Lower Loading Dose of Prasugrel Compared with Conventional Loading Doses of Clopidogrel and Prasugrel in Korean Patients Undergoing Elective Coronary Angiography: A Randomized Controlled Study Evaluating Pharmacodynamic Efficacy

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Background and Objectives: Although prasugrel allows for rapid and potent platelet inhibition, the efficacy and safety of lower doses of prasugrel for patients of East Asian ethnicity has not yet been investigated. We compared the effect of a lower loading dose (LD) of prasugrel with conventional LDs of clopidogrel and prasugrel in Korean patients.

Subjects and Methods: Forty-three Korean patients undergoing coronary angiography were enrolled in the study. Participants were randomly administered LDs of clopidogrel 600 mg, prasugrel 30 mg or prasugrel 60 mg prior to coronary angiography. Platelet reactivity was assessed at baseline and at the time of peak platelet inhibition using light transmission aggregometry (LTA), the VerifyNow assay, and multiple electrode aggregometry.

Results: Although baseline platelet reactivity between the groups showed no significant differences, at the time of peak platelet inhibition, the prasugrel 30 mg (18.9 ± 10.0%) and 60 mg groups (13.8 ± 10.8%) showed significantly more potent platelet inhibition than the clopidogrel 600 mg group (52.9 ± 15.8%; p<0.001) by LTA. However, there were no significant differences between the prasugrel 30 mg and 60 mg groups (p=0.549).

Conclusion: The loading effect of prasugrel 30 mg was more potent than clopidogrel 600 mg and was not significantly different from prasugrel 60 mg. (Korean Circ J 2014;44(6):386-393)

KEY WORDS: Prasugrel; Clopidogrel; Platelet function tests; Population heterogeneity; Coronary artery disease.

Introduction

Although clopidogrel and aspirin have been the backbone of antiplatelet therapy for coronary artery disease (CAD) patients, clopidogrel has several limitations including delayed onset of peak concentration and pharmacodynamic inter-patient variability, which can result in high on-treatment platelet reactivity (HPR). These drawbacks are known to be associated with adverse cardiovascular outcomes. In comparison to clopidogrel, prasugrel has a more advantageous metabolic pathway, allowing for more rapid and potent platelet inhibition. Updated guidelines recommend prasugrel as a first line antiplatelet agent or stipulate its preference over clopidogrel for patients with acute coronary syndrome.

However, a number of concerns have been raised in relation to the differences in pharmacodynamic and pharmacokinetic responses to prasugrel in East Asian ethnicities. 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 in comparison to conventional prasugrel LD when administered to healthy Korean subjects.

We compared the antiplatelet effects of a lower prasugrel LD (30 mg) with both a conventional clopidogrel LD of 600 mg and prasugrel...
60 mg in Korean patients undergoing elective coronary angiography.

Subjects and Methods

Eligibility

Patients between 18 and 80 years of age with stable or unstable angina undergoing elective coronary angiography were eligible for the study. Those with a previous history of transient ischemic attack or stroke, intracranial neoplasm, or uncontrolled malignant disease were excluded. Additionally, those with a history of antiplatelet 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 50 kg were also ineligible. All of the subjects who participated in the study provided written informed consent prior to participation.

Study objective and design

This study was designed as a prospective, randomized, open-label active controlled study to compare the pharmacodynamic effects of LD of clopidogrel 600 mg, prasugrel 30 mg, and prasugrel 60 mg. Enrolled patients were randomly assigned to either the clopidogrel 600 mg group, prasugrel 30 mg group or prasugrel 60 mg group on a 1:1:1 ratio using Excel (Microsoft Corporation, Redmont, DC, USA).

Platelet reactivity was measured at baseline and at the time of peak platelet inhibition. The time of peak platelet inhibition was defined as 2 hours after administration of LD for the prasugrel groups and 6 hours after LD for the clopidogrel group. Coronary angiography with or without percutaneous coronary intervention (PCI) was performed in accordance with the current recommended guidelines.

The study design was approved by the Institutional Review Board of Dong-A University Hospital and was registered at www.clinicaltrials.gov (NCT02070159).

