Comparison of P2Y12 receptor inhibition by clopidogrel and prasugrel in patients undergoing percutaneous coronary intervention

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Abstract

Dual antiplatelet treatment (DAPT) with aspirin and clopidogrel is vital after percutaneous coronary intervention (PCI). Clopidogrel and prasugrel act on P2Y12 platelet surface receptors. Both these P2Y12 inhibitors are pro-drugs and depend on cytochrome system of the liver for their conversion to active metabolite. There is growing concern regarding suboptimal response in platelet inhibition by clopidogrel. Verify Now system got approval by Federal Drug Administration, USA, for assessing platelet function as its result is almost comparable to gold standard Light Transmission Aggregometry (LTA). There are no data on the prevalence of clopidogrel resistance in Bangladeshi population. Prasugrel, as an antiplatelet drug, is a newer introduction in this country. This study will show light on the efficacy of these drugs on our population especially in patients who undergo PCI where DAPT is mandatory. A total 120 (60 diabetics) patients with Acute Coronary Syndrome (ACS), were alternatively given 600 mg clopidogrel loading dose (LD) followed by 75 mg maintenance dose (MD) daily or 60 mg LD of prasugrel followed by 10 mg MD daily. Five samples of blood were taken at different time intervals over a period of 2 weeks. Measurement of percent inhibition of P2Y12 was done by VerifyNow. Patients who showed less than 20% inhibition (clopidogrel resistant) at any stage were switched to prasugrel. The outcomes of clopidogrel, prasugrel and clopidogrel switched to prasugrel groups were then compared. Nearly half (46.7%) of the patients in the clopidogrel group was found resistant to the drug as opposed to none in the prasugrel group. No difference was found between diabetic and non-diabetic subjects with respect to drug resistance. Intracoronary blood samples showed high degree of platelet inhibition with prasugrel. There was a gradual decline of platelet inhibition over two weeks with prasugrel. Almost fifty percent of the population is clopidogrel resistant in our study. Prasugrel is a much more potent antiplatelet drug and should be preferred in patients undergoing PCI. Prasugrel may also show resistance over time.

Introduction

Platelet inhibition occurs by a number of mechanisms (Fig A). Aspirin acts intracelluarly by inhibiting cyclooxygenase pathway. Most important platelet surface receptors are P2Y12 and Glycoprotein IIbIIIa (GPIIbIIIa). P2Y12 inhibitors are available as oral form and GPIIbIIIa inhibitors are available as parenteral form.

There are a number of P2Y12 receptor inhibitors like clopidogrel, prasugrel and ticagrelol. Both clopidogrel and prasugrel are pro drugs, require metabolism by cytochrome system of liver and binds irreversibly to platelet surface P2Y12 receptor. Ticagrelol is not a prodrug and does not require conversion to active form and reversibly binds with the receptor. Dual antiplatelet treatment (DAPT) with aspirin and clopidogrel is currently recommended in patients undergoing PCI[1]. Despite important clinical benefits of clopidogrel, significant limitations exist[2]. Even with the use of such therapy, a substantial number of subsequent ischemic events may occur[3,4]. Besides, there is interindividual variability in the response to clopidogrel[5,6]. Subjects with suboptimal platelet inhibition by clopidogrel are at increased risk of cardiovascular ischemic events, particularly after PCI[6-9] .The mechanisms leading to a poor response to clopidogrel have not yet been fully elucidated and are most likely multifactorial. In addition to

lack of compliance, clinical factors, such as, diabetes, obesity, insulin resistance, food habit concomitant use of other drugs especially proton pump inhibitors and the nature of the coronary events may contribute to the variability of the clopidogrel response[10]. There is ample evidence that response to clopidogrel is also influenced by pharmacokinetic variables such as intestinal absorption and metabolic activation in the liver, both of which, in turn, are affected by genetic polymorphisms[11-13]. Patients with type 2 diabetes mellitus (T2DM) are characterized by enhanced platelet reactivity and reduced *in vitro* responsiveness to antiplatelet agents. Recent studies have shown that T2DM patients have reduced response to P2Y12 receptor antagonists compared with nondiabetic subjects[6,14].

Studies of higher loading doses (LDs) and maintenance doses (MDs) of clopidogrel have reported small but statistically significant improvements in the speed of onset, intensity, and consistency of inhibition[6,15-17]. Although there are limited prospective data to support clinical superiority[18,19], many clinicians use higher doses of clopidogrel in clinical practice, and recent guidelines support this practice in selected patients[20,21]. As P2Y12 receptor plays a pivotal role in platelet aggregation, poor platelet response to clopidogrel may be overcome by the use of more potent P2Y12 antagonists or higher doses of clopidogrel[22].

