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Original Research Article

Evaluation of cardiovascular events and bleeding complications in patients of Acute Coronary Syndrome on various antiplatelet drugs: an observational study in a tertiary care center in Eastern India

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ABSTRACT

Background: This study is to determine the clinical profile of Acute Coronary Syndrome (ACS) patients, to observe cardiovascular events in patients with ACS undergoing Percutaneous Coronary Intervention (PCI) and to evaluate the bleeding complications with various antiplatelet agents.
Methods: This hospital based observational study included patients of ACS presenting between February 2015 to August 2016 who received PCI and were on dual antiplatelet agents.
Results: Among 200 patients presenting with ACS mean age was 58.67, there was male predominance and 52.5% presented with STEMI. Cardiovascular death was seen in 2.5% patients and all cause mortality was seen in 3.5% patients. The incidence of Non-fatal myocardial infarction was more in Clopidogrel group (5%) as compared to Prasugrel (4%) and Ticagrelor (2%) group. Non-fatal stroke was seen in 2% patients and incidence was similar in each of the three groups. Incidences of target vessel revascularization (TVR) and stent thrombosis were more in the Clopidogrel group as compared to Prasugrel and Ticagrelor. TIMI Major and Minor bleeding with Prasugrel was higher than clopidogrel and Ticagrelor and TIMI minimal bleeding was seen in 2% patients and was similar in all three groups.
Conclusions: Patients receiving clopidogrel has more numbers of CV death, all cause death, non-fatal MI, TVR and stent thrombosis in comparison to the groups receiving Prasugrel or Ticagrelor and on comparing Prasugrel and Ticagrelor, the two drugs are similar in efficacy but, Ticagrelor has better safety outcomes.

Keywords: Acute Coronary Syndrome, Antiplatelet drugs, Percutaneous coronary intervention

INTRODUCTION

Thrombosis caused by a ruptured or eroded atherosclerotic plaque is the usual underlying mechanism of acute coronary syndromes.[1] Aspirin and heparin reduce the risk of death from cardiovascular causes, new myocardial infarction, and recurrent ischemia, but there is still a substantial risk of such events in both the short term and the long term.[2,3] The important role of antiplatelet agents in the management and prevention of the complications after ACS and percutaneous coronary intervention (PCI) is related directly to the physiological events.[4] Thienopyridine antiplatelet agents interfere with platelet activation and aggregation induced by ADP. There are 3 members of the thienopyridine class of antiplatelet agents currently available for clinical use: ticlopidine, clopidogrel, and the prasugrel. All 3 agents are prodrugs and require conversion to an active metabolite to exhibit an antiplatelet effect. The thienopyridine clopidogrel, the most widely used P2Y12 inhibitor, has a number of important limitations which can be partly overcome with prasugrel, a new thienopyridine agent that is more

efficiently metabolized to its active form and whose magnitude and consistency of platelet ADP inhibition is greater than clopidogrel.[5] Ticagrelor (AZD6140), the first reversibly binding oral P2Y12 receptor antagonist, has the potential to address many of the limitations of thienopyridine therapy.[6] Treatment with prasugrel and ticagrelor results in higher and more consistent levels of platelet inhibition than standard- or higher-dose clopidogrel.[7,8]

From the Indian perspective, there is an inherent dearth of data regarding anti-platelet treatment strategies used and related outcomes in ACS patients due to variation in antiplatelet treatment patterns and outcomes. This study collected and evaluated the effect of various anti-platelet drugs and their safety outcomes in patients of ACS undergoing Percutaneous Coronary Intervention.

METHODS

This hospital based observational study included patients of Acute Coronary Syndrome (STEMI, NSTEMI or unstable angina) aged between 18-75 years; who had undergone PCI and were on dual antiplatelet drugs between February2015 to August2016. Patients with Acute Coronary Syndrome who were on medical management or had undergone CABG, active pathological bleeding (Ex. Peptic ulcers, Severe hepatic failure), simultaneous use of fibrinolytics, allergic reaction to active compounds, CKD patients with eGFR ≤30, Age ≥75 years were excluded. Informed consents were taken from all the patients and the ethics committee approval was obtained prior to study initiation.

