

ORIGINAL ARTICLE

A Comparative Study of Safety and Efficacy of Clopidogrel and Prasugrel in Reducing Major Adverse Cardiovascular Events after Percutaneous Coronary Intervention

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ABSTRACT

Background: Elective PCI involves a lot of patient preparation particularly regarding the modulation of platelet and coagulation function in the periprocedural period. Clopidogrel, when added to aspirin, has demonstrated considerable success at reducing thrombotic complications of acute coronary syndrome (ACS) and/or percutaneous coronary intervention (PCI) compared to aspirin alone. Whereas prasugrel is a novel antiplatelet agent that recently received Food and Drug Administration (FDA) approval for the treatment of patients with ACS undergoing PCI.

Objective: Comparison of efficacy and safety of clopidogrel and prasugrel in reducing MACE (major adverse cardiovascular events) after PCI. **Methods:** The study was a parallel group, randomized, controlled single blinded, unicentric study. The study was conducted between January 2021 and June 2022, in the Cardiac Catheterization Lab of Department of Cardiology, ICVS, R G Kar Medical College and Hospital, West Bengal, India. In this study, consecutive adult patients, >20 years of age, of both sexes, undergoing elective PCI at the Cath Labs of Department of Cardiology, fulfilling the inclusion criteria within the specified period of time were evaluated.

Results and Conclusion: Prasugrel is more effective than clopidogrel in preventing complications of PCI. It has significantly better favorable outcomes of PCI than clopidogrel. Prasugrel use results in more adverse events in PCI than clopidogrel, but the adverse events are minor in nature.

Keywords: Clopidogrel, prasugrel, major adverse cardiovascular events, percutaneous coronary intervention

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INTRODUCTION

The widespread availability of percutaneous coronary intervention (PCI) capable centers across most cities in India has led to an exponential growth of PCI volumes and it has become the most performed cardiac therapeutic procedure all over the world. In India, the twin epidemics of diabetes and hypertension has led to an alarmingly high

prevalence of coronary artery disease (CAD) even among the socially disadvantaged population and PCI offers an acceptable and effective therapy for millions with ischemic heart disease (IHD) both in terms of reduction of mortality and morbidity. 300-600mg loading dose of clopidogrel is usually administered 2-6 hours before the procedure along with 325mg of aspirin. Up to 100 IU/kg

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of UFH are given i.v. during the procedure with monitoring of ACT¹.

Antiplatelet therapy should be optimized in the treatment of vascular disease as platelets play an important role in cardiovascular disease both in the pathogenesis of atherosclerosis and in the development of acute thrombotic events¹. Thus, antiplatelets are the mainstay of treatment for patients with acute coronary syndrome (ACS) who have undergone percutaneous coronary intervention (PCI)².

Aspirin has long been used as antiplatelet drug in vascular disease. Clopidogrel, when used as combination drug with Aspirin, has shown promise in reducing thrombotic complications of ACS and/or PCI compared to Aspirin alone³. Despite clopidogrel's efficacy in preventing myocardial infarction (MI), Stroke or mortality in patients with ACS it has several shortcomings that reduce its clinical effectiveness, such as delayed onset of action, lesser inhibition of platelets and significant variation in patients' responses⁴. Both the efficacy and shortcomings of Clopidogrel has escalated the need for similar but superior antiplatelet drugs.

Prasugrel is a newer antiplatelet that has recently been used for the treatment of patients with ACS undergoing PCI. In preclinical studies, it is found to be more potent and to have faster onset of action than clopidogrel. Prasugrel showed increased inhibition of platelet aggregation than 75 mg of clopidogrel. There is also evidence that thienopyridine resistance is less in case of prasugrel than clopidogrel. These factors prompted the need in evaluating the effects of prasugrel for the prevention of thrombotic events after PCI.⁵⁻⁷

Therefore, we proposed a study to compare efficacy and safety of clopidogrel and prasugrel in reducing major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI).

METHODS

The study was a parallel group, randomized, controlled single blinded, single-centre study. The study was conducted between January 2021 and June 2022. The study subject's screening and recruitment was carried out at the Cardiology indoor patients' department of R.G Kar Medical College. Preparatory groundwork, data analysis was carried out at the Department

of Pharmacology, R.G Kar Medical College, West Bengal India. Sample size calculation yielded 50 subjects in each group. Expecting 10% dropout the total subjects to be recruited would be approximately 60 subjects in each group. In the study 57 subjects received Prasugrel and 60 subjects received Clopidogrel.

Screening for subject eligibility was performed on the very first visit, based upon the following criteria.

