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CLOPIDOGREL VERSUS PRASUGREL IN PATIENTS UNDERGOING ELECTIVE PERCUTANEOUS CORONARY INTERVENTION

Shah Zeb[1], Ibrahim Shah[2], Mohammad Adil[3], Jabar Ali[4], Hikmatullah Jan[5], Adnan Mahmood Gul[6], Mohammad Hafizullah[7]

[1-6] Department of Cardiology Lady Reading Hospital Peshawar, Pakistan
[7] Khyber Medical University, Peshawar, Pakistan

Address for Correspondence:

Shah Zeb,

Department of Cardiology Lady Reading Hospital Peshawar, Pakistan

E-Mail:

drshahzeb.mohmand@yahoo.com

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Contribution
SZ, IS, MA concieved the idea, planned the study and drafted the manuscript. JA, HJ helped in acquisition of data and did statical analysis. AMG, MH drafted the manuscript and critically reviewed manuscript. All authors contributed significantly to the submitted manuscript.

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ABSTRACT

Objective: To compare short term clinical outcomes in patients on Clopidogrel and Prasugrel undergoing elective percutaneous coronary interventions.

Methodology: This comparative study was conducted in Department of Cardiology department, Postgraduate Medical Institute Govt. Lady Reading Hospital Peshawar from 1st June 2012 to 31st March 2013. Patients undergoing elective PCI for significant lesions on coronary angiography of both genders having weight ⩾ 60 Kg and baseline platelets aggregation as platelets aggregation of ⩾5 ohm. All patients were followed for 1 month.

Results: A total of 148 patients were included in the study. Group A had 74 patients using Clopidogrel and group B contained 74 patients using Prasugrel. Group A had 55 (74.3%) males while group B had 56 (75.7%) males (p=0.85). Mean age was 54.9±11.2 years in group A and 57.7±8.7 years in group B (p = 0.09). Mean percent difference between basal and follow up platelet aggregation was 52.96±24.77 ohm in group A and 82.25±14.34 ohm in group B (p= 0.001). At 01 month follow up 03 (4%) episodes of major bleeding occurred in Prasugrel group which led to discontinuation of the drug while minor bleeding episodes in 7 (9.5%) patients. There was NSTEMI ACS in 3 (4.1%) patients and STEMI in 01 (1.35%) in Clopidogrel group while 2 STEMI patients in Prasugrel group. Number of deaths were 2 in prasugrel group and 1 in clopidogrel group Composite of death, major bleeding, stroke, ACS was 7 (9.5%) in Prasugrel group and 6 (8%) in Clopidogrel group (p=0.09).

Conclusion: There is no short term clinical benefit of Prasugrel over Clopidogrel in elective percutaneous coronary intervention.

Key Words: Bleeding, Clopidogrel, Prasugrel, Percutaneous Coronary Intervention

INTRODUCTION

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. Antiplatelets should be given before PCI followed by maintenance therapy to decrease the mortality and morbidity due to stent thrombosis.[9] The action of both Clopidogrel and Prasugrel is related to an adenosine diphosphate (ADP) receptor on platelet cell membranes. Both drugs specifically and irreversibly inhibit P2Y12 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 CYP2C19 gene.[10] Unlike Clopidogrel, Prasugrel is not a prodrug so does not require extensive metabolism in liver and is not affected by CYP2C19 gene. Its antiplatelet effect is more optimal and consistent which is associated with improvement in mortality and morbidity.[9,10] 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.[11-13]

The rationale of the study was to know the effectiveness of Clopidogrel and Prasugrel in elective PCI in our local population. There are lots of differences in our and western population such as body mass index, ethnicity, CYP2C19 gene polymorphism on which the metabolism of these drug depend. Aim of this study was to evaluate short term clinical outcomes in patients receiving Prasugrel versus Clopidogrel after elective percutaneous coronary interventiont.

METHODOLOGY

This comparative study was conducted in Department of Cardiology, Lady Reading Hospital, Peshawar from 1st June 2012 to 31st March 2013. Sample size in each group was calculated using 95% proportion of efficacy of Prasugrel and 79% proportion of efficacy of Clopidogrel for platelet inhibition for elective PCI cases with 80% power of the test using WHO sample size calculator. Sample was collected by consecutive non probability sampling technique. Patients undergoing elective PCI were randomly allocated to two groups by lottery method. All patients undergoing elective PCI for demonstrable significant lesions on coronary angiography with stable angina with age ranging from 35-75 years, both genders having weight $\geqslant$ 60Kg. Patients with chronic renal failure and baseline platelets aggregation of $\geqslant$ 5 ohm chronic liver diseases and bleeding disorders were excluded. Hospital ethical committee approved the study. 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 coronary were included in the study. Major bleeding was defined as any intracranial bleeding (excluding microhemorrhages $<$10 mm evident only on gradient-echo MRI), clinically overt signs of hemorrhage associated with a drop in hemoglobin of $\geqslant$ 2 g/dL, fatal bleeding i.e. bleeding that directly results in death within 7 days and patients requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug).

