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Original Article

Comparison of Clinical Effectiveness of Ticagrelor and Clopidogrel in Post Percutaneous Transluminal Coronary Angioplasty (PTCA) Patients Approaching A Tertiary Care Hospital in South India

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ABSTRACT

Introduction: Dual antiplatelet therapy is recommended for prevention of secondary cardiovascular events in acute coronary syndrome patients who undergo percutaneous transluminal coronary angioplasty (PTCA). This therapy includes aspirin with either of a P_2Y_{12} platelet receptor inhibitor like clopidogrel or ticagrelor. **Methodology:** A retrospective cohort study with 1 year follow up which compared clopidogrel and ticagrelor for determining clinical effectiveness in post PTCA patients through the incidence of primary and secondary end points. Primary end points included cardiovascular death, Myocardial Infarction (MI), unstable angina, secondary revascularization and Congestive Heart Failure (CHF). Secondary end points were bleeding and dyspnea. **Results:** Age, gender, cardiovascular risk factors, concomitant medications administered and angioplasty specifications like the number of stents, type of stents and approach route were in comparable between clopidogrel and ticagrelor groups. The primary end points, a composite of cardiovascular death, unstable angina and secondary revascularization occurred more in the clopidogrel group (9%) than in ticagrelor group (5%) in 12 months follow up period. The secondary end points, a composite of bleeding and dyspnea were observed more in the ticagrelor group (11%) compared to clopidogrel group (5%). **Conclusion:** The use of ticagrelor prevents the incidence of secondary cardiovascular events in post PTCA patients to a greater degree than clopidogrel in comparable risk groups. Our observation revealed that ticagrelor was found to be better drug than clopidogrel as a prophylactic antiplatelet drug though there was increased incidence of dyspnea and bleeding in ticagrelor group.

Keywords: Antiplatelets, Ticagrelor, Clopidogrel.

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INTRODUCTION

Acute Coronary Syndromes (ACS) is the most common cause of death due to cardiovascular causes worldwide. It is a condition that arises from atherosclerosis of the coronary arteries with thrombosis superimposition.[1] Unstable angina and Myocardial Infarction (MI) including both ST Segment Elevation MI (STEMI) and Non ST Segment Elevation MI (NSTEMI) collectively refers to ACS.[2] Around one-third of ACS patients will undergo PTCA and stenting.[3] Coronary stenting is done either using Bare Metal Stents (BMS) or Drug Eluting Stents (DES).

Anti platelets are group of medicines that stop platelets from sticking together and forming a blood clot. Anti platelet drugs decreases platelet aggregation and inhibit thrombus formation.[4] Dual anti platelet therapy (DAPT), usually combination of aspirin and a P_2Y_{12} platelet receptor inhibitor, is recommended for a prolonged time after stent implantation in order to avoid potentially catastrophic stent thrombosis. DAPT beyond 1 year after placement of a drug eluting stent, as compared with aspirin therapy alone, significantly reduced the risks of stent thrombosis and major adverse cardiovascular and cerebrovascular events.[5]

Aspirin, an irreversible inhibitor of cyclooxygenase 1 and 2 (COX 1 and COX 2) enzymes causes inhibition of platelet dependent prostaglandin derivative thromboxane A2 (a known vasoconstrictor) formation and thus platelet aggregation.[6] Clopidogrel is a thienopyridine which irreversibly inhibits the binding of ADP to its receptor on platelets preventing GP IIb/IIIa receptor complex activation and thereby inhibits platelet aggregation.[7] Ticagrelor is a cyclopentyltriazolopyrimidine anti platelet which reversibly and non competitively binds to the ADP P_2Y_{12} receptor on the platelet surface resulting in prevention of the ADP mediated activation of Glycoprotein IIb/IIIa receptor (GP IIb/IIIa receptor) complex and reduction of platelet aggregation.[8] Prasugrel is another thienopyridine with mechanism of action similar to that of clopidogrel.[9]