Many laboratory tests are available to measure platelet function. LTA is still considered the gold standard for assessing platelet function; however it is difficult to set up for common clinical use. The trade names of the tests which are CE marked & FDA approved are Aggregometry, PFA-100, Verify Now, Plateletworks, Platelet Mapping and Aspirinworks. These tests are performed on whole blood samples and designed for point-of-care testing to provide rapid results[23]. The VerifyNow System (Accumetrics Inc, San Diego, Calif) is a point-of-care turbidimetry-based optical detection system that measures platelet-induced aggregation[24]. The VerifyNow P2Y12 assay has been well correlated with ADP-induced platelet aggregation by LTA[25-27]. This system measures platelet-induced aggregation as an increase in light transmittance and uses a proprietary algorithm to report values in P2Y12 reaction units (PRU) and also as percent inhibition. A higher PRU or a lower percent inhibition connotes the same meaning – the lesser inhibition of platelet. PRU value above 208 and percent inhibition less than 20% is considered as suboptimal response or resistance[28-30]. The present study was intended to compare the impact of a LD and MD dose of clopidogrel and prasugrel in inducing platelet inhibition in high risk ACS patients undergoing PCI.

Materials and Methods

The present prospective comparative clinical study was conducted in the Department of Cardiology, Ibrahim Cardiac Hospital & Research Institute (ICHRI), Dhaka from January 2012. All adult ACS patients (≥18 years) with TIMI (Thrombolysis In Myocardial Infarction) score 3 or more and willing to undergo PCI (if needed) were eligible to participate in the study. Patients of ACS with platelet count < 150,000/cu-mm or at high risk of bleeding following LD of clopidogrel or prasugrel or suffering from chronic renal failure (serum creatinine > 2 mg/dl) or patients getting prasugrel were excluded from the study.

Blood samples were collected before giving LD of clopidogrel or prasugrel and were kept for maximum of 4 hours (as blood samples kept for more than 4 hours are not recommended for P2Y12 assay) at ICHRI Laboratory. TIMI score was calculated from the following factors, each having score of '1': a) age ≥65 years, b) ≥3 risk factors for coronary artery disease (CAD) (family history of CAD, hypertension, hypercholesterolemia, diabetes, or current smoker), c) known CAD (stenosis ≥50%) d) aspirin use in last 7 days, e) severe angina (≥2 episodes within last 24 hours) f) ST change (≥0.5 mm) in ECG and g) positive cardiac marker. Written consent was obtained from each study subjects who voluntarily participated in the study. The study commenced on obtaining approval from the Ethical Review Committee of Ibrahim Cardiac Hospital & Research Institute.

Based on predefined eligibility criteria, a total 188 patients were initially selected and were given either 600 mg clopidogrel or 60 mg of prasugrel as LD irrespective of their previous intake of clopidogrel. Of the 188 patients 39 underwent coronary artery bypass graft (CABG), 14 refused PCI and 15 withdrew themselves from the study leaving 120 to finally participate in the study. Of the 120 subjects included in the study, 60 were initially assigned to clopidogrel (30 diabetic) and 60 to prasugrel group (30 diabetic). According to study protocol the subjects who exhibited clopidogrel resistance at any stage of the study, were switched to prasugrel, and was treated as another group. Thus, the study subjects finally formed three groups-clopidogrel group (n=23), clopidogrel to prasugrel group (n=37) and prasugrel group (n=60). All the baseline characteristics and

outcomes were then compared among the three groups. Blood samples from all patients were collected for Troponin-I, blood glucose, HbA1c, S. creatinine, S. electrolytes levels. All patients received aspirin as well. Platelet reactivity was evaluated by the Verify Now P2Y12 assay before LD (1st sample), 6-24 hours after LD of clopidogrel or prasugrel – just before PCI (2nd sample), during PCI (3rd sample from coronary blood after balloon dilatation), 24 hours after PCI (4th sample) and 2 weeks after PCI (5th sample). A cut-off value of <20% platelet inhibition was considered as resistance. Results were expressed as percent inhibition of P2Y12. Clopidogrel resistant patients were again subdivided into three categories as 0% inhibition, 1 to <10% and 10 to <20% inhibition. Statistical analysis was done comparing percent inhibition values among clopidogrel, clopidogrel switched to prasugrel and prasugrel groups.

Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA), version 16. The test statistics used to analyze the data were Chi-square (χ^2) or Fisher's Exact Probability Test, McNemer χ^2 Test, Student's t-Test and Paired-sample t-Test. The data presented on categorical scale were compared between groups using Chi-square (χ^2) or Fisher's Exact Test and within group before and after intervention using McNemer χ^2 Test, while the data presented on continuous scale were compared among the groups using one-way ANOVA and Repeated Measure ANOVA and were expressed as mean or standard error of mean (SEM). Level of significance was set at 0.05 and p<0.05 was considered significant. The findings obtained from data analysis are documented below.

Results

Baseline demographic and clinical characteristics of the study subjects are shown in Table I. The subjects in the clopidogrel and clopidogrel switched to prasugrel groups were somewhat older compared to those of prasugrel group. However, prasugrel group had more male (91.6%) than clopidogrel group (82.6%) and clopidogrel to prasugrel group (75.7%). While the BMI was almost identical among the three groups, diabetic subjects were higher in clopidogrel group (56.5%) than those in prasugrel (50.0%) and clopidogrel switched to prasugrel group (45.9%). However, prevalence of hypertension was higher in the latter two groups than the clopidogrel group. The distributions of TIMI score and HbA1C were almost similar among the three groups. The

incidences of unstable angina and LVF were observed to be higher in the switched group compared to clopidogrel and prasugrel group.

**Table I:** Baseline clinical and laboratory chracteristics

Variables	Group			p-value
	Clopidogrel (n=23)	Clopidogrel switched to Prasugrel (n=37)	Prasugrel (n=60)	
Age* (years)	55.09±11.09	56.92±11.26	50.78±8.66	0.312
BMI* (kg/m²)	24.30±4.25	25.10±2.89	25.91±3.54	0.830
Male#	19(82.6)	28 (75.7)	55 (91.6)	0.095
Diabetes#	13 (56.5)	17 (45.9)	30 (50.0)	0.728
Hypertension#	11 (47.8)	25 (67.6)	40 (66.7)	0.228
TIMI score*	3.61±0.722	3.97±0.96	3.92 0.99	0.794
HbA1C*	8.03±3.17	7.13±1.34	7.79 2.36	0.651
ACS Type#				
UA	10 (43.5)	18 (48.66)	24 (40.0)	0.706
NSTEMI	13 (56.5)	19 (51.4)	36 (60.0)	
LVF#	1 (4.3)	3 (8.1)	2 (3.3)	0.570

Figures in the parentheses denote corresponding percentage.
*Data were analysed using ANOVA statistics and were presented as mean ± SD.
#Data were analysed using Chi-square (χ2) Test.

Nearly half (46.7%) of the patients had <20% platelet inhibition of platelet measured after 6–24 hours of 600 mg loading dose of clopidogrel. Among the resistant or suboptimal responders, 26.7% showed 0% inhibition, 16.7% showed 1 to <10% and 3.3% 10 to <20% inhibition (Fig. 1). There was no resistance in the prasugrel group.