Rest of bleeding episodes were defined as minor bleeding. A detailed informed consent was obtained. Baseline platelet activity was checked using Chronolog Whole-blood aggregometer model 591.Group A was given Clopidogrel 600mg loading dose 06 hours before PCI orally and then 75mg once daily. Group B was given 60mg of loading dose of Prasugrel 06 hours before PCI orally and continued as 10 mg once daily. Venous blood sample of 02cc was taken using 21gauge standard needle syringe after 06 hours of loading dose just before PCI. Platelets activity was checked again by the same operator and same chronolog aggregometer model 591. These patients were followed for 30 days. Patients above 75 years, weight less than 60kg, history of transient cerebrovascular events/ stroke, chronic liver disease, chronic renal disease, bleeding disorders, platelets less than one 100,000/uL were excluded.

All the detailed information was collected through a specially designed proforma with their contact numbers and address. All the patients were called after 2 weeks and then after one month of stent deployment. After one month data regarding all the variable i,e bleeding episodes, TIA/CVA, Stent thrombosis, STEMI, NSTEMI, angina episodes were collected. Stent thrombosis was defined as definite or confirmed event (symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis). Probable event (unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis)

All the data was analyzed using SPSS version 16. Mean $\pm$ standard deviation 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. $p<0.05$ 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. Of them group A had 74 patients using Clopidogrel and group B had 74 patients using Prasugrel. Group A had 55(74.3%) males while group B had 56(75.7%) males (p=0.85). Mean age was 54.9±11.2 years in group A and 57.7±8.7 years in group B (p = 0.009)as shown in Table 1.

Mean baseline platelet aggregation before drug administration ± SD was 10.43±1.9 ohm and 10.12±2.2 ohm (p=.36) in group 1 and 2 respectively. On follow up platelet aggregation 6 hours after drug administration was 5.00± 3.04 ohm in group 1 and 1.83±1.7 ohm in group 2 (p=0.001). Percent difference between basal and follow up platelet aggregation was 52.96±24.77 ohm in group A while it was 82.25±14.34 ohm in group B (p= 0.001). About 63(85.15%) of group A had inhibition of platelets aggregation > 10% as compared to 72 (97.3%) of group B (p = 0.009) (Table 2).

Hypertension was found in 23 (31.1%) in group A and 25(33.8%) patients in group B. Diabetes was present in 20(27%) in group A and 19(25.75) in Group B. Fourteen (18.9%) were smokers in Group A and 15 (20.3%) in group B. Family history of coronary artery disease was present in 8 (10.8%) in males and 10(13.5%) in females. There was past history of coronary artery disease in 9(12.2%) in group A and in 9(12.2%) in group B. Past history of CABG in 5(6.75%) patient in group A and 4(5.4%) in group B while patients lost to follow up were 04 and 05 in group A and group B respectively. Atrial fibrillation was present in 4(5.4%) and 3(4%) patients of Prasugrel and Clopidogrel groups respectively.

Statistical analysis was done for intention to treat basis. At 01 month follow up 3(4%) had episodes of major bleeding in Prasugrel group which led to discontinuation of the drug. While minor bleeding was found in 7(9.5%) patients. There was 1(1.35%) episode of major bleeding in Clopidogrel group. While 5(6.75%) patients had minor bleeding episode in Clopidogrel group. In Clopidogrel group NSTEMI ACS occurred in 3(4.1%) patients and STEMI in 01(1.35%) and 2(2.7%) patients had NSTEMI ACS in Prasugrel group. There were 2(2.7%) all cause deaths in Prasugrel and 1(1.35%) in Clopidogrel group. There was no peri procedurel myocardial infarction in Prasugrel group while one occurred in Clopidogrel group. There was 1 perforation in Prasugrel group which led to pericardial tamponade treated with drainage, FFPs and platelets concentrate transfusion with anticoagulation reversal. There was 1 intracranial hemorrhage in Prasugrel group .The composite of death, CVA, ACS, stent thrombosis was 7(9.5%) in Prasugrel and 6(8%) in Clopidogrel group (p=0.09). There was no episode of ischemic CVA in any group (Table 3).

DISCUSSION

This study demonstrated that Prasugrel causes more platelets aggregation inhibition 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 in patients with stable CAD undergoing elective PCI was 97% as compared to Clopidogrel which was 87%(p v = 0.009). An evaluation of Prasugrel vs. Clopidogrel was done in the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation (PRINCIPLE-TIMI 44) study.[15] It was carried out on 201 subjects with stable CAD, who were randomized to Prasugrel and Clopidogrel groups respectively undergoing elective PCI. Prasugrel was found as more efficacious antiplatelet agent as compared to Clopidogrel; 74.8±13.0% Vs. 31.8±21.1%; (p<0.0001). In study by Jernberg T et al, the response rate to Prasugrel was 68.4% as compared to Clopidogrel in which response rate was 30%(p<0.0001).[16] This study enrolled patients with stable coronary artery disease. In a study 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 (p=0.05).[17] In this study enrolled patients with acute coronary syndrome however in 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.[18] 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%, 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