Statistical analysis

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 20.0.1 and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. One-way analysis of variance (one-way ANOVA) was a technique used to compare means of three or more samples for numerical data (using the F distribution). A chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Explicit expressions that can be used to carry out various t-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test. Once a t value is determined, a p-value can be found using a table of values from Student's t-distribution. If the calculated p-value was below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis was rejected in favour of the alternative hypothesis. p-value ≤0.05 was considered for statistically significant.

RESULTS

Among total 200 patients presenting with acute coronary syndrome mean age was 58.67±10.41, there was male predominance (66.5%) and most of them presented with STEMI (52.5%). Age and sex were matched in three groups receiving clopidogrel, prasugrel or ticagrelor. DES was used during PCI in 187 patients (93.5%) and BMS was used in 13 patients (6.5%) and 62 required multi vessel PCI (31%). 77 patients were obese with BMI >30kg/m^2 (38.5%), 104 were hypertensive (52%), 73 were diabetic (36.5%), 92 were hyperlipidemic (46%), 82 subjects were smokers (41%), 38 patients had family history of CAD (19%), 27 patients had past history of myocardial infarction (13.5%), 30 patients had CrCL<60ml/min (15%).

Baseline characteristics of the patients of ACS undergoing PCI according to different types of antiplatelet drugs are described in Table 1.

Cardiovascular death was seen in 5 patients (2.5%) among total 200 ACS admissions who underwent PCI (3%, 2% and 2% in clopidogrel, prasugrel and ticagrelor group respectively) and all cause mortality was seen in 7 patients (3.5%) (4%, 4% and 2% in the clopidogrel, prasugrel and ticagrelor group respectively).

Non fatal myocardial infarction was seen in 8 patients (4%). Though the incidence of Non-fatal MI was more in Clopidogrel group as compared to Prasugrel and Ticagrelor group but the difference was not statistically significant. Non-fatal stroke was seen in 4 patients (2%) and incidence was similar in each of the three groups. TVR (target vessel revascularization) within one year of PCI was seen in 4 patients (2%) and stent thrombosis was seen in 6 patients (3%). Incidences of TVR and stent thrombosiswere more in the Clopidogrel group as compared to Prasugrel and Ticagrelor group but the difference was not statistically significant (Table 2).

TIMI major bleeding was seen in 4 patients (2%) (2%, 4% and 0% in clopidogrel, prasugrel and ticagrelor group respectively) and TIMI minor bleeding was seen in 6 patients (3%) (3%, 4% and 2% in clopidogrel, prasugrel and ticagrelor group respectively). TIMI major and minor bleeding with Prasugrel was higher than clopidogrel and Ticagrelor but the difference was not statistically significant. TIMI minimal bleeding was seen in 4 patients (2%) and was similar in all three groups.

Table 1: Base line characteristics of patients of ACS undergoing PCI according to the different types of antiplatelet intake.

	Clopidogrel	Prasugrel	Ticarelor	Total
Number of patients	100	50	50	200
Mean age (years)	58.92	59.46	57.40	58.68
SEX				
male	65	34	34	133
female	35	16	16	67
Types of ACS				
STEMI	52	25	28	105
NSTEMI	18	8	8	34
UA (Unstable Angina)	30	17	14	61
BMI (Body Mass Index)				
<30Kg/m^2	63	29	31	123
>30Kg/m^2	37	21	19	77
Hypertension				
yes	50	28	26	104
no	50	22	24	96
Diabetes Mellitus				
yes	38	18	17	73
no	62	32	33	127
Hyperlipidemia				
yes	45	23	24	92
no	55	27	26	108
Smoking				
yes	41	21	20	82
no	59	29	30	118
Family history of Coronary Artery Diseases				
yes	20	10	8	38
no	80	40	42	162
Past history of Myocardial Infarction				
yes	14	8	5	27
no	86	42	45	173
Creatinine clearance				
<60ml/min	14	8	8	30
>60ml/min	86	42	42	170
STENT used				
BMS	7	3	3	13
DES	93	47	47	187
Multi-vessel PCI (percutaneous coronary intervention)				
yes	33	15	14	62
no	67	35	36	138

Table 2: Outcome of ACS patients undergoing PCI according to intake of different types of antiplatelet intake.

