Post-PCI Clinical Outcomes of Reduced Dose Prasugrel in Comparison to Clopidogrel

ABSTRACT

Introduction: Patients with ACS undergoing PCI with drug-eluting stent (DES), a one-year regimen with Dual Antiplatelet therapy (DAPT) is recommended to avoid thrombotic events in which any of the two-combination therapy comprising of a P2Y12 inhibitor (Clopidogrel or Prasugrel) and thromboxane A2 inhibitor (Aspirin) is given.
Objectives: This study highlights the differences between the two DAPT regimens (clopidogrel + aspirin, reduced dose prasugrel + aspirin) for primary bleeding events post PCI within 48-72 hours, and calculates MACE events at (15 days, 3 months, 6 months) post PCI.
Methods: It was a single-centered, prospective study done in a teritary care hospital. The study included 100 subjects with ACS who underwent PCI with DES using clopidogrel or reduced dose prasugrel as the antiplatelet agent along with aspirin. All the patients were observed for primary bleeding events post PCI within 48 hours while in-patient. 15 days, 3 months, and 6 months after their discharge, and initiation of DAPT bleeding and ischemic events were observed. Alongside, MACE events and ADRs were observed 6 months duration.
Results: There were 50 patients in clopidogrel group and 50 patients in reduced dose Prasugrel group. Mean age of the study population in the clopidogrel group was 60.3000± 6.670 years (mean ± SD). The mean age of the study population in the reduced dose prasugrel group was 60.1600± 8.39913 years (mean ± SD). There were no events as such in the reduced dose prasugrel group whereas, in the clopidogrel group, 1 patient (2.5%) had an In-hospital major bleeding event post PCI. Two patients from the clopidogrel group and four patients from the prasugrel group died and the cause was unascertained. Minor bleeding events were higher in the Reduced dose Prasugrel group when compared to the clopidogrel group within 6 months post PCI.
Conclusion: This study suggests that Reduced dose prasugrel is as safe and efficacious as clopidogrel to prevent stent thrombosis and prevent bleeding events in elderly and in patients of weight 50-60 kgs, post- PCI. Hence, reduced dose Prasugrel as well as clopidogrel can be used in routine clinical practice in patients with high bleeding risk post-PCI. However, studies with a larger sample size and study duration are needed to confirm the above findings.

Keywords: Dual Antiplatelet Therapy (DAPT); Percutaneous Coronary Intervention (PCI); Drug-Eluting Stents; Acute Coronary Syndrome (ACS); Major Adverse Cardiovascular Events (MACE.)

1. INTRODUCTION

The cornerstone for a good prognosis of post percutaneous intervention is the choice of antiplatelet in DAPT regimen alongside Aspirin [1,2]. DAPT regimen post- PCI reduces the risk of MI due to clot formation but contrarily there is a risk of bleeding due to excess antiplatelet activity. Hence, an antiplatelet should be chosen by considering the bleeding risk of individual patients. Clopidogrel along with ASA has been found to have the least risk of MI with an increased risk of minor bleeding [3]. However, prasugrel and ticagrelor showed greater benefits towards ischemic endpoints in large, randomized trials [4,5]. Depending on the bleeding risk, ischemic risk, and risk of stent thrombosis present in different patient groups it is necessary to calculate the risk-benefit ratio in different patients depending on their weight, age, creatinine clearance.

No history of cerebrovascular accident, and other risk factors associated with the above-mentioned complications and decide a particular DAPT regimen to avoid the risks associated. There is coronary ischemia and stent thrombosis as adverse clinical outcomes due to delayed onset of clopidogrel (several hours after ingestion) and

variability in response among different patients [6,7].

For patients having weight less than 60 kg and/or age greater than or equal to 75 years there is an increased risk of bleeding and hence reduced dose prasugrel 5 mg following a loading dose of 60 mg has been a better option for better clinical outcomes. So far there has been no study comparing the two groups in the Indian population (standard-dose clopidogrel and reduced dose prasugrel), especially in a routine clinical scenario. Thus, this study was conducted in a tertiary care hospital, Princess Esra Hospital, and Owaisi Hospital at Hyderabad.

