Original Article

Evaluation of the relative efficacy and safety of prasugrel and clopidogrel in medically managed high risk UA / NSTEMI ACS population

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ABSTRACT

Background: *The term "acute coronary syndrome" encompasses unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) and ST-segment elevation myocardial infarction (STEMI). Antiplatelet therapy is one of the cornerstones of therapy in UA/NSTEMI.*

Objective: *To compare efficacy and safety of Prasugrel and clopidogrel both theinopyridines antiplatelet drugs in high risk (TIMI Score 3 or more) medically managed UA/NSTEMI.*

Materials and Methods: A prospective, randomized study was conducted in GNDH, Amritsar. 100 patients were included, 50 patients received Prasugrel and 50 received clopidogrel. Outcomes like angina episodes, bleeding, stroke, ischemic ECG changes, and arrhythmia were compared during hospital stay and follow-up for 3 months.

Results: *Prasugrel was associated with significant lower incidence of major adverse cardiac event (MACE) 9 compared to 19 with clopidogrel during hospital stay. During follow up for 3 months 2 events occurred with Prasugrel and 3 with clopidogrel which were non-significant.*

Conclusion: *Use of Prasugrel was associated with less number of MACE than the patients who were on clopidogrel. Although for the individual adverse coronary events, except for angina there was no statically significant difference, but when the total MACE observed during the study was compared, it was significantly less in the patient on Prasugrel therapy. Safety of the Prasugrel in present study was identical to clopidogrel.*

Key Words: *Unstable angina, non ST elevation myocardial infarction, prasugrel, clopidogrel*

Introduction

Unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) is characterized by an imbalance between myocardial oxygen supply and demand. Most often, the syndrome develops because of decreased myocardial perfusion resulting from coronary narrowing caused by non-occlusive thrombus formation subsequent to disruption of an atherosclerotic plaque. Unstable angina is defined as angina pectoris (or equivalent type of ischemic discomfort) with at least one of three features; (1) occurring at rest (or minimal exertion) and usually lasting >20 minutes (if not interrupted by nitroglycerin administration); (2) being severe and described as frank pain, and of new onset i.e., within 1 month; and (3) occurring with a crescendo pattern i.e., more severe, prolonged, or frequent than previously.[1] Antiplatelet therapy is one of the cornerstones of therapy in UA/NSTEMI.

Despite advances in the management of symptomatic atherosclerotic disease, thromboembolic complications still occur at sites of plaque instability. Endothelial disruption and platelet recruitment, activation, and aggregation are fundamental to the

pathogenesis of arterial thrombosis.[2] Aspirin has been the mainstay of antiplatelet therapy, preventing platelet aggregation with irreversibly inhibiting the formation of thromboxane A2, which reinforces the effects of other physiologic platelet agonists, such as adenosine diphosphate (ADP) and collagen.[3] Although a standard dose of aspirin has been shown to reduce the risk of vascular occlusion by as much as 25%,[4] most arterial thrombotic events still occur in patients who are currently taking aspirin.

Adenosine diphosphate (ADP) is recognized as one of the most important mediators of both physiologic hemostasis and thrombosis. [5-7] The thienopyridine derivatives are antiplatelet agents that, by covalently binding to a cysteine residue of the $P2Y_{12}$ receptor, irreversibly modify the platelet $P2Y_{12}$ receptor. Consequently, platelets are affected for the remainder of their lifespan (7–10 days). However, only 60–70% of the ADP receptors are sensitive to the effects of thienopyridines. [8-10]

The thienopyridines are prodrugs that must be metabolized in vivo into active form. Both Prasugrel and clopidogrel require CYP450 metabolism for the generation of active metabolites, but the pathways leading to conversion to the active metabolites differ between the prodrugs. [11,12] The short-term and long-term benefits of dual-antiplatelet therapy with aspirin and clopidogrel have been established for patients with acute coronary syndromes and those undergoing percutaneous coronary intervention (PCI).[13-17]

