasbiswas A *et al*. percentage inhibition of platelet aggregation for prasugrel was 82.5% and for clopidogrel it was 71.10% with a *p*-value 0.01.[11] This study also enrolled patients with acute coronary syndrome but study protocol was similar to our study in which loading dose of prasugrel and clopidogrel was evaluated. In a sub study of the TRITON TIMI 38 trail, Mean MPA with ADP 20 mM was significantly lower in prasugrel- than in clopidogrel-treated subjects at both 1 and 2 h post-loading dose (46.5+7.7 vs. 73.7+1.5%, mean+SE, $p=0.004$).[14] This low level of platelet inhibition in study as compared to our study can explained by the fact that platelet aggregation was measured after two hours of loading dose administration. In our study it was done after six hours as our patient population was having stable angina as compared to that study which enrolled patients with ACS. In a sub study of JUMBO trail, analysis of GPIIb/IIIa free patients suggested that loading with 60 mg prasugrel resulted in a rapid significant 80% platelet inhibition at four hours after coronary intervention as compared to clopidogrel with an IPA of 50-70%.[15]

CONCLUSION

Prasugrel is more efficacious than clopidogrel in term of inhibition of platelets aggregation

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