Original Article

Comparison of lower loading dose of prasugrel with conventional loading dose of prasugrel in Indian patients undergoing percutaneous coronary interventions

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ABSTRACT

Background: Although conventional 60 mg of prasugrel allows for rapid and potent platelet inhibition within 30 min after loading dose, the efficacy and safety of lower doses of prasugrel in Indian patients has not yet been investigated.
Objective: The study sought to compare the efficacy of a lower loading dose of prasugrel with conventional loading dose of prasugrel in Indian patients.
Material and methods: Three hundred thirty-two Indian patients undergoing elective percutaneous coronary intervention (PCI) were enrolled in the study. Participants were randomly administered loading doses of prasugrel 60 mg (group A, $n = 166$) or 30 mg (group B, $n = 166$) before undergoing elective PCI in a 1:1 manner. Primary efficacy end point was composite of in-hospital death and stent thrombosis at 96 h, while safety end point was in-hospital bleeding.
Results: The two groups did not differ in their baseline characteristics. The primary efficacy end point was 0.6% in both the conventional 60 mg loading dose (LD) and lower 30 mg LD groups (p = not significant). Minor bleeding was significantly less in group B [Bleeding Academic Research Consortium 1, A = 6.63% vs B = 1.81%, odds ratio (OR) = 3.86, 95% confidence interval (CI) = 1.06—14.08, $P = 0.05$]. Major bleeding was higher in group A (A = 3.61%, vs B = 1.81%, OR = 2.04, 95% CI = 0.50—8.29, $P = 0.50$).
Conclusion: In Indian patients, 30 mg of prasugrel loading is as effective as 60 mg of prasugrel with significantly less minor bleeding.
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1. Introduction

Prasugrel is a more potent P2Y12 inhibitor with faster onset of action (<1 h) and minimal interindividual variability than clopidogrel. It is a prodrug that requires a single CYP-dependent conversion to the active metabolite but has more efficient absorption and rapid conversion to active metabolite in contrast to clopidogrel.[1–3] In addition, common functional CYP genetic variants do not affect prasugrel active drug metabolite levels, and it provides more uniform and more potent inhibition of platelet aggregation compared with clopidogrel.[2,4] Prasugrel was approved in 2009 by the Food and Drug Administration as an alternative to clopidogrel for dual antiplatelet therapy in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) based largely on the results from the TRITON-TIMI 38 trial, which compared the effects of clopidogrel and prasugrel in patients with ACS undergoing PCI.[5] The evidence on safety and efficacy of prasugrel among patients undergoing elective PCI is limited. Also, a number of concerns have been raised in relation to the differences in pharmacodynamic and pharmacokinetic responses to prasugrel in East Asian ethnicities.[6,7] It has been demonstrated that a lower prasugrel loading dose (LD) can result in more potent pharmacodynamic effects than clopidogrel 600 mg with comparable efficacy to conventional prasugrel LD when administered to healthy Korean subjects.[8] The efficacy and safety of lower doses of prasugrel in Indian patients has not been investigated. We compared the efficacy of a lower LD 30 mg of prasugrel with conventional 60 mg LD of prasugrel in Indian patients undergoing elective PCI.

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2. Methods

2.1. Study population

It was a prospective double-blind single-center study, which included patients (18–70 years) admitted in coronary care unit from January 2014 to February 2015 with stable or unstable angina undergoing elective PCI. Those with a previous history of transient ischemic attack or stroke, intracranial neoplasm, or uncontrolled malignant disease were excluded. In addition, those with a history of antiplatelet other than aspirin or anticoagulation treatment within the previous month, contraindications to the study drug, bleeding diathesis, hemoglobin <10 g/dL, platelet count <100000/mm^3, significant renal insufficiency defined as a glomerular filtration rate <60 mL/min/1.73 m^2, significant hepatic impairment defined as serum liver enzyme or bilirubin >3 times normal limit, and body weight less than 60 kg were also ineligible. All the subjects who participated in the study provided written informed consent before participation.