	Clopidogrel	Prasugrel	Ticagrelor	Total	P-value
Cardio-Vascular death	3	1	1	5	0.9025
All cause death	4	2	1	7	0.8009
Non fatal Myocardial Infarction	5	2	1	8	0.6766
Non fatal stroke	2	1	1	4	1.000
Target vessel revascularisation	3	1	0	4	0.4652
Stent thrombosis	4	1	1	6	0.7092
TIMI major bleeding	2	2	0	4	0.4652
TIMI minor bleeding	3	2	1	6	0.8421
TIMI minimal bleeding	2	1	1	4	1.000

DISCUSSION

Among the total 200 patients presenting with acute coronary syndrome, the mean age was 58.67±10.41 which is comparable to other studies done in India, that is, CREATE registry (56 ± 13 years), Jose and Gupta study (57±12 years) and study by Sharma (54.71±19.90years) but lower than the western population as in COURAGE trial (62±5 years).[9-11] The skewed gender distribution towards male (66.5%) in our study can be attributed to the gender bias and atypical presentation, which is also a feature in Interheart study and its South Asian cohort (overall male, 76% and South Asian cohort, 85%).[12] Patients in India who have acute coronary syndromes have a higher rate of STEMI than do patients in developed countries which is also seen in CREATE registry and Sharma study. In our study also the most common presentation among ACS patients is STEMI (52.5%) whereas in reports from developed countries including the European Heart Surveys, fewer than 40% had STEMI.[13-17]

The prevalence of obese patients was 38.5% which was less than the prevalence seen in South Asian cohort of INTERHEART study (44.2%).[12] The prevalence of hypertension in South Asian cohort of INTERHEART study (31.1%) was comparatively lower than in our study (52%) but near to other Indian studies like CREATE registry (37.7%), Jose and Gupta study.[9,10] In the present study the prevalence of diabetes was 36.5%, which was higher than the prevalence reported in the CREATE Registry (30.4%), and in a similarly aged population from (10.5%) South Asian countries in the INTERHEART study. The higher prevalence of diabetes and hypertension could be explained by the comparatively higher development and increasing epidemic of CAD in India.[18] Dyslipidemia was found in 46% of this study population which was less than seen in TRITON-TIMI 38 Trial (56%) and PLATO trial (46.6 %).[19,20] The prevalence of tobacco smoking was high in the present study (41%) comparable to CREATE Registry(40.2%) and study by Sharma et al (49%).[21] In CREATE REGISTRY and TRITON TIMI 38 Trial, the prevalence of patients with past history of myocardial infarction was 17.5% and 18% respectively and in study by Yadav et al, family history of coronary artery disease was there in 14%.[21] DES was used during PCI in 187 patients (93.5%) and BMS was used in 13 patients (6.5%). In TRITON-TIMI 38 Trial, BMS was used in 47.5% and DES was used in 48%. Incidence of multi vessel PCI was 31% in our study which is comparatively higher than TRITON-TIMI 38 Trial (14%).

