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A comparative study of Clopidogrel Versus Prasugrel in unstable coronary artery disease managed conservatively

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Abstract
Background: Dual anti-platelet therapy is cornerstone in the management of patients with acute coronary syndrome (ACS). The most commonly prescribed combination is aspirin (A) and clopidogrel (C). However, both drugs have the problem of drug resistance (5-40% and 30%, respectively), resulting into vascular events. Prasugrel (P), the newer antiplatelet agent is supposedly better because of different pharmacokinetic profile. However, it is not approved for use in patients with ACS not undergoing intervention.
Aim: The present study was aimed at evaluating the effects of P and C on recurrent angina, MI, and stroke within 30 days in patients with ACS managed conservatively, with similar background therapy.
Methods: This study was done on 63patients presenting with ACS, diagnosed on the basis of clinical history, ECG findings and cardiac enzymes changes, managed conservatively. The patients were randomized in a1:1 fashion in two groups. The group 1 patients received P (60 mg loading followed by 10 mg P.O. daily, dose was reduced to 30 mg loading and 5 mg maintenance dose in patients aged > 75 years and weight < 60 kgs) and the group 2 patients received C (300mg loading followed by 75 mg P.O. daily). Patient in both the groups received aspirin (325 mg loading followed by 75 mg P.O. daily), atorvastatin (40 mg P.O. daily), weight adjusted enoxaparin and antianginal therapy as appropriate. There were no significant demographic differences between patients in the two groups.
Result: The study showed that patients on P responded better, irrespective of age, sex, presence or absence of diabetes, dyslipidemia, ECG changes, and troponin positivity.
There was a relative risk reduction of 35.61% (relative risk (RR), 0.64; 95% confidence interval (CI), 0.44-1.01; P=0.05) in the incidence of composite of primary end points in the group receiving prasugrel.
No major or minor bleeding episodes were seen in any patient. Although our study is under powered, it creates space for a larger study with prasugrel to find out the true significance of our observation.
Conclusions: The present study concluded that prasugrel significantly reduces the incidence of composite of refractory ischemia, MI and CV death and non-significantly reduced refractory ischemia, MI and CV death in patients of ACS managed conservatively.

Keywords: Psychiatric disorders, suicide, suicide attempt; first admission; recurrent admission; schizophrenia; bipolar disorder; depression; substance abuse disorder

Introduction

Coronary artery disease is a major public health problem worldwide including India. Despite major advances in prevention and treatment it remains to be a leading cause of death worldwide contributing to 15% of all cause mortality [1].
Coronary artery disease comprises of two subsets of patients i.e. stable coronary artery disease and unstable coronary artery disease. Unstable coronary artery disease is also referred to as acute coronary syndrome (ACS). ACS accounts for approximately 2.5 million hospital admissions worldwide annually and 30-40% of all diagnosed acute coronary cases are non ST-elevation (NSTE) ACS [1, 2]. It results from acute obstruction of a coronary artery. It may present as unstable angina (UA) or Non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI) or sudden cardiac death (SCD).
There are two approaches for the management of ACS [3]. Early invasive (aggressive) approach- this involves treating patients aggressively with coronary intervention along with medical treatment to stabilize ischemia.

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Early conservative approach: This involves treating patients aggressively with drugs to stabilize ischemia, and then evaluate non-invasively.

The decision is usually based upon the risk stratification of these patients which can be done on the basis of TIMI score [4, 5]. However, in our country early invasive treatment is not easily and widely available and patients often have poor financial support, so we have to depend upon an aggressive medical treatment in these patients. Risk during this critical phase can be reduced by optimal antiplatelet and anticoagulant therapy in conservatively treated patients as well as patients scheduled for coronary intervention.

Prasugrel, is an orally administered, P2Y12 receptor antagonist that has prompt, more potent, and more persistent inhibition of platelet aggregation than currently approved doses of clopidogrel. In a large randomized clinical trial, it was found to be more effective than clopidogrel in reducing the events in patient with both, STEMI and NSTEMI undergoing percutaneous coronary intervention (PCI). It is currently approved for use in patients with ACS undergoing PCI as an alternative to clopidogrel [6].

The purpose of the present study was to find out the effectiveness of prasugrel in patients not undergoing coronary interventions in a 1:1 randomized study in two groups of patients.