2. OBJECTIVES

To assess the safety and efficacy of reduced dose Prasugrel group

3. DESIGN AND SETTINGS

It was a single-centered, observational and prospective study that was carried out in Princess Esra hospital for a period of 6 months, that is, from August 12, 2020, to February 5, 2021. A total of 100 subjects who underwent PCI receiving a DAPT regimen with either of the two drugs mentioned in the study were selected. Of 100 patients, 50 patients were present in the clopidogrel group and 50 in the reduced dose prasugrel group. All these subjects were explained about the objectives of the study. Written informed consent was taken from all the subjects. The study was initiated after approval of the Institutional Ethics Committee.

3.1 Inclusion Criteria

- Patients greater than 18 years of age
- Patients who have undergone PCI
- Patients receiving dual antiplatelet therapy
- Patient willing to give consent
- Weight (50-60kg) for prasugrel and irrespective of weight for clopidogrel group.

3.2 Exclusion Criteria

3.2.1 Conditions where antiplatelets are contraindicated

- History of stroke (for low dose Prasugrel group).
- Pregnant women.
- Thrombocytopenia.

3.2.2 Other conditions

- Patients not willing to give consent.
- Hypersensitivity to the drugs or any of its recipients.
- History of gastrointestinal or genitourinary bleeding of clinical significance within the previous 6 weeks.

4. METHODS

4.1 Protocol

Based on the selection criteria of our study, patients who have underwent percutaneous coronary intervention (PCI) were selected from the in-patient department of Princess Esra hospital. Patients less than 75 years of age or weight < 60 kg were given either reduced dose Prasugrel (60mg-5mg OD) or standard dose clopidogrel (600mg -75 mg OD). All patients with history of old CVA were given clopidogrel. For patients included in clopidogrel group, a loading dose of 600 mg was given followed by a maintenance dose of 75 mg, and for patients included in reduced dose prasugrel group 60 mg loading dose followed by a maintenance dose of 5 mg. The patients were followed up during their hospital stay after PCI for 2 days (48 hours) and were monitored for primary bleeding post PCI (arterial access site bleeding, retroperitoneal, gastrointestinal, genitourinary bleeding, intracranial hemorrhage, cardiac tamponade, a decrease of ≥ 3 g/dl in Hemoglobin blood transfusion post PCI). After 48 hours patients were discharged and called up after 15 days to assess for any bleeding and ischemic complications. The primary endpoint was the composite of all-cause mortality, MI, disabling stroke, and rehospitalization for cardiovascular causes or bleeding at 6 months. The patients were called up at 3 months and 6 months and assessed for MACE events (MI, Stent thrombosis, ischemic stroke, death or Angina) throughout 6 month follow up period; rate of major and minor bleeding using TIMI definition for bleeding within 15-days ,3-months and 6-month durations.

Our secondary outcome was to compare the adverse events in both groups within 6 months duration.

4.2 Analysis of Outcomes

The study endpoints included the rate of all-cause death, myocardial infarction (MI), angina, Ischemic stroke or stent thrombosis; the rate of major and minor bleeding using the thrombolysis in myocardial infarction (TIMI) definition at 2 days, 15 days, 3 months and 6 months period.

4.3 Statistical Analysis

The study data was analyzed using Chi-square test, independent t-test, and Wilcoxon signed-rank test. The continuous variables were presented as mean ± standard deviation (SD) and the categorical variables as numbers. Statistical analysis was done using graph SPSS version 20.

5. RESULTS

5.1 Clinical Characteristics

The mean age of the study population in the clopidogrel group was 60.3000± 6.670 years (mean ± SD whereas in the reduced dose prasugrel group was 60.1600± 8.39913 years (mean ± SD).

5.2 Indications for PCI

Among study subjects, the major indication for PCI was Acute MI (79%) in which ST elevated myocardial infarction (STEMI) was 44% and non-ST elevated myocardial infarction (NSTEMI) was 35%, unstable angina 13% and chronic stable angina 8% constituted most subjects.

5.3 Medications

Most of the patients were given the following medications on discharge Table 2.

5.4 Past Medical History

Past medical history of patients in the clopidogrel and prasugrel group is represented in Fig. 8.

5.5 Clinical Outcomes

Post PCI, all the study subjects were started with DAPT either with Reduced dose Prasugrel or Clopidogrel alongside Acetyl Salicylic Acid(ASA).

5.5.1 In-Hospital

1 patient in the Clopidogrel group had an In-hospital major bleeding event whereas there was no major bleeding event in the reduced dose Prasugrel group.