Fig 2 compares the percentage inhibition of P2Y12 among the three study groups at five different time intervals. Before loading dose the mean inhibition of P2Y12 in clopidogrel group was 33.17%, in prasugrel group was 19.18% and clopidogrel switched to prasugrel group was 5.08%. The degree of inhibition 6–24 hours after LD was 53.74%, 86.8% and 17.43%, in the three groups respectively. The 3rd sample taken from coronary artery after balloon dilatation before PCI showed reduced percentage inhibition of P2Y12 in all the three groups (27.26%, 60.90% and 6.14% in clopidogrel, prasugrel and clopidogrel to prasugrel groups respectively). The percentage inhibition of P2Y12 following PCI (after 24 hours of PCI) was observed to increase again to 56.13%, 87.98% and 55.89% in clopidogrel, prasugrel and clopidogrel to prasugrel groups respectively, but the increase was significantly steeper in clopidogrel switched to prasugrel group than was observed in clopidogrel and prasugrel groups (p<0.001). In the next 2 weeks following PCI percentage inhibition of P2Y12 decreased in all the three groups, but it was more so in the prasugrel group than in the other two groups (p<0.001). There were significant differences in P2Y12 inhibition in the three groups in all the five samples of blood collected over a period of two weeks (Table II).
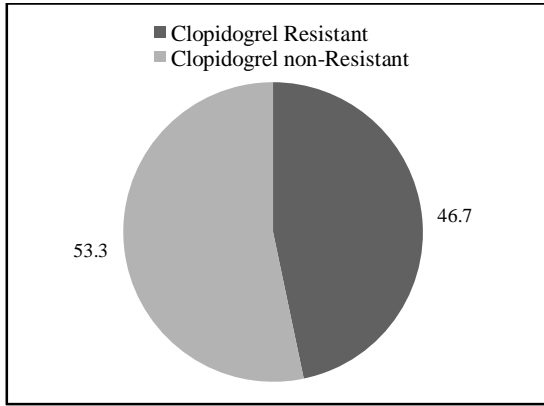
Fig 1: Clopidogrel resistance (<20% inhibition by VerifyNow) measured 2-24 hours after 600 mg of clopidogrel LD
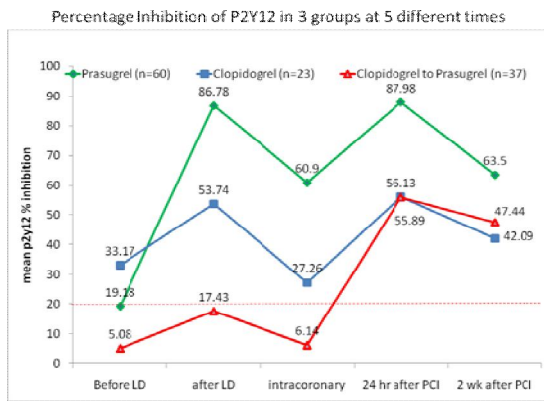
Fig. 2 Platelet Inhibition by clopidogrel, prasugrel and clopidogrel switched to prasugrel before LD, 6-24 Hr after LD and in intracoronary blood after balloon dilation and 2 weeks after PCI

Table II: Comparison platelet inhibition activities at different time intervals before and intervention anteplatelet drugs

P2Y12 % inhibition*	Group			p-value
	Clopidogrel (n=23)	Clopidogrel switched to Prasugrel (n=37)	Prasugrel (n=60)	
Before LD	33.17±3.92	5.08±1.14	19.18±2.89	<0.001
After LD	53.74±5.88	17.43±3.58	86.78±2.47	<0.001
Intracoronary	27.26±5.53	6.14±2.58	60.90±2.81	<0.001
24-hours after PCI	56.13±5.58	55.89±5.53	87.98±1.47	<0.001
2 weeks after PCI	42.09±4.68	47.44±5.24	63.50±3.43	0.002

* Data were analysed using ANOVA statistics and were presented as mean ± SEM.

Discussion

Risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization at 14 days is 13.2% and 19.9% if TIMI score is 3 or 4 respectively[31]. The sampled patients who were randomly assigned to clopidogrel and prasugrel had mean TIMI score of more than 3, implying that all these patients were at high risk. Clopidogrel resistance has been reported worldwide and varies from country to country and even between study to study within country. The resistance is reported to be high in Asians (>55%)

(because of high genetic polymorphism of the enzyme responsible for conversion of clopidogrel to its active metabolite), compared to that in Whites (30%) and Blacks (40%)[32].

Lee et al reported that the rate of clopidogrel resistance defined as a % inhibition <40% was 42.9%[33]. Malinin et al reported that 21% of the participants had % inhibition <30%[24]. Shim et al reported that the rate of clopidogrel resistance (defined as a percent inhibition <20%) was 40%.[28] Godino et al reported that the rate of clopidogrel resistance defined as a % inhibition of ≤15% was 21%[34]. The wide variation is also partly because of the difference between investigators' options regarding the cut-off value which should be considered as suboptimal and also because of the different time interval taken between drug intake and measurement of blood samples. In our study we took <20% inhibition as suboptimal or resistant. The data derived from the analysis showed that nearly half (46.7%) of the patients did not achieve 20% platelet inhibition 6 to 24 hour after 600 mg of LD of clopidogrel. A total of 37 (61.7%) patients were switched to prasugrel by the investigators at different stages during the two week study period due to suboptimal response. Switching to prasugrel from clopidogrel was done mostly after suboptimal response after LD (46.7%) and the rest (15%) after the 4th sample i.e. 24 hours after PCI. If we considered the whole study period of two weeks then clopidogrel resistance is much higher (61.7%) compared to any other studies.

Before LD, the mean inhibition of P2Y12 in clopidogrel, prasugrel and clopidogrel switched to prasugrel groups were 33.1, 19.1 and 5.08% respectively. This was observed because most of the patients were referred to this tertiary care hospital with preloaded clopidogrel. The 3rd sample taken from target coronary artery after balloon inflation showed reduced inhibition in all the three groups which was expected as plaque disruption causes high thrombogenic environment due to activation of platelets.