Aims and objectives: To evaluate the efficacy and safety of prasugrel versus clopidogrel in the clinical outcome of patients with UA, NSTEMI, and STEMI with the objective to assess all cause mortality, myocardial infarction, stroke and recurrent ischemic episodes.

Methodology: This was a prospective study, carried out over a period of one academic year in the Department of Medicine, BRD Medical College and associated Nehru Chikitsalya, Gorakhpur (U.P.). The study comprised of 63 cases of UA, NSTEMI and STEMI (male 48, female 15), diagnosed on the basis of Braunwald's definition of UA (Braunwald clinical classification of UA/NSTEMI) [7]. Diagnosis of NSTEMI was made on the basis of elevated cardiac enzymes (troponin I and CKMB) [8, 7].

Inclusion criteria- Patients more than 30 years of age judged to have ACS. An informed written consent was obtained from all the patients enrolled in the study.

Exclusion criteria- patients with stable angina, prinzmetal angina, bleeding diathesis, anemia, thrombocytopenia, a history of pathological intracranial findings and history of TIA, stroke [9]. The selected patients were subjected to detailed evaluation of history and physical examination at time of registration in the study.

Clinical profiling of the patients was done. Presenting symptoms, general and cardiovascular examination were recorded. A 12 lead ECG was obtained in all the patients at the time of presentation and repeated as needed. Routine tests like hemoglobin, total leukocyte and differential leukocyte count, platelet count, random blood sugar, serum urea and creatinine and urine examination, fasting lipid profile, cardiac biomarkers- CK-MB, Trop I, chest X-ray in PA view, 2D- Echocardiography (for assessment of regional wall motion abnormalities and left ventricular ejection fraction or any other abnormality) were done. The follow-up schedule of the patients included symptomatic assessment,

BP monitoring, heart sounds, respiratory sounds, ECG, 2D-Echocardiography. Primary end points-Refractory ischemia, MI, Stroke, Death were recorded at time of presentation and on 30th day. The study was a 1:1 randomized comparative trial in which patients were divided into two groups:
Group (1) Aspirin + LMWH + β blockers + Statin + Clopidogrel Group (2) Aspirin + LMWH + β blockers + Statin +Prasugrel

Dose of clopdogrel: 300 mg loading dose, 75 mg maintenance dose.

Dose of prasugrel: 60 mg loading dose, 10 mg maintenance dose.
Dose of Prasugrel was reduced to 30 mg loading and 5 mg maintenance dose in patients having age > 75 years, and weight < 60 kgs.

Statistical test of significance- Z score was applied as test of significance and P values were calculated by standard statistical tables [10]. The study was approved by Institutional Ethics Committee.

Observations- The total number of patients included in the study was 63. Among them 76.2% were males 23.8%females. 42.85% were ≥65 years of age. The overall mean age was 58.9±7.86 years and the male to female ratio was 3.2:1.

Table 1: Clinical profile of the patients

Clinical Features	Clopidogrel group (%)	Prasugrel group (%)	Z test	P value
Chest Pain and other symptoms	86.66	87.87	0.5388	0.59
Known CAD	13.33	9.09	0.3889	0.70
Prior Aspirin Users	6.66	0	1.4255	0.15
Prior Antihypertensives Users	3.33	6.0	0.5843	0.56
Hypotension	6.66	12.12	0.8366	0.40
Bradycardia	10	1.58	1.0162	0.30
Tachycardia	6.66	12.12	0.8366	0.40
Hypertensive	2.0	9.09	1.2358	0.21
Diabetic	13.33	18.18	0.5259	0.60
Pedal Edema	3.33	12.12	1.3690	0.16
Hepatic Congestion	0	0	1.7014	0.08
Pulmonary Rales	36.66	36.36	0.2306	0.80
Muffled Heart Sounds	3.33	6.06	0.5843	0.56

All the patients had chest pain. In clopidogrel group, 86.66% patients (26 out of 30) had other symptoms like breathlessness, anxiety, diaphoresis, radiation, etc compared with 87.87% patients(29 out of 33) in prasugrel group. The difference was not significant (Z=0.5388848, p> 0.05).In the clopidogrel group 13.33% patients had history of prior CAD compared with 9.09% patients in prasugrel group. The difference was also not significant (Z=0.3889221, p=0.70). Prior aspirin users were 6.66% (2 out of 30) in clopidogrel group and none in prasugrel group (Table 1).