Clopidogrel has proved useful for the prevention of ischaemic stroke, myocardial infarction, and vascular death in patients with symptomatic atherosclerosis.[18] Beyond its anti-aggregatory effect, it reduces the formation of platelet–leukocyte conjugates in patients with ACSand decreases the expression of activated platelet-dependent inflammatory markers such as CD40 ligand (a potent stimulus of vascular inflammation) and CD62 P-selectin in patients undergoing percutaneous coronary intervention (PCI).[19-21]

Important limitations of clopidogrel remain, such as only a modest antiplatelet effect, with substantial interpatient variability and a delayed onset of action. Small clinical studies have suggested that patients with a reduced pharmacologic response to clopidogrel may be at increased risk for adverse clinical events, including myocardial infarction and coronary-stent thrombosis. [22-27]

As with clopidogrel, the prasugrel active metabolite binds to cysteine sulphydryl groups in the $P2Y_{12}$ receptors irreversibly, rendering the receptors unable to respond to ADP and producing inhibition of platelet function for the lifetime of the affected platelet. Prasugrel differs from clopidogrel, however, in that it has a more rapid onset of action after oral administration, it achieves greater and more consistent platelet inhibition in individual patients and thus its antiplatelet effects are much more predictable. [28,29] This is achieved mainly because the metabolism of the drug differs from that of clopidogrel and far greater and more predictable amounts of active metabolite are produced. For example, polymorphisms in CYP2C9 and CYP2C19 genes do not affect prasugrel metabolism, unlike the metabolism of clopidogrel. [30]

The effects of Prasugrel are time and dose dependent with a single, oral 40-60 mg loading dose (LD) producing rapid and consistent inhibition of ADP-stimulated platelet aggregation, with a near-maximal effect seen in healthy volunteers 60-90 minutes after dosing.

This effect is maintained for at least 24 hours, reflecting the irreversible nature of platelet inhibition. [31]

Material and Methods

The study was conducted on 100 patients of high risk Unstable Angina (UA)/Non ST elevation myocardial infarction (NSTEMI) admitted to Guru Nanak Dev Hospital, Amritsar. It was an open label randomized trial where patient were allocated to two groups of 50 each who fulfilled the inclusion and exclusion criteria.

Inclusion Criteria

- Ischemic symptoms lasting 10 minutes or more and occurring within 72 hours before randomization
- A TIMI risk score of 3 or more
- Either ST-segment deviation of 1 mm or more or elevated levels of a cardiac biomarker of necrosis
- Had a medical management strategy decision made with reasonable certainty that neither PCI nor CABG is planned for treatment of the index event

Exclusion Criteria

- Patient not giving informed consent.
- Patient likely to undergo PCI/coronary intervention
- Previous or planned PCI or CABG as treatment for the index event.
- PCI/CABG within previous 30 days
- STEMI as the index event
- Cardiogenic shock, Refractory ventricular arrhythmias, NYHA Class IV CHF within the previous 24 hours
- History of ischemic or hemorrhagic stroke, TIA, Intracranial neoplasm, arteriovenous fistula
- History of spontaneous GI or non-GI bleeding requiring hospitalization for treatment, unless definitive Rx has occurred and there is low likelihood of recurrence
- Hemodialysis or peritoneal dialysis
- An increased risk of bleeding, anemia, thrombocytopenia, a history of pathologic intracranial findings, or the use of any thienopyridine within 5 days before enrollment.
- Age >75 years, body weight <60kg on entry.

In group-A patients received aspirin and prasugrel (40 mg loading dose with 10 mg maintenance dose) with standard anti-ischemic treatment and group-B patients received aspirin and clopidogrel (300 mg loading dose with 75 mg maintenance dose). Patients coronary and non-coronary outcome were measured during hospital stay and during follow up for upto 3 months.