Resistance to an anti platelet agent is a phenomenon where the platelet function after anti platelet therapy and the baseline platelet function do not differ significantly. Around 16-50% of patients treated with clopidogrel have resistance to clopidogrel. There are 3 main mechanisms that account for the clopidogrel resistance. They include variability in absorption that is influenced by polymorphism of ABCB1 gene, variable function in the activity of CYP450 isoenzyme (CYP2C19) that is influenced by Single Nucleotide Polymorphisms (SNPs) and also drug interactions.[10]

Some trials involved in the comparison of anti platelets like clopidogrel, ticagrelor and prasugrel includes Platelet Inhibition and Patient Outcomes (PLATO) trial by Wallentin L *et al*, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON TIMI) 38 trial by Wiviott SD *et al*, Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin- Thrombolysis in Myocardial Infarction (PEGASUS TIMI) 54 trial by Bonaca MP *et al* and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial by Yusuf S *et al*.[11-14]

METHODOLOGY

A retrospective cohort study with 1 year follow up was designed. Patients of all age groups who underwent Percutaneous Transluminal Coronary

Angioplasty (PTCA) between 1st June 2013 and 31st May 2014 and on treatment with dual antiplatelets consisting of 100 mg aspirin once daily with 90 mg ticagrelor twice daily or 150 mg aspirin with 75 mg clopidogrel once daily were included in the study. Patients from other Nationality and an inability to adhere to study procedures were excluded from the study. 100 patients from each group (ticagrelor 90 mg twice daily and clopidogrel 75 mg twice daily for the first month followed by 75 mg once daily) were selected by random sampling using SPSS software version 17.

Patient details including pertinent laboratory data and drug therapy details were collected from electronically maintained medical records database and cross checked with manually maintained medical records wherever necessary. Information regarding the demographics of patients including age, sex, and social history, cardiovascular risk factors including hypertension, diabetes mellitus and dyslipidemia, respiratory problems including bronchial asthma and COPD, details of angioplasty (date of procedure, stent/stents used, coronary artery vessel involved, approach site and adjuvant medication), and concomitant medications administered were collected.

The patients after PTCA were categorized into 2 groups according to the antiplatelet medication administered as clopidogrel group and ticagrelor group and all eligible patients were followed up for 1 year. The clinical effectiveness of these study drugs were assessed based on the incidence of primary and secondary end points. Primary end points included cardiovascular death, MI, unstable angina, secondary revascularization and CHF. Secondary end points were bleeding and dyspnea. Elevations in the serum creatinine and uric acid levels were also monitored. All these outcomes were assessed in both the study groups and compared. Brain Natriuretic Peptide (BNP) levels and Left Ventricular (LV) function of patients who developed dyspnea were also collected. The patients who did not have regular follow up visit or complete laboratory investigation data were contacted telephonically. The time of occurrence of primary and secondary endpoints were noted at 1st month, 3rd month, 6th month and 12th month and laboratory investigation data were also collected at the same time intervals along with baseline values.

A nested case control study was conducted in the clopidogrel group to rule out association of risk factors like systemic hypertension, diabetes mellitus, dyslipidemia and social history of smoking with primary end points. The patients who developed primary end points were taken as cases and controls (4 controls for one case) matched for age and sex were selected from the clopidogrel cohort who did not develop any end point. Total 9 cases and 36 controls were selected.

Statistical calculators were used to calculate mean and standard deviation. Data were analyzed using SPSS software version 17.0 and P value was determined using Chi square test. T test was used to determine the percentage change in lab values. The data were tabulated, analyzed and compared with data from other studies.

RESULTS

100 patients within the age range of 59.69 ± 10.7 years were started on dual antiplatelet therapy with ticagrelor and aspirin, 100 patients with age range of 62.38 ± 10.1 years were started on clopidogrel and aspirin during the study period (Table 1). In the ticagrelor group, 88% were male, 73% had dyslipidemia, 60% had systemic hypertension and 63% had diabetes mellitus while in the clopidogrel group, 83% were male, 77% had dyslipidemia, 60% had systemic hypertension and 53% had diabetes mellitus. Routine follow up was conducted for these patients at 1 month, 3 months, 6 months and 12 months.