Inclusion Criteria:

All patients of acute coronary syndrome who

- i. Were man or non-pregnant woman of 20-65 years of age.
- ii. Who have undergone elective or urgent PCI with intended coronary stenting.
- iii. Had a native target coronary artery stenosis >70 % (by visual Estimation) and to be amenable to stenting by operator with approved Coronary stents. (Multi lesion or multi vessel stenting is acceptable if all lesions were treated in a single staged procedure).

Exclusion Criteria:

- i. ST segment elevation myocardial infarction who underwent Pharmacological thrombolysis with in last 24 hours.
- ii. Target lesion in a saphenous vein graft or arterial conduit graft.
- iii. Stenosis of coronary artery <70% (by visual estimation of the operator)
- iv. Bleeding risk like history of bleeding diathesis, recent major surgery significant trauma.
- v. Stroke within last 2 years/ intracranial neoplasm. History of cerebrovascular disease.
- vi. Uncontrolled And severe hypertension.
- vii. History of oral anticoagulant drug intake or any anti platelet drug for last 10 days.
- viii. Any investigational drug /device with in previous 30 days.

Parameters Studied:

1. **Safety parameters-** Major or minor bleeding

according to the TIMI classification scale

a. Major bleeding-

Bleeding that causes hemodynamic compromise requiring specific treatment; Bleeding that requires urgent intervention; Clinically acute bleeding, requiring transfusion of >1.1 U of packed red cells or whole blood; bleeding, causing a decrease in hemoglobin of ≥ 3 g/dl.

b. Minor bleeding-

Hematuria without trauma (e.g., from instrumentation). Prolonged or repeated episodes of epistaxis. Gastrointestinal Hemorrhage; Hemophysis; Subconjunctival hemorrhage; Hematoma >5 cm or leading to Prolonged or new hospital stays; bleeding, causing a decrease in hemoglobin of 2 to 3 .

2. Efficacy parameters:

a. Primary end points: Cardiovascular death, non fatal Myocardial Infarction, and non fatal Stroke.

b. Secondary end points: Clinically suspected stent thrombosis, complication rates including slow flow, arrhythmias, and access site complications.

All patients admitted with ACS were screened for study. The patients were managed according to guidelines given by NYHA (New York Heart Association). The patients were included in trial provided inclusion criteria were satisfied. The patients were given either with 300 mg of clopidogrel 8 hours before or 60 mg prasugrel 30 minutes before of PCI as a loading dose. After that angiography was done to document stenosing lesion in coronary artery and if present, whether stentable or not. If the lesion was stentable then stenting was done with either with drug eluting stent or bare metal stent. After that the group that was loaded with clopidogrel was maintained on 75 mg/ day of clopidogrel and that was loaded with prasugrel was maintained on 10 mg/ day of prasugrel. The patients were evaluated for efficacy and safety parameters on day 1, day 2, day 7, day 30 and 6 months of stenting or as necessary. All the data collected were entered in MS-Excel and

analyzed by appropriate statistical methods using EPI INFO 7 statistical software.

RESULTS

A total of 57 patients were administered prasugrel (group a) and 60 patients were given clopidogrel (group b) before elective PCI. Patients were randomly allocated to either group using standard randomization tables. The median age of patients in either group was 56 years, and a majority of the patients were in the 5th and 6th decades. Patients aged >65 years were excluded from the study by prior exclusion criteria. There was no difference in between the 2 groups in terms of average age at entry and age distribution of the patients (Table 1). Sex distribution of the patients was expectedly overwhelmingly in favour of males with 14.03% patients in prasugrel group and 21.6% in clopidogrel group being females. However, there was no significant difference between groups (Table 2).

TIMI Risk Score:

TIMI risk score is a prognostication scheme that categorizes a patient's risk of death and ischemic events in patients with UA/NSTEMI, and thereby helping therapeutic decision making.

TIMI Score Calculation (1 point for each):

- Age > 65
- Aspirin use in the last 7 days (patient experiences chest pain despite ASA use in past 7days)
- At least 2 angina episodes within the last 24hrs
- ST elevation of at least 0.5mm on admission
- Elevated levels of cardiac biomarkers
- Known cases of Coronary Artery Disease (CAD) (coronary stenosis $\geq 50\%$)
- At least 3 risk factors for CAD, such as: Hypertension $\rightarrow 140/90$ or on antihypertensive, positive history of smoking, hypercholesterolemia, diabetes mellitus, and Family history of CAD

Score Interpretation:

- Score of 0-1 = 4.7% risk
- Score of 2 = 8.3% risk
- Score of 3 = 13.2% risk
- Score of 4 = 19.9% risk
- Score of 5 = 26.2% risk
- Score of 6-7 = at least 40.9% risk