Table 1: Demographic Characteristics of Patients in Group A&B

Baseline Characteristics	Group A, n=74(%)	Group B, n=74(%)	P-value
Age (mean±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 (mean±SD)	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

Clopidogrel and 82.3±14.3 for Prasugrel in our study. This difference occurred because we 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 (p=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 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<0.0001.[15] 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).[16] 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 p-value 0.01.[17] 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).[18] This low level of platelet inhibition in study as compared to our study can be 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%.[19]

Table 3: Adverse Outcome Clopidogrel Vs. Prasugrel

Variables	GroupA n (%)	Group B n (%)	P-value
Major bleeding	1(1.35%)	3(4%)	0.09
Minor bleeding	5(6.75%)	7(9.5%)	
All cause Death	1(1.35%)	2(2.7%)	
ACS	3(4%)	2(2.7%)	
Acute stent thrombosis(STEMI)	1(1.35%)	0	
Hemorrhagic CVA	0	1(1.35%)	

Prasugrel is a third-generation thienopyridine which has been recently approved for use. It has a more favorable pharmacokinetic and metabolic profile compared to Clopidogrel.[20] Like Clopidogrel, Prasugrel is an inactive pro-drug that requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite with an antiplatelet effect equivalent to that of Clopidogrel.[21,22] However, compared with Clopidogrel which is activated in a two-step process, Prasugrel is more efficiently transformed into its active metabolite (reactive thiol group) in a single-step process.[21,22] Thus, Prasugrel produces a better and more potent blockade of the P2Y12 receptors demonstrated by a faster, more potent and more predictable platelet inhibition observed in pharmacodynamic studies comparing Prasugrel versus high dose Clopidogrel.[20] In general, platelet inhibition occurs 30 minutes after an oral loading dose of 60 mg Prasugrel, with the maximum inhibition seen at 2-4 hours.[15,16] Revista, Candiello et al, confirmed greater platelet inhibition in patients receiving a loading dose of 60 mg Prasugrel compared with Clopidogrel in a population of 83 consecutive and stable patients after successful PCI.[23] This was demonstrated by the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) - TIMI (Thrombolysis in Myocardial Infarction) trial, which reported a significant reduction in death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[9]

In our study, age was similar between two groups of patients. Mean age in Prasugrel and Clopidogrel groups was 54±11 and 57±8 years respectively (p= 0.09). The age of our study patients was comparable to other studies done on this subject. In a study by Wiviott SD et al, the mean age in Prasugrel and Clopidogrel arms was 64 and 63.8 years respectively. The relatively younger age in our study subjects is because of the fact that coronary artery disease occur at younger age in Asian people. In the JUMBO sub study which was carried out on the efficacy of Prasugrel and Clopidogrel, the mean age in Clopidogrel and Prasugrel was 63.8 and 64.3 respectively.[19] At present, no prospective randomized studies have demonstrated benefits of using a

more potent alternative antiplatelet regimen (such as higher-dose Clopidogrel, Prasugrel, or ticagrelor) for patients with stable CAD PCI patients identified at increased risk for events on Clopidogrel by either a polymorphism in CYP2C19 or high on-treatment residual platelet reactivity. In fact, the first such randomized trial to examine this hypothesis was GRAVITAS trail which reported no benefit of doubling the standard daily dose of Clopidogrel (from 75 to 150 mg per day) after PCI in patients with high on-treatment platelet reactivity.[25] Importantly, after successful DES implantation in this study cohort, the 6-month composite rate of cardiovascular death, MI, or stent thrombosis was low in both groups (2.3% at 6 months) despite higher on-treatment platelet reactivity with standard-dose Clopidogrel. This study supports our study that no overall benefit of Prasugrel over Clopidogrel in term of composite of death, MI, stent thrombosis or major bleeding.

Similarly no benefits occur in case of stable coronary artery disease of Prasugrel over Clopidogrel. In TRITON-TIMI 38 Prasugrel was tested against Clopidogrel for a duration of 15 months in combination with aspirin in both ST elevation myocardial infarction (STEMI) and NSTE-ACS. The objective of the trial was to assess the benefit-risk balance of switching from Clopidogrel to a more potent platelet inhibitor -Prasugrel, in a population of invasively-treated patients only. Prasugrel therapy was associated with significantly reduced rates of cardiovascular death/myocardial infarction/stroke, (9.9% vs12.1%; RR 0.81; $P < 0.001$) and also stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding (0.4% vs 0.1%; RR 4.19;$P < 0.002$).[24] This study does not support our findings because they included only ACS patients, but we included patients with stable coronary disease patients here. In TRIOLOGY ACS study Prasugrel had no benefit over Clopidogrel in terms of primary outcomes in ACS patients treated noninvasively. They support our findings but these patients did not undergo PCI.[24]

CONCLUSION

There are no short term clinical benefits of Prasugrel over Clopidogrel in patients undergoing elective percutaneous coronary intervention with stable coronary artery disease. Further studies are required in STEMI and NSTEMI patients to look for Prasugrel effect in this group of patients besides looking at long term effects in stable CAD patients.

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