The primary end points, a composite of cardiovascular death, unstable angina, MI, secondary revascularization and Congestive Heart Failure (CHF) occurred in 5% of patients in the ticagrelor group and 9% in the clopidogrel group. In ticagrelor group, cardiovascular death occurred for 1% patients, unstable angina for 3% patients and secondary revascularization for 1% patients whereas in clopidogrel group, cardiovascular death occurred for 2% patients, unstable angina for 4% patients and secondary revascularization for 3% patients. But MI and CHF did not occur in either of the groups.

The secondary end points, a composite of bleeding and dyspnea occurred in 11% patients in ticagrelor group and 5% patients in clopidogrel group. In ticagrelor group, 1% patients had bleeding and 10% patients had dyspnea and in clopidogrel group, 5% patients had dyspnea and no patients had bleeding (Table 2 and 3).

The percentage increase of creatinine and uric acid from baseline was higher in the ticagrelor group than in the clopidogrel group throughout the follow up period (13.5 ± 19.2 vs 8.6 ± 21.9 for creatinine and 15.8 ± 27.9 vs 5.4 ± 23.2 for uric acid at 12th month).

DISCUSSION

In the PLATO trial by Wallentin L *et al*, the primary endpoint which was a composite of cardiovascular death, MI or stroke occurred in 11.7% of patients receiving clopidogrel and only 9.8% of patients receiving ticagrelor (P<0.001). MI occurred in 6.9% patients in the clopidogrel group and 5.8% patients in ticagrelor group (P=0.005). Death from vascular causes occurred in 5.1% in clopidogrel and 4% in ticagrelor (P=0.001). Stent thrombosis including definite, probable and possible stent thrombosis occurred in 3.8% in clopidogrel patients and 2.9% in ticagrelor patients.[12] In PEGASUS TIMI 54 trial by Bonaca MP *et al* conducted at 1161 sites in 31 countries, the primary outcome, a composite of death by cardiovascular causes, MI or stroke occurred in 7.85% in ticagrelor 90 mg group (ticagrelor 90 mg compared to placebo; P=0.008), 7.77% in ticagrelor 60 mg group (ticagrelor 60 mg vs placebo; P=0.004) and 9.04% in placebo group. In the present study, similar dosing schedule of 90 mg twice daily was followed by all patients taking ticagrelor. As the study is retrospective, we could not compare different doses of ticagrelor.[13]

The present study compared ticagrelor against clopidogrel in post PTCA patients who received aspirin. The primary endpoint which is a composite of cardiovascular death, unstable angina, MI, secondary revascularization and CHF were higher in patients taking clopidogrel than patients taking ticagrelor (P=0.407). There was no difference statistically between ticagrelor and clopidogrel despite ticagrelor being considered as a more potent antipletelet drug. The limited sample size may be the reason for not obtaining a statistically significant difference in this study. Individually cardiovascular death, secondary revascularization due to stent thrombosis and unstable angina occurred more in clopidogrel group compared to ticagrelor group. Unstable angina and CHF were included in our study as composite end point in addition to the above mentioned studies so as to observe their occurrence in the study population, but there was not a significant difference in both the groups. No patients developed MI and CHF during the 12 months follow up period among both the study drug groups.

In the PLATO trial, the rates of major bleeding were not different in the two study groups (11.6% in ticagrelor group and 11.2% in clopidogrel group). In CURE trial by Yusuf S *et al*, the major bleeding was significantly higher in the clopidogrel compared to placebo (3.7% vs 2.7%; P=0.001).[14] In the PEGASUS TIMI 54 trial, incidence of TIMI major bleeding was higher in ticagrelor 90 mg and 60 mg groups (2.6% and 2.3% respectively) compared to 1.06% in placebo group (P<0.001 for each dose vs placebo).[13] In a study by Cannon CP *et al* 152 sites in 14 countries, the rates of overall bleeding (major and minor) were 9.2%, 10.2% and 10.2% respectively with clopidogrel 75 mg once daily, ticagrelor 90 mg twice daily and ticagrelor 180 mg twice daily. These studies classified bleeding into major bleeding, life threatening bleeding, minor bleeding, non-CABG related bleeding etc.[15]