Cardiovascular death was seen in 2.5% patients and all cause mortality was seen in 4 patients (2%) (more in the clopidogrel group than prasugrel or ticagrelor). In TRITON-TIMI-38, PLATO and PRAGUE-18 trials both cardiovascular death and all cause mortality were less with prasugrel and ticagrelor than with clopidogrel.In the (GRAPE) Registry, the incidence of all cause mortality was 6.2% with clopidogrel and 2.9% with Prasugrel and Ticagrelor.[23] Non fatal myocardial infarction was seen more in clopidogrel than other two groups and non-fatal stroke was similar in all three groups. In PRAGUE-18 Trial, the incidence of non-fatal myocardial infarction was 1.3% with Prasugrel and 1.2% with Ticagrelor. In TRITON-TIMI 38 Trial, the incidence of non-fatal myocardial infarction was 7.3% with Prasugrel vs. 9.5% with Clopidogrel and this difference was statistically significant. In TRITON-TIMI 38 Trial, at 15 months, the incidence of non-fatal stroke was 1% with both Prasugrel and Clopidogrel. TVR (target vessel revascularization) within one year of PCI was seen in 4 patients (2%) (3%, 2% and 0% in clopidogrel, prasugrel and ticagrelor respectively). In TRITON-TIMI 38 Trial, GRAPE registry and PRAGUE-18 trial, incidence of Urgent target-vessel revascularization were less with Prasugrel and ticagrelor than with Clopidogrel and it was similar with Prasugrel and Ticagrelor. In TRITON-TIMI 38 Trial and PLATO trial prasugrel and ticagrelor were associated with lower incidence of Stent thrombosis than clopidogrel. In PRAGUE-18 Trial, at 1 month, the incidence of stent thrombosis was 0.5% with Prasugrel and 0.9% with Ticagrelor but the difference did not reach statistical significance. Contrary to the above studies, in this study, at 12 months, the incidence of Stent thrombosis was more in Clopidogrel (4%) than Prasugrel (2%) or Ticagrelor group (2%) but the difference did not reach statistical significance.

TIMI major bleeding was seen in2%patients and TIMI minor bleeding was seen in 3% patients. Both were higher with Prasugrel than with clopidogrel or Ticagrelor but the difference was not statistically significant. TIMI minimal bleeding was seen in 4 patients (2%) and was similar in all three groups. In the PLATO Trial, at 12 months, incidence of TIMI Major bleeding was 7.7% and 7.9% with clopidogrel and Ticagrelor respectively and the difference was statistically insignificant. In the TRITON TIMI 38 Trial, at the end of 15 months, patients treated with prasugrel, 146 (2.4%) had at least one TIMI major hemorrhage that was not related to CABG, as compared with 111 patients (1.8%) treated with clopidogrel and the difference was statistically significant. Also, greater in the prasugrel group was the rate of life-threatening bleeding (1.4% vs. 0.9%; P =0.01), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; P =0.23) and fatal bleeding (0.4% vs. 0.1%; P =0.002). In PRAGUE-18 Trial, at 1 month, the incidence of TIMI major bleeding was 0.6% with Prasugrel and 0.7% with Ticagrelor but the difference did not reach statistical significance.

CONCLUSION

Prevalence of acute coronary syndrome is on the rise all across the world. Although relative percentage of STEMI is decreasing over the last few decades in large global registries, in Indian population prevalence of STEMI is still high. Mean age of presentation of myocardial infarction is less in Indian population as compared to the western world. Use of dual anti-platelets in the form of aspirin plus P2Y12 inhibitors (clopidogrel, Prasugrel or

ticagrelor) is recommended after ACS undergoing PCI. As far as the baseline characteristics of ACS patients are concerned, our patients had more hypertension and diabetes, in comparison to other studies, but prevalence of other risk factors like hyperlidemia, history of smoking, family history of CAD, past history of MI, depressed renal function, obesity were more or less similar. Among the subgroups, patients receiving clopidogrel has more numbers of CV death, all cause death, non-fatal MI, TVR and stent thrombosis in comparison to the groups receiving Prasugrel or ticagrelor and on comparing Prasugrel and Ticagrelor, the two drugs are similar in efficacy but, ticagrelor has better safety outcomes. Our study didn't meet the statistical significance probably due to small sample size and low power of the study.

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