5.5.2 Fifteen days follow up

One patient from the Prasugrel group who died early was a sick patient who had recovered from cardiogenic shock and acute renal failure. He had mid LAD total occlusion which was stented. Post-stenting, he had distal LAD perforation which was sealed with prolonged balloon dilation and protamine reversal. He recovered and was discharged but 15 days later, he went into cardiogenic shock and expired, there were no other documented ischemic events. Two patients from the Prasugrel group had gum bleed and one patient from both the groups had epistaxis as a minor bleeding event.

Chart 1. Study population in the clopidogrel group

Age Interval (Years)	Group		P-Value
	Clopidogrel	Prasugrel	
50-59	20	25	0.1091
60-69	27	24	
70-79	3	1	

Fig. 1. Age wise Distribution

Most of the study subjects were of the age group 60-69 years (51%) followed by 50-59 years (45%) and 70-79 years (4%) which was the least prevalent group. The sex ratio of the study subjects was (male: female) 1.3:1 in the clopidogrel group and 1:1.3 in the prasugrel group.

Fig. 2. Gender distribution

Chart 2. Body Mass Index (kg/m^2)

BMI	Total		Group		P-value
	N	%	Clopidogrel	Prasugrel	
BMI<25	84	84	39	45	1
BMI>25	16	1	11	5	

Fig. 3. BMI

The number of patients in the prasugrel group that were underweight was more when compared to the clopidogrel group.

Clinical characteristics of the subjects are summarized in Table 1

Fig. 4. Indication for PTCA

Chart 3. Paris risk scores calculated before enrollment

	Paris bleeding risk score				
	Low risk (0-2)	**Intermediate risk (3-4)**	**High Risk ≥5**	**Mean**	**P-Value**
Clopidogrel	7	15	28	4.76	*0.160*
Prasugrel	8	5	37	5.4	

Fig. 5. Paris bleeding risk score

Chart 4. Paris ischemic risk score

	Paris Ischemic risk score				
	Low risk (0-2)	**Intermediate risk (3-4)**	**High risk ≥5**	**Mean**	**P-Value**
Clopidogrel	7	19	24	4.4	*0.087*
Prasugrel	9	22	19	3.8	

Fig. 6. Paris ischemic risk score

Fig. 7. Medications

Fig. 8. Past medical history

Chart 5. Data statistics

	Mortality		P-Value	Major Bleeding		P-Value
	Clopidogrel	**Prasugrel**		**Clopidogrel**	**Prasugrel**	
In-Hospital	0	0		1	0	
15 Days	0	1		0	0	
3 Months	0	0		0	0	
3-6 Months	2	3		0	0	
6 Months (Cumulative)	2	4	*0.3997*	1	0	*0.315*

Fig. 9. All cause mortality and major bleeding

Chart 6. Minor bleeding

	Minor bleeding					
	Gum bleed		P-Value	Epistaxis		P-Value
	Clopidogrel	Prasugrel		Clopidogrel	Prasugrel	
In-Hospital	0	0		0	0	
15 Days	0	2		1	1	
3 Months	0	3		0	0	
3-6 Months	0	0	*0.022*	0	0	*1.000*
6 Months (Cumulative)	0	5		1	1	

Fig. 10. Minor bleeding

Table 1. Clinical characteristics of the subjects are summarized

	Clopidogrel (n= 50)	Prasugrel (n=50)	P value
Age			
50-59	20	25	
60-69	27	24	0.1091
70-79	3	1	
Sex			
Male	27	21	0.2298
Female	23	29	
BMI			
BMI<25	13	15	
BMI≥25	37	35	0.1955
Ejection Fraction (EF%)			
≤40	15	15	
≥40	35	34	0.4317
No. of Stents			
1	20	21	
2	30	28	0.5789 Z
3	0	1	
Medical history			
DM	27	23	0.4237
HTN	39	40	0.8061
Smoker	9	5	0.249
Tobacco	5	2	0.2397
Ethanolic	3	6	0.2945
Creatinine clearance, (mL/min)			
Reduced	13	22	
Increased	135.7	208	0.1249
Median	57.50	51.55	
Type of ACS			
STEMI	21	23	
NSTEMI	17	18	0.9115
USA	7	6	
CSA	5	3	
Previous cardiovascular events			
Prior PCI (%)	6	3	0.2945
Prior CABG (%)	5	3	0.4610

Table 2. Most of the patients were given the following medications on discharge

1. Tab. Prasugrel 5mg or Clopidogrel 75mg OD
2. Tab. Atorvastatin 40mg OD
3. Tab. Aspirin 150mg or 325 mg OD.
4. Tab. Telmisartan OD

5.5.3 Three months follow up

No mortalities or major bleeding or ischemic events were seen. Three patients from the Prasugrel group had gum bleed as a minor bleeding event.