2.2. Study protocol

The study patients received LD of prasugrel and underwent elective PCI in accordance with the current recommended guidelines. They were observed for 96 h in the hospital for efficacy and safety-related end points.

2.3. Randomization

They were randomized in a 1:1 manner using a table of randomized numbers containing double digits randomization codes (from 11 to 50) generated using a computer program. Randomization codes were allotted to the enrolled patients by starting at random point in the table. Patients receiving codes from 11 to 30 received conventional LD 60 mg of prasugrel (group A) and those with codes from 31 to 50 received low-dose 30 mg of prasugrel (group B). Randomization was performed at entry before starting any treatment.

2.4. End points

2.4.1. Efficacy-related end points

Primary efficacy end point was composite of in-hospital death from all causes and stent thrombosis at 96 h. Secondary end points were composed of in-hospital death from all causes at 96 h, in-hospital stent thrombosis at 96 h, and composite end point (death from all causes and stent thrombosis) at 24 and 48 h.

2.4.2. Safety-related end points

Safety outcomes included bleeding events. The Bleeding Academic Research Consortium (BARC) classification was used to classify various bleeding patterns.[9] Strokes were classified as hemorrhagic, ischemic, or ischemic with hemorrhagic conversion. Brain imaging was performed in all patients with suspected stroke.

2.4.3. Statistical analysis

The statistical analysis was performed using IBM SPSS statistics version 20 (Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were presented as absolute number and proportion (%). Comparisons of categorical variables were made using the chi-square test and Fisher exact test, as indicated. Data were analyzed using the two-tailed test to identify differences between groups and analysis of variance for repeated measures with Bonferroni correction for intragroup data. Nominal data were analyzed using the chi-square test. All efficacy analyses are based on the intention-to-treat principle. We considered 95% confidence intervals (CIs) that excluded unity, or, equivalently, $p < 0.05$, as statistically significant. No a priori sample size calculation was performed because the present investigation was a pilot study.

3. Results

From January 2014 to February 2015, of 768 PCIs, 677 (88.15%) were elective PCI. Three hundred thirty-two (49.04%) patients undergoing elective PCI met the study criteria and were enrolled in the study. These patients were randomized in a 1:1 manner into two groups: group A received conventional 60 mg LD of prasugrel ($n = 166$ patients) and group B received lower LD 30 mg of prasugrel ($n = 166$ patients) (Fig. 1).

Baseline demographic and clinical characteristics are shown in Table 1. The mean age was 57.01 ± 10.65 years, and 74.2% of the patients were men. Mean left ventricular ejection fraction was 46 ± 8%. The two groups were similar in baseline demographic and clinical characteristics (Table 1).

3.1. Efficacy-related end points

One patient (0.6%) in group A died due to cardiac tamponade, while one patient in group B (0.6%) had stent thrombosis. Primary efficacy end point of composite of in-hospital death from all causes and stent thrombosis at 96 h was 0.6% in both the conventional 60 mg LD and lower 30 mg LD groups [p = not significant (NS)] (Table 2).

Secondary efficacy end points of in-hospital death from all causes at 96 h [A = 0.6% vs B = 0%, odds ratio (OR) = 3.02, 95% CI = 0.12–74.62, p = NS] and in-hospital stent thrombosis at 96 h (A = 0.0% vs B = 0.6%, OR = 0.33, 95% CI = 0.01–8.19, p = NS) were not significantly different between the two groups (Table 2).