A vast majority of patients (70.1% vs 63.3%; $p=0.13$) in either group had a 'WI risk score of 2-3 with only some low-risk patients (22.8% vs 31.6%; $p<0.01$) and an occasional very high risk subject. The number of low-risk patients in prasugrel group were significantly lower than in clopidogrel group and this was a limitation of the study resulting probably from selection or randomization bias (Table 3). A significant fraction of patients in either group were diabetics — either diagnosed on admission or previously known to be diabetic and mostly on OHAs. 33.3% in prasugrel group and 35% subjects in clopidogrel group had diabetes. An average of 1.28 stents were deployed in both group A (prasugrel) and group B patients (clopidogrel). The mean number of stents deployed in this study was very much on the more conservative side compared to other western studies because a large proportion of patients with diabetes and multivessel disease were commonly referred for CABG because of cost benefits and lack of insurance cover and financial constraints barred deployment of multiple stents in a single patient. The majority of the procedures performed were on one artery. A total of 14 multivessels angioplasties were performed in each group with almost all of these being in maximum two arteries. 75.4% of all PCI in prasugrel group and 76.7% in clopidogrel group were single vessel PCI showing no significant difference in subject allocation (Table 4). 43.8% of all stents deployed in group A were DES and similarly 45.4% in group B were DES. A majority of diabetics received DES. The rate of efficacy was significantly reduced in favor of prasugrel (7.01% vs. 21.66%; $p<0.05$) (Table 5). The difference between the treatment groups with regard to the rate of the primary end point was largely related to a significant reduction in non-fatal myocardial infarction (3.5% vs. 16.7%; $p<0.01$) (Table 6). Most of the individual secondary outcome measures in the study were equivalent in the 2 study groups namely access site complications (14% vs. 10%); arrhythmia (10.5% vs. 8.3%) and slow flow phenomenon (19.3% vs. 23.3%) (Table 7). However, a very important secondary endpoint is more common in e, stent thrombosis was significantly the clopidogrel group than in the prasugrel arm (1.7% vs. 13.33%, $p<0.05$) (Table 7). Overall composite secondary endpoints were no different between the groups (55% vs. 45%). 5.3% of subjects in the prasugrel group had major bleeding complications compared to

3.3% in the clopidogrel group. There was a trend towards more major bleeding complications with prasugrel, but it was not statistically significant (Table 8). Similarly, TIMI minor bleeds were also more frequent in Prasugrel group (19.29%) compared to clopidogrel group (5%) and this reached statistical significance ($p<0.05$) (Table 9).

Table 1: Age and sex distribution of the patients

Drug	Total Patients	<50 years	50- 55 years	56-60 years	61-65 years
Clopidogrel	60	10	14	18	18
Prasugrel	57	10	13	15	19

Table 2: Sex distribution of the patients

Drug	Total Patients	Male	Female
Clopidogrel	60	47	13
Prasugrel	57	49	8

Table 3: TIMI Risk Score

Drug	Total Number of Patients	0-1	2	3	≥ 4
Clopidogrel	60	19	22	16	3
Prasugrel	57	13	24	16	4

Table 4: Distribution of PCI

Drug	Total Patients	Multiple Vessels PCI	Single Vessel PCI	p-value
Clopidogrel	60	14(23.33%)	46(76.67%)	0.95
Prasugrel	57	14(24.56%)	43(75.44%)	

Table 5: Stents deployed in the study

Stents Deployed	Prasugrel	Clopidogrel
Total Stents	73	77
DES	32	35
BMS	41	42

Table 6: Primary Efficacy Parameters

Drug	Total Patients	Cardiovascular Death	Non-Fatal MI	Non-Fatal Stroke
Clopidogrel	60	3(5%)	10(16.67%)	0
Prasugrel	57	2(3.5%)	2(3.5%)	0

Table 7: Secondary Efficacy Parameters

Drug	Total Patients	Stent Thrombosis	Arrhythmia	Access Site Complications	Slow Flow
Clopidogrel	60	8(13.33%)	5(8.33%)	6(10%)	14(23.33%)
Prasugrel	57	1(1.75%)	6(10.52%)	8(14.03%)	11(19.29%)

Table 8: Primary safety parameters

Drug	Total Patients	TIMI Major Bleeding	p-value
Clopidogrel	60	2(3.33%)	0.95
Prasugrel	57	1(1.75%)	

Table 9: Secondary safety parameters

Drug	Total Patients	TIMI Minor Bleeding	p-value
Clopidogrel	60	3(5.00%)	0.03
Prasugrel	57	11(19.29%)	

DISCUSSION

The risk of myocardial ischemic events in patients with acute coronary syndromes has been shown to be reduced by means of antiplatelet therapy with the use of aspirin and, even more effectively by dual antiplatelets with aspirin and ticlopidine or clopidogrel, inhibitors of the p2y12 adenosine diphosphate receptor as compared with the use of aspirin alone.²

Our results show that the treatment of patients, with prasugrel (a 60-mg loading dose, followed by a 10-mg maintenance dose), as compared with clopidogrel at the standard, approved dose, resulted in a significant 14.65% (21.66%-7.01%) absolute reduction primary efficacy end point (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). The rates of ischemic events were also reduced in the Prasugrel group, with a 13.16% (16.66%-3.508%) absolute reduction of myocardial infarction and a 11.58% absolute reduction for stent thrombosis, a rare but potentially devastating clinical event across the spectrum of Acute Coronary Syndrome (ACS) age group, severity of disease it was

unaffected by whatever concurrent medications were advised.