Results

Total 100 patients were enrolled divided in two groups of 50 patients each. The mean age of group-A was 54.52; mean age of group-B was 56.98. In group-A most of the patients were in 50-59 years age group while in group-B majority of the patients were in 60-69 years age group (Table-1).

In group-A majority of the patients (52%) were male as well as in group-B (60%). Female constituted 48% of the group-A and 40% of the group-B. In group-A most of the patients were in 50-59 years age group while in group-B majority of the patients were in 60-69 years age group.

Most common risk factor in group-A was hypertension which was present in 58% of the patients and in group-B it was present in 52 % of the patient. Second most common risk factor was obesity 42% in group-A and 40% patients in group-B. The least common risk factor was family history of coronary artery disease which was present only in 14% of patients in group – A and 12% in group – B. (Table 2, Fig. 1)

Table 1: Age distribution of study groups

AGE(years)	GROUP-A(n=50)	GROUP-B(n=50)
30-39	2	3
40-49	10	6
50-59	19	16
60-69	16	20
70-75	3	5
Mean age ± SD(years)	54.52±10.01	56.98±10.06

Table: 2 Risk factor profile at admission

	Group-A(n=50)	Group-B(n=50)	p-value
Current smoker	14	14	N.S.
Diabetes mellitus	12	13	N.S.
Hypertension	29	26	N.S.
Family history	7	6	N.S.
Obesity(BMI>25)	21	20	N.S.
Lifestyle	17	19	N.S.
Raised cholesterol	15	12	N.S.

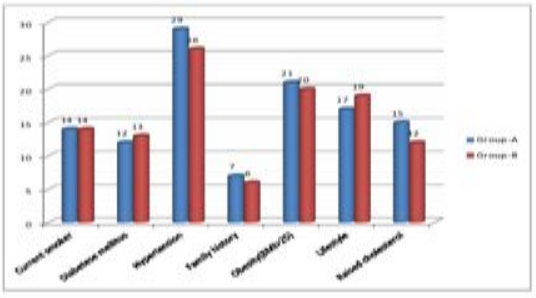

Fig. 1 Risk factor profile of study groups

TIMI Score on presentation

TIMI RISK score of both the study groups' patient was comparable with the difference being statistically non-significant. The mean TIMI Risk score of group-A was 3.18±0.38 and of group-B was 3.24±0.43. The most common TIMI risk score element occurring in the both the study group was ST deviation of 0.5 mm or more. The second most common factor present was episodes of two or more chest pain in previous 24hrs. The least common element was the known coronary artery disease in the past. A total of 159 elements were present in group-A and 162 were present in group-B.

Events during hospital stay

During hospital stay all the major adverse coronary event were recorded. Numbers of deaths were equal in both the study group. One patient expired in Group-A and one in Group-B. Left ventricular failure (LVF) was observed in two patient in Group-A and in four patient in Group-B. Recurrent angina occurred in 3 patient in Group-A and 9 patient in Group-B ($p<0.05$). Ischemia with ECG changes was noted in 3 patients in Group-A and 5 in Group-B patients. No major or minor bleeding episodes were there in both the study groups during stay at hospital. Similarly, there was no arrhythmia or stroke in both the study groups during hospital stay (Table 3, Fig. 2).

Table: 3 Events during stay in the hospital

Events	Group A (n=50)	Group B (n=50)	p-value
Death	1	1	-
Major bleeding episode	Nil	Nil	-
Minor bleeding episode	Nil	Nil	-
Arrhythmia	Nil	Nil	-
Left Ventricular Failure(LVF)	2	4	N.S.
Recurrent angina	3	9	<0.05
Stroke	Nil	Nil	-
Ischemia with ECG Changes	3	5	N.S.
Total MACE	9	19	<0.05