Table 2: Troponin I Status

Status	Clopidogrel group		Prasugrel group		Z test	P value
	No.	%	No.	%		
Normal	03	10.0	03	9.09	0.1227	0.90
Elevated	27	90.0	30	90.91	0.1227	0.90
Total	30	100.0	33	100.0		

Troponin I was elevated in 90% patients (27 out of 30) in the clopidogrel group compared with 90.9% patients (30 out of 33) in the prasugrel group. The difference in the status of troponin I positivity in the two groups was not significant (p=0.90) (Table 2).

Table 3: Echocardiographic Findings

Status	Clopidogrel Group		Prasugrel Group		Z test	P value
	No.	%	No.	%		
Normal	3	10.0	3	9.09	0.1227	0.90
RWMA	27	90.0	30	90.90	0.1227	0.90
EF < 40%	6	20.0	10	30.30	0.9383	0.90
EF ≥ 40%	24	80.0	23	69.69	0.9383	0.90

The difference in status of 2D-echocardiography parameters in the two groups was not significant (p=0.90) (table 3). The patients in both groups, clopidogrel and prasugrel, did not differ in use of drugs like β-blockers, CCBs, diuretics, and non-hemodynamic antianginal drugs.

Table 4: Number of Lipid Abnormalities

Lipids	Clopidogrel group		Prasugrel group		Z Test	P value
	No.	%	No.	%		
Normal	03	10.0	01	3.03	1.1330	0.25
Abnormal	27	90.0	32	96.97	1.1330	0.25
High TC	05	16.66	10	30.30	1.6107	0.10
High TGs	10	33.33	07	21.21	1.1718	0.24
High LDL-C	16	53.33	26	78.78	0.9722	0.33
Low HDL-C	11	36.66	17	51.51	1.4031	0.16

All the patients had their lipid profile estimated at the time of enrolment in the study. In the clopidogrel group, 16.66% patients had high TC, 33.33% had high triglyceride levels, 53.33% had high LDL-C, and 36.66% had low HDL-C, whereas in prasugrel group, proportion was 30.30%, 21.21%, 78.78%, and 51.51%, respectively (according to NCEP ATP III criteria). The difference between two groups was not significant for any of these parameters (p >0.05) (Table-4).

Table 5: Primary and Composite of Primary End Point

Primary end points	Clopidogrel group		Prasugrel group		RR (%)	Z test	P value
	No.	%	No.	%			
Refractory Ischemia	13	46.42	10	33.33	28.19	1.018	0.31
MI	3	10.71	2	6.66	37.81	0.5488	0.58
CV Death	5	17.85	3	10.0	43.97	0.8671	0.38
Total of composite of refractory ischemia, MI, death	21	75.0	15	53.33	35.61	1.96079	0.05

The overall incidence of composite of primary end points was 75% (21 out of 28) in clopidogrel group compared with 53.33% in prasugrel group. Thus, there was a relative risk reduction of 35.61% in the incidence of composite of primary end points in the group receiving prasugrel, which was significant (z=1.96079, p=0.05) (Table 5).

Adverse effects- None of the patient in the study showed any adverse effect of prasugrel, which include TIMI major (intracranial bleed and bleeding which requires blood transfusion) or TIMI minor (e.g. epistaxis, gum bleeding etc. not requiring blood transfusion) bleeding episodes. The drug was well tolerated by all the patients.