However, 24 hours after PCI platelet inhibition increased in all 3 groups but the increase was significantly steeper in clopidogrel switched to prasugrel group than was observed in clopidogrel and prasugrel groups (p < 0.001). In the subsequent 2 weeks following PCI percentage inhibition of P2Y12 decreased in all the three groups, but the decrease was significantly faster in the prasugrel group than in the two other groups (p<0.001). Overall evaluation reveals that prasugrel group exhibited significant improvement from its 19.1% P2Y12 inhibition at baseline to 63.5% at end-point of the study, while the clopidogrel group did not

show any commendable improvement in P2Y12 inhibition activity during the same period (from 33.1% to 42.1%). Clopidogrel switched to prasugrel group, although initially had attenuated P2Y12 inhibition activity, showed dramatic improvement when switched to prasugrel group indicating that clopidogrel-resistant patients are not resistant to prasugrel. However, steady declining trend of P2Y12 inhibition activity in prasugrel group during the 2 weeks period after PCI indicates that, at time, prasugrel group may develop resistance.

Consistent with the findings of the present study, Wiviott and colleagues demonstrated that PCI patients loading with 60 mg prasugrel resulted in greater platelet inhibition than a 600-mg clopidogrel loading dose. Previous reports have shown that suboptimal clopidogrel responsiveness poses considerable risk of ischemic events.[35] Loading dose (600 mg) have been proposed as a strategy to accelerate and enhance platelet inhibition compared with a standard loading dose of 300 mg and improve short-term clinical outcomes compared with standard clopidogrel therapy.[17,36] However, findings of the present study show that antiplatelet effects of even 600 mg of clopidogrel loading-dose are not enough in achieving desired therapeutic effect in about half of the patients undergoing PCI where DAPT drugs are essential in preventing stent thrombosis. In addition patients who are suboptimal responders to clopidogrel show high thrombogenic milieu (low p2y12 activity) inside the coronary artery after balloon dilation compared to prasugrel as revealed in the study of the 3rd sample.

As patients rely on their daily maintenance dose of DAPT consisting of aspirin and clopidogrel for prevention of stent thrombosis, present guidelines are emphasizing the role of prasugrel to be superior. Caution should be exercised to prescribe clopidogrel alone in patients who cannot tolerate aspirin as many patients are clopidogrel non-responders. Our study reveals that improvements in platelet inhibition are transient and confined to the period of high doses of clopidogrel therapy and therefore, long-term maintenance strategy with standard recommended doses seems to be suboptimal in most patients. This is also true for prasugrel, as was evident from the data of percent inhibition of P2Y12 after 24 hours (87.9%) and 2 weeks of PCI (63.5%).

P2Y12 inhibitor antiplatelet drugs have been used for over 15 years for the prevention of coronary stent thrombosis in patients undergoing percutaneous coronary intervention with stent placement. Now, Prasugrel is available in our country. Ticagrelol and other P2Y12 inhibitor drugs are available in other countries. Although prasugrel is similar to clopidogrel, it is about 10 times more potent and has a quicker onset of action. Data from the largest trial comparing clopidogrel and prasugrel indicate that this increased potency and quicker onset of prasugrel equate to a reduction in major adverse cardiovascular events, although higher rates of major bleeding were reported. Prasugrel also differs from clopidogrel in that it may be less prone to drug-drug interactions and patient non-responsiveness, although further research is needed in both of these areas. Overall, the data suggest that prasugrel might be a promising treatment option for patients with acute coronary syndromes who are undergoing percutaneous coronary interventions.[37]

Conclusion: From the findings of the study and discussion thereof it can be concluded that in patients of ACS loading dose of prasugrel cause substantial inhibition of platelet function compared to clopidogrel. Clopidogrel resistance was found in nearly fifty percent of the patients. Suboptimal responders after clopidogrel show a staggering improvement in platelet inhibition after switching to prasugrel, indicating that clopidogrel-resistant patients well-responds to prasugrel. Platelet activity inside the coronary artery after balloon dilatation increases due to disruption of plaque causing high thrombogenic milieu where prasugrel is much more superior compared to clopidogrel. The level of inhibition of platelet function by prasugrel gradually decreases over a period of two weeks which raises concern whether long term therapy with prasugrel will lead to a state of suboptimal response. Study on a larger population along with identification of genetic polymorphism of cytochrome enzymes is thought to be necessary to answer these questions.

Acknowledgement

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