Measurement of platelet reactivity

Platelet reactivity was measured using three different methods; light transmission aggregometry (LTA), the VerifyNow assay (Accumetrics, San Diego, CA, USA), and multiple electrode aggregometry (MEA, Dynabyte Medical, Munich, Germany). Blood samples for the assessment of platelet reactivity were collected via direct venipuncture at the antecubital fossa or via the arterial sheath in patients who had already been punctured via the radial or femoral arterial sheath at the time of assessment. The numerical results of LTA were expressed as a percentage, VerifyNow assay as P2Y12 reaction units (PRU), and the MEA, as arbitrary units (U).

For comparisons of the extent of platelet inhibition using LTA, VerifyNow, and MEA devices, we compared the percent inhibition for each unit. Percent inhibition was calculated using the following formula: % inhibition={(baseline reactivity unit-peak reactivity unit)/baseline reactivity unit}×100.

The incidence of HPR and low on-treatment platelet reactivity (LPR) in each group were also compared. The HPR was defined as the results of LTA ≥48% or ≥55%, MEA ≥242 or ≥275, and VerifyNow assay MEA 37 U or 54 U at the time of peak platelet inhibition. The LPR was defined as LTA <12, MEA <19, and the prasugrel 30 mg group who were indicated for maintenance on dual antiplatelet therapy continued to receive conventional maintenance doses (MD) of clopidogrel or prasugrel as per the decision of the primary physician. Participants of the study were observed for adverse clinical events for 24 hours and followed-up 7 days later via an outpatient visit or telephone interview.

Sample size calculation and statistical analysis

The results of platelet reactivity was expected to be normally distributed with a standard deviation of less than 0.2, and the difference in platelet inhibition between the clopidogrel 600 mg group and the prasugrel 30 mg group was assumed to be 30%. Considering a 30% higher concentration of active metabolites in East Asian ethnicity on average and an approximately 20% difference in platelet inhibition between 10 mg and 20 mg prasugrel LDs, the response difference between the prasugrel 30 mg and 60 mg groups was also assumed to be 30%. The minimum number of subjects in each group required was calculated to be nine subjects in order to provide a 90% power to detect the mean differences. Regarding the scarcity of previous studies on lower LDs of prasugrel and possible data loss, we decided to allocate at least 13 subjects in each group.

Results were expressed as mean±standard deviation and multiple comparisons including platelet reactivity for each group were analyzed by 1-way analysis of variance followed by Dunnett’s T3 post hoc test. Values of p<0.05 were considered significant. In addition,
we also performed independent t-tests and Kruskal-Wallis tests with Dunnett’s T3 post hoc test for confirmation. For comparisons of nominal variables, a cross-tabulation with a Fisher’s exact test was used. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 14 (SPSS Inc., Chicago, IL, USA). All statistical tests were carried out at the 0.05 significance level.

Results

Between January 2012 and January 2013, 54 patients were screened for eligibility. Of the screened subjects, three were excluded due to age greater than 80 years, three due to a history of stroke, one due to significant kidney dysfunction, and four declined to participate. In total, 43 patients were randomized, all of whom completed the study. The mean age was 63.4±10.2 years, mean body weight was 66.0±10.7 kg and 36 patients (83.7%) were male. By random assignment, 14 patients (32.6%) were allocated to the clopidogrel group, 15 patients (34.9%) to the prasugrel 30 mg group, and 14 patients (32.6%) to the prasugrel 60 mg group. Hypertension was reported for 25 patients (58.1%), 17 patients had diabetes mellitus (39.5%), and 23 patients (53.5%) were smokers. PCIs were performed in 28 patients (65.1%), of which the incidence showed no significant difference between study groups. Adverse cardiovascular events including stent thrombosis, bleeding, and adverse drug reactions were not observed during the study period. There were no significant differences in clinical characteristics of the enrolled patients between study groups (Table 1).

The mean baseline platelet reactivity of the enrolled patients was 65.0±11.9% by LTA, 323.1±68.2 PRU by VerifyNow, and 57.9±20.8 U by MEA, and platelet reactivity was significantly reduced at the time of peak platelet inhibition; 28.3±21.2% by LTA, 145.1±105.3