Table 1: Demographic and baseline characteristics of patients in the study groups

Characteristics	Clopidogrel	Ticagrelor
Demographics		
Mean age	62.38 ± 10.1 years	59.69 ± 10.7 years
Male sex	83 (83%)	88 (88%)
Personal history		
Alcohol use	19 (19%)	9 (9%)
Smoking	23 (23%)	16 (16%)
Cardiovascular risk factors		
Systemic hypertension	60 (60%)	60 (60%)
Diabetes mellitus	53 (53%)	63 (63%)
Dyslipidemia	77 (77%)	73 (73%)
Concomitant medications administered		
Nitrates	35	41
Beta blocker	90	96
ACE inhibitor	11	8
ARB	27	30
Calcium channel blocker	11	7
Statins	100	100
PTCA specifications		
Number of stents		
No stent	1	2
1 stent	63	58
2 stents	30	27
3 stents	5	9
4 stents	0	4
5 stents	1	0
Type of stents		
DES	86	80
BMS	5	6
POBA	1	2
DES and BMS	2	1
DES and POBA.	6	11
Approach route for PTCA		
Right Femoral Artery	98	96
Right Radial Artery	1	3
Left Femoral Artery	1	1

The secondary endpoints of the present study were a composite of bleeding and dyspnea. Occurrence of secondary endpoints were higher in ticagrelor group than in clopidogrel group (P=0.118). Bleeding occurred only in one patient in the ticagrelor group in the first month.

As the incidence of endpoints are small, all composite endpoints whether in primary endpoints or secondary endpoints were clubbed together for analysis.

In PLATO trial, the incidence of dyspnea in ticagrelor group was 6% higher compared to clopidogrel group but in a study by Storey RF *et al*, there was 20.9% increase in incidence of dyspnea in ticagrelor group compared to clopidogrel group.[13,16] In the present study, dyspnea occurred in 5% of patients on treatment with clopidogrel and 10% patients on treatment with ticagrelor. On analysis of the time of onset of dyspnea in ticagrelor group, it was found that 5% of patients had complaints of dyspnea at 1 month follow up, 1% patients at 3 months, 3% patients at 6 months and 1% patients at 12 months and in clopidogrel group 4% patients at 6 months follow up and 6% patients at 12 months follow up. Ticagrelor was stopped after the occurrence of dyspnea in about 6 patients and were started on clopidogrel, following which their condition improved. CHF due to LV systolic dysfunction as the mechanism of dyspnea was ruled out because BNP levels and LV systolic function were also analysed and it was found to be within normal range.

Ticagrelor causes increase in adenosine levels by inhibiting the reuptake of adenosine by inhibition of a sodium independent equilibrative nucleoside transporter mainly ENT 1. It also induces release of Adenosine Triphosphate (ATP) from human RBCs in a dose dependent fashion. Increased adenosine levels can activate vagal-C fibres causing dyspnea. These effects of ticagrelor on adenosine reuptake and ATP release results in induction of dyspnea.[17] Another mechanism for dyspnea is ticagrelor mediated P2Y12 receptor inhibition. These receptors are expressed in neuronal tissues to inhibit neuronal signaling. So, inhibition of these receptors, results an increase in neuronal signaling and thereby dyspnea sensation.[18-20]

In the PLATO trial, there was slight increase in the creatinine and uric acid levels on treatment with ticagrelor than clopidogrel during the study period.[13] In PEGASUS TIMI 54 trial, creatinine level elevation occurred