3.2. Safety-related end points

Bleeding events are shown in Table 3. The most common bleeding event noted was access site–related procedural blood loss or hematoma (BARC 1 and BARC 2). Eleven patients (6.63%) in group A and three patients (1.81%) in group B had small hematoma at the access site (BARC 1) which did not cause drop in hemoglobin, did not require any intervention, and regressed spontaneously. One patient (0.6%) in group A had large hematoma (BARC 2) at the femoral access site causing a hemoglobin drop of 1.5 gm/dl but did
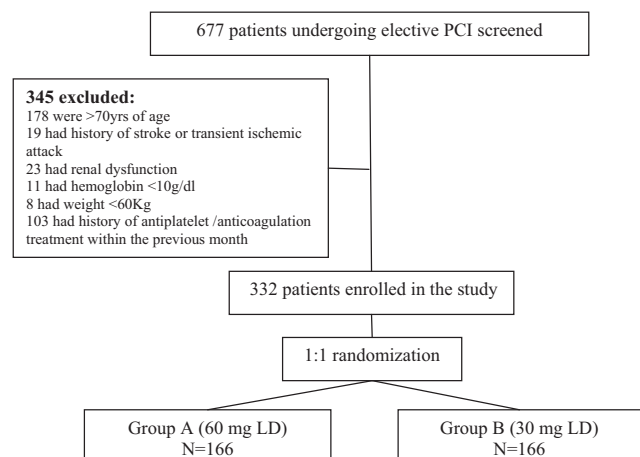

Fig. 1. Flow of patients in the study. LD, loading dose; PCI, percutaneous coronary intervention.

Table 1
Baseline demographic and clinical characteristics.

Characteristics	Group A ($n = 166$)	Group B ($n = 166$)	*p* value
Age (years), median (IQR)	58 (42—64)	56 (44—62)	NS
Male (%)	59	54	NS
Weight (Kg)	78	74	NS
Median (IQR)	62.5 (51.5—71.5)	64.5 (53.5—76.5)	NS
Diabetes mellitus (%)	31	29	NS
Hypertension (%)	48	44	NS
Unstable angina (%)	34	37	NS
Platelet counts (lac/μL)	2.8	2.6	NS
Hb (gm%) mean ± SD	13.7 ± 1.3	13.2 ± 1.6	NS
CrCl (ml/min)	110	116	NS
EF (%)median (IQR)	49 (32—64)	51 (36—69)	NS

CrCl, creatinine clearance; EF, ejection fraction; Hb, hemoglobin; IQR, interquartile range (25th and 75th percentile); NS, not significant; SD, standard deviation.

not require blood transfusion and hematoma regressed with compression. One patient in group A (0.6%) and one patient in group B (0.6%) developed hematuria (BARC 2) requiring bladder irrigation and discontinuation of prasugrel. One patient in group A (0.6%) and one patient in group B (0.6%) had hematemesis (BARC 3a) requiring blood transfusion and endoscopic intervention of bleeder. Three patients in group A (1.81%) developed cardiac tamponade due to coronary perforation, two patients (1.2%) recovered with pericardiocentesis and blood transfusion (BARC 3c), while one patient (0.6%) died (BARC 5). One patient (0.6%) in group B developed intracranial hemorrhage (BARC 3b). Minor bleeding (BARC 1) was significantly less in group B (A = 6.63% vs B = 1.81%, OR = 3.86, 95% CI = 1.06—14.08, $p = 0.05$). Major bleeding (BARC 2—5) was higher in group A (A = 3.61%, vs B = 1.81%, OR = 2.04, 95% CI = 0.50—8.29, $p = 0.50$).

4. Discussion

East Asians have a greater concentration of the active metabolite and greater platelet inhibition than whites during prasugrel treatment even after adjusting for body weight.[6] In Korean patients undergoing elective PCI, the mean value of platelet reactivity in the prasugrel 30-mg group was not significantly different from the prasugrel 60-mg group. The prasugrel 30-mg and 60-mg groups showed significantly lower platelet reactivity than the clopidogrel 600-mg group.[8] Similar platelet inhibition was seen with 15 mg LD of prasugrel and 300 mg LD of clopidogrel in Japanese patients.[7] Five mg/day maintenance dose of prasugrel in Korean patients was shown to be more potent than clopidogrel of 75 mg/day.[10] This might be related to the plasma concentration of the active metabolite of prasugrel in Asian groups being found to be higher than that in white groups.[11] The lower mean body weight of Asian subjects compared with white subjects may contribute to the higher concentration of the active metabolite in Asians.