Discussion: Acute Coronary Syndrome (ACS) is one of the leading causes of mortality worldwide including India. The present ACC/AHA guidelines recommend early invasive strategy for management of these patients except for the low risk patients who can be managed conservatively. Patients are more often managed with aggressive conservative therapy which comprises of dual antiplatelet therapy in the form of aspirin and clopidogrel and ancillary treatment mainly a beta-blocker and statins. Adding clopidogrel to aspirin increases antiplatelet response by 20% over that of aspirin alone, which contributes to nearly 50% antiplatelet action. Despite dual antiplatelet therapy, the patients of UA/NSTEMI develop recurrent ischemic events and/or death {9.3% patients still had recurrent ischemia, MI or death on dual antiplatelet therapy compared with 11.4% on aspirin alone (CURE trial)} [11]. This may be because of hypo-responsiveness or lack of response to the antiplatelet action of these agents, which is referred to as resistance (5-40% for aspirin and up to 30% for clopidogrel in various trials) [12, 13, 14]. Although aspirin resistance may be assessed by measuring urinary 11-dehydrothromboxane B$_2$, which is high in hypo- or non-responders[14], there are no surrogate laboratory parameters to measure resistance to the antiplatelet action of clopidogrel and the direct methods to assess its antiplatelet action (aggregometry) are too cumbersome to be used practically. Thus, resistance is judged clinically on the basis of increased incidence of recurrent ischemia, MI or death among the hypo- or non-responders. To overcome this shortcoming, addition of newer antiplatelet agents such as prasugrel, is likely to be effective. This has been approved for use in patients undergoing percutaneous coronary intervention [Class I indication, level of evidence A] [15, 16, 17].

Refractory ischemic, MI, CV death, Stroke and composites- The incidence of refractory ischemia as judged by recurring chest pain despite treatment was 43.33% (13 patients) in the clopidogrel group as compared with 30.3% (10 patients) in the prasugrel group. There was a risk reduction of 28.19% in the favour of prasugrel though it was not significant (z=1.018, p=0.31). MI occurred in 3 patients (10.0%) in clopidogrel group compared with 2 (6.06%) in the prasugrel group. There was a risk reduction of 37.81% in the favour of prasugrel, though not significant (z=0.5488, p=0.58). Five patients (16.66%) died in clopidogrel group compared with 3 patients (9.09) in prasugrel group. There was a reduction of 43.97% in favour of prasugrel, though not significant (z=0.8671, p=0.38). The overall incidence of composite of primary end points was 75% (21 out of 28) in clopidogrel group compared with 53.33% in prasugrel group(30 out of 33). Thus, there was a relative risk reduction of 35.61% in the incidence of composite of primary end points in the group receiving prasugrel, which was significant (z=1.96079, p=0.05). Several studies with antiplatelet agent aspirin have shown unequivocal improvement (approximately 50%) in outcomes in patients with ACS treated with aspirin alone. Adding clopidogrel further

reduces the outcomes by another 20% (CURE trial) [11]. A head to head comparison of aspirin versus clopidogrel (CAPRIE trial) [18]. Showed evidence in favour of clopidogrel over a follow-up of 1.91 years. This is also supported by CREDO trial [19]. Which yielded a relative risk ratio of 26.9% in patients undergoing elective PCI. However, despite the superiority of clopidogrel over aspirin, and add-on therapy, there remains a significant proportion of patients that still develop clinical end-points, pointing towards lack of efficacy of the therapeutic regimen.

Prasugrel, a newer thienopyridine, that has prompt, more potent, and prolonged action has been shown to be superior to clopidogrel in patients undergoing elective PCI (type 4) [20]. A post-hoc analysis of these patients has demonstrated a reduction in spontaneous MI (type 1) [20]. Not related to intervention, though not significant, as well. Our data also shows a significant reduction in vascular outcomes with prasugrel compared with clopidogrel. Thus, we found that prasugrel reduces the risk of refractory ischemia, MI and death in patients of STEMI/UA/NSTEMI. The drug was well tolerated without any adverse effect any patient.

Conclusions
The standard care today, for patients with acute coronary syndrome is PCI/CABG surgery (ACC/AHA and ESC class I indication, level of evidence A) [10, 11, 12]. Drug treatment consisting of dual antiplatelet blockade and enoxaparin along with β-blockers and statin also enjoy similar status. At the same time, resistance to antiplatelet actions of aspirin and clopidogrel is well known, for which easy markers are not available and occurrence of an event may be the first clue. Replacement of clopidogrel, with prasugrel may be a step that could overcome the problem of resistance to clopidogrel.

From the present study we conclude that prasugrel significantly reduces the incidence of composite of primary end points and non-significantly reduces refractory ischemia, MI and CV death individually, in patients of ACS managed conservatively. Therefore, in a country like ours, where mainly conservative strategy is utilized, scope of use of prasugrel in such patients is there. The current ACC/AHA and ESC guidelines also recommend the use of prasugrel for upstream management of patients with ACS undergoing PCI.

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