Table 2: Endpoints in the study groups

End point	Clopidogrel n=100	Ticagrelor n=100	P value
Primary end points: Cardiovascular death, MI, CHF, Secondary revascularization, Unstable angina	9	5	
Cardiovascular death	2	1	
MI	0	0	0.407
CHF	0	0	
Secondary revascularization	3	1	
Unstable angina	4	3	
Secondary end points: bleeding, dyspnea	5	11	
Bleeding	0	1	0.118
Dyspnea	5	10	
Percentage increase in serum creatinine from baseline value			
At 1 month	1.3 ± 14.1	5.0 ± 16.8	0.144
At 3 months	6.2 ± 20.9	8.3 ± 18.3	0.622
At 6 months	4.6 ± 17.9	12.4 ± 14.9	0.009
At 12 months	8.6 ± 21.9	13.5 ± 19.2	0.251
Percentage increase in uric acid from baseline value			
At 1 month	-6.6 ± 22.8	6.3 ± 18.7	0.045
At 3 months	1.7 ± 16.9	16.3 ± 17.9	0.098
At 6 months	3.5 ± 9.4	17.8 ± 20.6	0.001
At 12 months	5.4 ± 23.2	15.8 ± 27.9	0.284

Table 3: Association of risk factors in cases and controls from clopidogrel group.

Risk factors	Case n=9	Control n=36	P value
Hypertension	3	26	0.137
Diabetes Mellitus	5	19	1.000
Dyslipidemia	6	29	0.666
Smoking	3	9	0.682
Proton Pump Inhibitor	8	22	0.234

in 3.3% in ticagrelor 90 mg group, 3.43% in ticagrelor 60 mg group and 2.89% in placebo group and uric acid level elevation occurred in 2.28% in ticagrelor 90 mg group, 1.97% in ticagrelor 60 mg group and 1.51% in placebo group.[14]

In present study, there was increase in the creatinine and uric acid levels in ticagrelor group and clopidogrel group. At first, third, sixth and twelfth month the percentage increase of creatinine from baseline was higher in the ticagrelor group than in the clopidogrel group. Uric acid levels also increased in ticagrelor group and clopidogrel group except at the first month in clopidogrel group. At first month, there was increase in the percentage of uric acid from baseline in ticagrelor group while decrease in the percentage in clopidogrel group. At third month, sixth month and twelfth month, the percentage increase of uric acid values were higher in ticagrelor group than in clopidogrel group. Though statistically significant percentage increase in uric acid levels from baseline were observed at first, third and sixth months, it was not statistically significant at twelfth month. The study population also received Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blocker (ARBs) as concomitant medications which can cause increase in the creatinine levels. But as both the study drug groups received ACE inhibitors and ARBs in a comparable proportion, increase in creatinine and uric acid levels may not be directly related to concomitant drugs.

A nested case control study was conducted in the clopidogrel cohort since there was higher incidence of primary endpoints than ticagrelor. But there was no statistically significant association between risk factors like hypertension, diabetes mellitus, dyslipidemia and social history of smoking and primary endpoints as P values were high which may be due to limited sample size of the study drug. The greater incidence of primary end points in clopidogrel group may also be due to resistance exhibited by the drug.

CONCLUSION

The present study was aimed to compare efficacy and safety of clopidogrel-aspirin combination versus ticagrelor-aspirin combination in patients who underwent angioplasty. Patients were followed up for one year using cardiovascular death, MI, CHF, unstable angina and secondary revascularization as primary end points and bleeding and dyspnea as secondary end points. We observed that the incidence of primary end

points were less in ticagrelor group compared to clopidogrel group whereas incidence of secondary end points were more in ticagrelor group compared to clopidogrel group, but not statistically significant. Incidence of MI and CHF were absent in both the groups. On comparison between both the study drugs, no statistically significant difference was observed in both primary and secondary end points.

The incidence of dyspnea was observed much more in the ticagrelor group compared to clopidogrel group within the same ethnic groups. This may not be due to P_2Y_{12} receptor inhibition alone or drug class effect.

As all patients received same dosage schedule, further studies are required to find out whether changes in dose administered reduces incidence of dyspnea in this ethnic group.

Bleeding, another secondary endpoint occurred only in ticagrelor group in only one patient. Concomitantly administered drugs like organic nitrates, beta blockers, angiotensin converting enzyme inhibitors, angiotensin 2 receptor antagonist and statins for prevention of cardiovascular events were prescribed in comparable proportion in both the study groups.

Creatinine and uric acid levels were slightly increased in patients in the ticagrelor group compared to clopidogrel group, however the difference was not statistically significant.

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CONFLICT OF INTEREST

The author declare no conflict of interest.

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