In the present study, we compared 30 mg LD of prasugrel with a conventional 60 mg prasugrel LD in terms of clinical end points, that is, efficacy and safety end points. In contrast to previous studies, we did not assess platelet reactivity.

The ideal antiplatelet effect of prasugrel can be achieved when the risk of ischemic events is reduced without an increase in the risk of bleeding. Although the current recommended LD of 60 mg prasugrel lowered the risk of ischemic events, the potent antiplatelet efficacy of prasugrel resulted in an increased risk of bleeding events. Lower platelet reactivity is associated with an increased risk of bleeding, and it is consistent with the use of prasugrel.[11—13]

Table 2
Incidence of components of efficacy-related end points.

Events (in percent[a])	Group A ($n = 166$)	Group B ($n = 166$)	Odds ratio (95% CI)	*p* value
24 h				
Death	0	0	0	NS
Stent thrombosis	0	0.60	0.33 (0.01—8.19)	NS
Death/stent thrombosis	0	0.60	0.33 (0.01—8.19)	NS
48 h				
Death	0.60	0	3.02 (0.12—74.62)	NS
Stent thrombosis	0	0.60	0.33 (0.01—8.19)	NS
Death/stent thrombosis	0.60	0.60	1.00 (0.06—16.12)	NS
96 h				
Death	0.60	0	3.02 (0.12—74.62)	NS
Stent thrombosis	0	0.60	0.33 (0.01—8.19)	NS
Death/stent thrombosis	0.60	0.60	1.00 (0.06—16.12)	NS

CI, confidence interval; NS, not significant.
[a] The percentages are the observed rates of the key end points.

Table 3
Incidence of bleeding in two groups.

Category of bleeding	Group A ($n = 166$)	Group B ($n = 166$)	Odds ratio (95% CI)	*p* value
BARC 0	149	160	0.33 (0.13—0.86)	0.03
BARC 1	11	3	3.86 (1.06—14.08)	0.05
BARC 2	2	1	2.01 (0.18—22.41)	NS
BARC 3a[a]	1	1	1.00 (0.06—16.12)	NS
BARC 3b[b]	2	0	5.06 (0.24—106.22)	NS
BARC 3c[c]	0	1	0.33 (0.01—8.19)	NS
BARC 4[d]	0	0	Not estimable	NS
BARC 5[e]	1	0	3.02 (0.12—74.62)	NS

BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CI, confidence interval; ICH, intracerebral haemorrhag; NS, not significant.
[a] Hemoglobin drop 3 g/dL to <5 g/dL.
[b] Hemoglobin drop ≥5 g/dL.
[c] ICH imaging confirmed.
[d] CABG-related bleed.
[e] Imaging confirmed fatal ICH.

In the present study, the lower LD of 30 mg prasugrel resulted in similar efficacy and safety end points with lesser risk of minor bleeding compared with conventional 60 mg LD of prasugrel.

4.1. Study limitations

We note several limitations in the present study. First, this is a single-center study with a relatively small number of patients enrolled in the study. Second, other confounding factors such as access site—related (radial vs femoral) and procedure-related (single vessel vs multivessel, lesion characteristics, stent length, and so forth) factors were not controlled. Third, the platelet reactivity was not assessed. We only evaluated clinical parameters. Fourth, the study duration was short, that is, patients were followed up only for 96 h during their hospital stay. A large multicenter prospective study evaluating the clinical outcomes along with platelet reactivity assessment is needed to confirm the clinical benefits of a lower prasugrel LD.

5. Conclusion

In Indian patients, 30 mg prasugrel LD is as effective as conventional 60 mg prasugrel LD with significant less minor bleeding.

Conflicts of interest

All authors have none to declare.

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