The decrease in ischemic events we observed with Prasugrel in comparison with standard-dose clopidogrel was, however associated with a significant increase of bleeding. the rate of major hemorrhage was increased by 1.93% (5.26%-3.33%) with prasugrel. Bleeding episodes were more frequent in the Prasugrel group than in the clopidogrel group, both near the time of PCI and after PCI. TIMI minor bleeding was also more frequent in prasugrel group 14.29% (19.29%-5%) compared to clopidogrel group.

Among the elderly and among patients with a body weight of less than 60 kg, increased levels of the active metabolite of Prasugrel may have led to an increased risk of bleeding, owing to altered disposition of the drug or smaller body size. In comparison, a large fraction of patients without the risk factors had clinical benefit with the Prasugrel regimen, as compared with the Clopidogrel regimen.

Prasugrel causes increased levels of mean inhibition of platelet aggregation, and lower interpatient variability. considerable research has stated that there are many cases of hypo responsiveness to clopidogrel in patients with coronary artery disease who have undergone PCI. The data from our trial, which was adequately powered to evaluate clinical events, show that, as compared with standard-dose Clopidogrel therapy, Prasugrel with more effective inhibition of platelet aggregation is associated with fewer ischemic events. This effect might also be to some extent due to lower incidence of hypo responsiveness of platelets to prasugrel than clopidogrel.

Studies have shown that the degree of platelet inhibition by prasugrel within 30 minutes after treatment is similar to the peak effect of clopidogrel 6 hours after the dose had been given, suggesting that prolonged use may not be necessary for Prasugrel to achieve its effect. The more rapid onset of an antiplatelet effect with Prasugrel than with clopidogrel may have played an important role in the efficacy benefit, an assertion supported by the reduction in the rate of early myocardial infarction (before day 3) despite the lack of pretreatment.⁷⁻¹⁰

Partly because of data reporting an improved inhibition of platelet aggregation, many clinicians have started the use of a higher-than standard loading dose of Clopidogrel in patients with PCI. The clinical-efficacy data supporting the use of such higher-dose Clopidogrel have been from small studies and have been inconsistent.

The present study supports the hypothesis that higher degree of inhibition of adenosine diphosphate-induced platelet aggregation by means of the tested regimen of Prasugrel, is better effective in preventing ischemic events than by a standard regimen of Clopidogrel. However, this beneficial effect does not come without price. There is an increase in the rate of major bleeding. For considering the choice of antiplatelet regimens for the treatment of patients with acute coronary syndromes who are undergoing PCI, clinicians need to weigh the benefits and risks of inhibition of platelet aggregation.

Limitations of the present study:

1. Smaller number of subjects, which has a tendency to magnify any difference obtained between groups.
2. Short and limited period of study is insufficient to follow outcomes to ascertain outcomes in clinical cardiovascular disease.
3. The study did not objectively determine cost benefit ratio.

CONCLUSION

The thienopyridine antiplatelet agents are effective in reducing the risk of a second ischemic event

in patients with atherothrombotic disease. The thienopyridine clopidogrel is now recommended as dual therapy with Aspirin in secondary prevention for patients with both ST segment and non-ST segment ACS, including those undergoing PCI. Prasugrel is a novel thienopyridine with a faster onset of action and more potent antiplatelet effect than older agents. It has shown superiority over the currently accepted standard (clopidogrel) in reducing the risk of the composite primary end point of cardiovascular death, nonfatal MI, and nonfatal stroke in patients who undergo PCI following ACS at standard dosages, as well as reducing the risk of the composite secondary end points of stent thrombosis. The greatest benefit appears to be in patients with diabetes mellitus. However, the enhanced antiplatelet activity and greater efficacy seen with prasugrel in clinical trials has been accompanied by increased bleeding risk. Identification of patients who are at higher risk of bleeding episodes and attention to stoppage of therapy before surgery may help to guide therapeutic decisions and optimize outcomes.

Conflict of Interest: None declared.

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Ethical Clearance: This study was approved by the Institutional Review Board of R G Kar Medical College, Kolkata, West Bengal, India.

Authors' Contribution: All the authors were equally involved in the design of the study, data collection and analysis, manuscript writing, editing and final submission.

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