5.5.4 Three to six months follow up

Two patients from the Clopidogrel group and three patients from the Prasugrel group died. However, the cause of death was unascertained. There were no major, minor bleeding events or ischemic events observed.

Fig. 9 shows all-cause Mortality and Major bleeding throughout 6 months duration in Clopidogrel and reduced dose Prasugrel group.

Fig. 10 shows minor bleeding events throughout 6 months duration in Clopidogrel and reduced dose Prasugrel group.

There was one In-hospital major bleeding event seen in the Clopidogrel group (p-value 0.315) whereas no major bleeding events were in the Prasugrel group. No major ischemic events were seen in either of the groups throughout the 6-month follow-up duration. However, there was a death within 15 days due to cardiogenic shock and 3 Deaths in the reduced dose prasugrel group wherein the cause was unascertained. Clopidogrel group had two Deaths cause unascertained within 6 months duration (p-value 0.3997), there were no definite ischemic events. Minor bleeding events reported were higher in the reduced dose prasugrel group. There was no statistically significant difference between both groups.

6. DISCUSSION

Prasugrel a prodrug, gets converted into its active metabolite which binds irreversibly to P2Y12 inhibitor. This study compares bleeding and ischemic events among two groups comprising a P2Y12 inhibitor (either standard-dose clopidogrel or reduced dose prasugrel) alongside ASA. It showed that Reduced dose Prasugrel was as efficacious and safe as standard dose clopidogrel. Lower incidence of ischemic events and higher incidence of bleeding events were observed with administration of standard-dose prasugrel when compared to standard dose clopidogrel in the TRITON-TIMI trial [8]. In 2014 low dose prasugrel was approved for treatment in patients with ACS post-PCI as it has a lesser risk of bleeding events compared to standard dose prasugrel. Since then, reduced dose prasugrel has become a treatment of choice for patients with weight less than 60 kg and age greater than or equal to 75 years. The incidence of bleeding and ischemic events remains unclear due to older age, low weight, and comorbidities. The ISAR REACT 5 trial shows that the risk of ischemic events (death, MI, stroke) 1 year after randomization was lowered significantly in the prasugrel group compared to ticagrelor [9]. This study results are like those of a meta-analysis [10] and a study on Japanese patients post-PCI [11] as there was no significant difference in in-hospital mortality and incidence of stent thrombosis between the two antiplatelet regimens whereas when considering major bleeding events our study diverges from it as it shows 1 major bleeding event in the clopidogrel group. However, there was no significant difference. We also compared bleeding and ischemic risk between both groups through PARIS risk sores. 0-2 being low bleeding risk, 3-4 intermediate bleeding risk, and ≥5 as High bleeding risk. The number of patients having high bleeding risk (HBR) was more in the Reduced dose Prasugrel group when compared to the Clopidogrel group whereas patients having higher Ischemic risk scores were seen in the Clopidogrel group. A study conducted to validate the PARIS risk score suggested that such scores may turn out to be useful for predicting bleeding and ischemic risks after PCI with DES as well as facilitate clinical decisions for the optimal duration of DAPT and selection of Antiplatelets depending on bleeding and ischemic risk [12].

7. LIMITATIONS OF THE STUDY

This study was not a randomized clinical trial (RCT) and hence the presence of confounding factors may affect the study results. This study followed up patients only for a 6-month duration and the standard treatment with DAPT is at least for 12 months as a result there might be missed follow-up in the rest of 6 months resulting in missed clinical outcomes and adverse events. A study with a larger sample size and study duration should be conducted for a more reliable outcome.

8. CONCLUSION

This study suggests that reduced dose prasugrel is as safe and efficacious as clopidogrel to prevent stent thrombosis and bleeding events in elderly and low-weight patients post- PCI. Hence, reduced dose Prasugrel, as well as clopidogrel, can be used in routine clinical practice in patients with high bleeding risk post-PCI. No studies were comparing reduced dose prasugrel and clopidogrel in the Indian population and hence this study was carried out to fill this gap. However, studies with a larger sample size and longer study duration are needed to confirm the above findings.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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