Table 1. Baseline clinical characteristics of the enrolled patients

| Variables                  | Clopidogrel 600 mg (n=14) | Prasugrel 30 mg (n=15) | Prasugrel 60 mg (n=14) | p     |
|----------------------------|---------------------------|------------------------|------------------------|-------|
| Male gender, n (%)         | 12 (85.7)                 | 12 (80.0)              | 12 (85.7)              | 0.890 |
| Age (years)                | 63±10                     | 66±12                  | 61±8                   | 0.415 |
| Weight (kg)                | 67±11                     | 64±6                   | 71±12                  | 0.238 |
| Unstable angina, n (%)     | 7 (50)                    | 4 (26)                 | 5 (35)                 | 0.426 |
| Hb (g/dL)                  | 13.7±1.3                  | 13.2±1.6               | 14.2±1.3               | 0.228 |
| Hct (%)                    | 38.8±3.4                  | 38.2±4.4               | 41.1±3.8               | 0.159 |
| PLT (×10^3)/μL             | 208±40                    | 233±26                 | 223±50                 | 0.270 |
| TC (mg/dL)                 | 170±35                    | 177±34                 | 191±34                 | 0.273 |
| LDL-C (mg/dL)              | 102±36                    | 109±26                 | 111±32                 | 0.761 |
| Creatinine (mg/dL)         | 0.99±0.27                 | 1.01±0.23              | 1.01±0.16              | 0.942 |
| DM, n (%)                  | 6 (42.9)                  | 6 (40.0)               | 5 (35.7)               | 0.927 |
| HTN, n (%)                 | 9 (64.3)                  | 10 (66.7)              | 6 (42.9)               | 0.366 |
| Smoking, n (%)             | 5 (35.7)                  | 9 (60.0)               | 9 (65.3)               | 0.346 |
| PCI, n (%)                 | 12 (85.7)                 | 10 (66.7)              | 6 (42.9)               | 0.062 |

Data are expressed as number of cases (percentage) or mean±standard deviation. *The majority of enrolled patients presented with stable angina. Patients with evidence of myocardial infarction were not included in the study. Hb: hemoglobin, Hct: hematocrit, PLT: platelet, TC: total cholesterol, LDL-C: low density lipoprotein-cholesterol, DM: diabetes mellitus, HTN: hypertension, PCI: percutaneous coronary intervention

Table 2. Platelet function at baseline and peak platelet inhibition in each study group

| Method         | Clopidogrel 600 mg | Prasugrel 30 mg | Prasugrel 60 mg | p     |
|----------------|--------------------|-----------------|-----------------|-------|
| Baseline       |                    |                 |                 |       |
| LTA (%)        | 68.5±14.4          | 63.9±12.6       | 62.5±7.4        | 0.385 |
| VerifyNow (PRU)| 319.9±84.0         | 331.5±60.9      | 317.3±62.3      | 0.843 |
| MEA (U)        | 59.1±24.2          | 58.1±22.2       | 56.3±16.6       | 0.937 |
| Peak           |                    |                 |                 |       |
| LTA (%)        | 52.9±15.8          | 18.9±10.0       | 13.8±10.8       | <0.001|
| VerifyNow (PRU)| 272.2±53.0         | 105.7±70.1      | 60.2±28.3       | <0.001|
| MEA (U)        | 38.3±17.7          | 18.7±8.3        | 21.7±6.7        | <0.001|

Data are expressed as mean±standard deviation. LTA: light transmission aggregometry, MEA: multiple electrode aggregometry
PRU by VerifyNow, and 26.3±14.6 U by MEA (p<0.001 for all methods). The results of platelet reactivity at baseline and at the time of peak platelet inhibition in each study group are shown in Table 2. Baseline platelet reactivity between study groups using LTA (Fig. 1A), VerifyNow (Fig. 1B), and MEA (Fig. 1C) were not significantly different, whereas platelet reactivity at peak platelet inhibition using LTA (Fig. 1D), VerifyNow (Fig. 1E), and MEA (Fig. 1F) were significantly different. In the post hoc analysis, significant differences were observed between the clopidogrel 600 mg group and both prasugrel groups. However, there was no significant difference between the prasugrel 30 mg and 60 mg groups. Independent t-tests also showed consistent results.

The overall inhibition rate in the enrolled patients was 57.8±29.5% as measured by LTA, 54.1±33.4% by VerifyNow, and 52.5±33.4% by MEA. The inhibition rate in the clopidogrel 600 mg, prasugrel 30 mg, and prasugrel 60 mg groups were 22.8±19.3%, 70.8±14.6%, 78.9±14.9% by LTA (p<0.001), 12.3±15.9%, 67.8±19.1%, 81.1±8.8% by VerifyNow (p<0.001), and 32.3±17.1%, 66.2±13.8%, 58.1±19.5% by MEA (p<0.001), respectively. Post hoc analysis revealed significant differences between the clopidogrel group and both prasugrel groups, whereas no significant difference was present between the prasugrel 30 mg and 60 mg groups (Fig. 2).