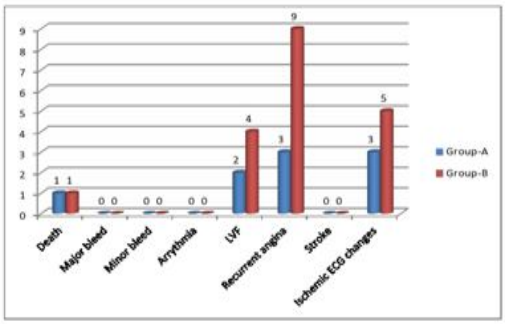

Fig. 2 Events during hospital stay

Events during follow up

All patients were followed up to 90 days and were called in clinic or any time when major coronary event occurred. In both the study groups within 90 days of follow up, one patient in Group-A and one patient in group-B suffered from minor bleeding episode. Ischemia with ECG changes occurred in one patient in Group-A and two patients in Group-B. There were no other significant events in both the study groups during the follow up of 90 days (Table-4, Figure-3).

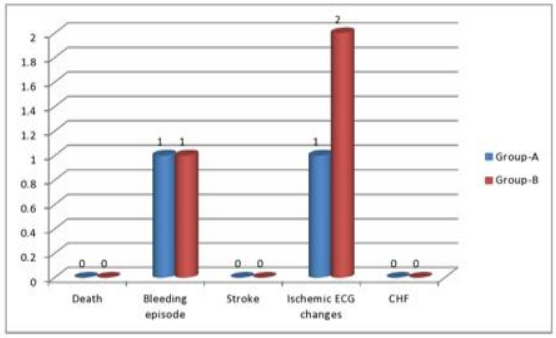

Fig. 3 Events occuring during follow up

Total events during the study

When total events during the study are concerned, a total of 11 events occurred in Prasugrel group and a total of 22 events occurred in Clopidogrel group (Figure-4).

Table: 4 Events after discharge from hospital

Events	Group A(n=50)	Group B(n=50)	p-value
Death	NIL	NIL	-
Bleeding episode	1	1	-
Stroke	NIL	NIL	-
Ischemia with ECG changes	1	2	N.S.
CHF	NIL	NIL	-
Total MACE	2	3	N.S.

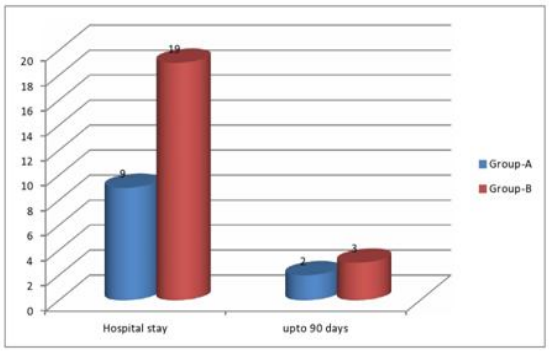

Fig. 4 Total events during study

Discussion

The mean age of group-A was 54.52; mean age of group-B was 56.98. In group-A most of the patients were in 50-59 years age group while in group-B majority of the patients were in 60-69 years age group (Table-1). In the TRITON-TIMI 38 trial the median age of patient in both the groups was 61 years. In the PRINCIPLE-TIMI 44 Trial, the mean age of the patient in Prasugrel group was 64 years while that of the clopidogrel group was 63.8 years. In the JUMBO-TIMI 26 trial, the median age of the patients in Prasugrel group was 59 years while that of clopidogrel group was 58 years.[32,33,34] Thus in relation to the age distribution, the patients in our study were of younger age than their counterparts in the earlier conducted studies. Heart disease are occurring in Indians 5 to 10 years earlier than in other population around the world (Hughes et al; Enas, Dhawan, et al).[35,36] According to the INTERHEART study, the median age for first presentation of acute MI in the South Asian (Bangladesh, India, Nepal, Pakistan, Sri Lanka) population in 53 years, whereas that in Western Europe, China, and Hong Kong in 63 years, with more men than women affected(Yusuf et al).[37]

In group-A majority of the patients (52%) were male as well as in group-B (60%). Female constituted 48% of the group-A and 40% of the group-B. In group-A most of the patients were in 50-59 years age group while in group-B majority of the patients were in 60-69 years age group.

Most common risk factor in group-A was hypertension which was present in 58% of the patients and in group-B it was present in 52 % of the patient. Second most common risk factor was obesity 42% in group-A and 40% patients in group-B. The least common risk factor was family history of coronary artery disease which was present only in 14% of patients in group-A and 12% in group-B (Table-2). In TRTON-TIMI 38 TRIAL, hypertension was the major risk factor (56% in Group-A and 52% in Group-B), followed by Obesity (42% in Group-A and 38% in Group-B). In PRINCIPLE-TIMI 44 TRIAL, dyslipidemia was present in 92.2% of Prasugrel group while 86.9% of the clopidogrel group of the patients. Similarly DM in 32.4% versus 29.4% of the Prasugrel and clopidogrel group of the patients. There were present 17.6% smokers in Prasugrel group and 16.2% in the clopidogrel group. In the JUMBO-TIMI 26 TRIAL, smokers were present in 23% of the Prasugrel group and 31% of the patient in the clopidogrel group. DM was present in 27% versus 25% of the Prasugrel and clopidogrel group of the patient respectively.

The mean TIMI Risk score of group-A was 3.18±0.38 and of group-B was 3.24±0.43. The most common TIMI risk score element occurring in the both the study group was ST deviation of 0.5 mm or more. It was present in 84% patients in group-A and in group-B. The second most common factor present was episodes of two or more chest pain in previous 24hrs which was present in 70% patients in group-A and 62% in group-B. The least common element was the known coronary artery disease in the past which was only in 4% cases of group-A and 2% cases of group-B. A total of 159 elements were present in group-A and 162 were present in group-B.

During hospital stay all the major adverse coronary event were recorded. Numbers of deaths were equal in both the study group. One patient expired in Group-A and one in Group-B. Left ventricular failure (LVF) was observed in two patient in Group-A and in four patient in Group-B. Recurrent angina occurred in 3 patient in Group-A and 9 patient in Group-B ($p<0.05$). Ischemia with ECG changes was noted in 3 patients in Group-A and 5 in Group-B patients. No major or minor bleeding episodes were there in both the study groups during stay at hospital. Similarly, there was no arrhythmia or stroke in both the study groups during hospital stay. Thus it is clear that patients on Prasugrel had lower incidence of adverse coronary events like LVF, Recurrent angina, and ischemia with ECG changes than the patient on clopidogrel therapy. When the total No. of major adverse cardiac events observed during the hospital stay is compared, they are significantly more in Clopidogrel group than Prasugrel group (19 vs 9). All patients were followed up to 90 days and were called in clinic or any time when major coronary event occurred. In both the study groups within 90 days of follow up, one patient in Group-A and one patient in group-B suffered from minor bleeding episode. Ischemia with ECG changes occurred in one patient in Group-A and two patients in Group-B. There were no other significant events in both the study groups during the follow up of 90 days. A total of 2 MACE occurred in Group A while 3 in Group B (p value>0.05). Prasugrel and Clopidogrel were comparable in their efficacy up to 3 month after stabilization of unstable angina. Bleeding was not observed more frequently in Prasugrel group treated patient in present study unlike other studies.

When the total number of major adverse cardiac events observed during the study period in both the study group were compared, there was a significant difference ($p<0.05$) between the two groups, in relation to the events during hospital stay. Considering the total MACE after discharge from hospital and to follow up, occurred 2 events in Prasugrel group and 3 events in clopidogrel group. The number of MACE after discharge was also more in clopidogrel group (although statistically non-significant). When total events during the study are concerned, a total of 11 events occurred in Prasugrel group and a total of 22 events occurred in Clopidogrel group.

Safety of the Prasugrel in present study was identical to clopidogrel. There was no increased risk of bleeding associated with prassugrel in our study. Prasugrel could be particularly useful in our country where high grade UA/NSTEMI patients either can't afford coronary intervention or it is not available in the centers where patient primarily presented.

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