Details of predefined HPR incidence are shown in Table 3. There was one case of HPR in the prasugrel 30 mg group when HPR was defined as PRU ≥242, and HPR was not observed in the prasugrel 60 mg group. Although the prasugrel groups showed very low incidence of HPR, the clopidogrel 600 mg group showed various incidence of HPR according to different methods and cut-off values.

Incidences of predefined LPR are shown in Table 4. Although the clopidogrel 600 mg group showed very low incidence of LPR, both...
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prasugrel groups exhibited a relatively higher incidence of LPR. Incidence in the prasugrel 30 mg group was lower than in the prasugrel 60 mg with LTA and VerifyNow methods, whereas it was higher when using the MEA assay.

**Discussion**

Although prasugrel treatment reaches a higher active metabolite peak concentration more rapidly, higher platelet inhibition after prasugrel LDs and MDs has been reported in patients of East Asian ethnicity over their Caucasian counterparts in pharmacodynamic and pharmacokinetic studies. Subsequently, lower LDs and MDs of prasugrel were shown to exhibit lower platelet reactivity when compared with clopidogrel 300 mg LD and 75 mg/day MD in Japanese CAD patients. Previously, we reported a more rapid, potent, and consistent platelet inhibition when using 30 mg LD of prasugrel compared with 600 mg LD of clopidogrel, with comparable platelet inhibition to 60 mg LD of prasugrel in healthy Korean subjects. In this study, which was conducted with Korean CAD patients undergoing elective coronary angiography, we confirmed these findings.

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**Table 3.** Incidence of predefined HPR in each study group

| Method | Cut-off value | Group | Clopidogrel 600 mg | Prasugrel 30 mg | Prasugrel 60 mg | p |
|--------|--------------|-------|-------------------|----------------|----------------|---|
| LTA    | 48 (%)       |       | 10 (71.8)         | 0 (0)          | 0 (0)          | <0.001 |
|        | 55 (%)       |       | 8 (57.1)          | 0 (0)          | 0 (0)          | <0.001 |
| VerifyNow | 242 (PRU)  |       | 11 (78.6)         | 1 (6.7)        | 0 (0)          | <0.001 |
|        | 275 (PRU)    |       | 6 (42.9)          | 0 (0)          | 0 (0)          | 0.001  |
| MEA    | 50 (U)       |       | 5 (35.7)          | 0 (0)          | 0 (0)          | 0.003  |
|        | 54 (U)       |       | 3 (21.4)          | 0 (0)          | 0 (0)          | 0.035  |

Data are expressed as number (percentage). HPR: high on-treatment platelet reactivity, LTA: light transmission aggregometry, MEA: multiple electrode aggregometry, PRU: P2Y12 reaction units

**Table 4.** Incidence of predefined LPR in each study group

| Method | Cut-off value | Group | Clopidogrel 600 mg | Prasugrel 30 mg | Prasugrel 60 mg | p |
|--------|--------------|-------|-------------------|----------------|----------------|---|
| LTA    | 12 (%)       |       | 0 (0)             | 4 (26.7)       | 6 (42.9)       | 0.025 |
| VerifyNow | 85 (PRU)  |       | 0 (0)             | 7 (46.7)       | 10 (71.4)      | <0.001 |
| MEA    | 19 (U)       |       | 1 (7.1)           | 7 (46.7)       | 6 (42.9)       | 0.046  |

Data are expressed as number of cases (percentage). LPR: low on-treatment platelet reactivity, LTA: light transmission aggregometry, MEA: multiple electrode aggregometry, PRU: P2Y12 reaction units

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![Fig. 2. Comparison of inhibition (%) between study groups. Percent inhibition was significantly lower in the clopidogrel 600 mg group than for both prasugrel groups. However, there was no statistical difference between the prasugrel groups. LTA: light transmission aggregometry, MEA: multiple electrode aggregometry.](http://dx.doi.org/10.4070/kcj.2014.44.6.386)
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. In addition, a 30 mg LD of prasugrel did not increase the incidence of HPR. The highest incidence rate of HPR was observed in the clopidogrel group.

In the study of Yokoi et al., they prospectively compared a lower LD and MD of prasugrel with an LD of clopidogrel 300 mg and MD of clopidogrel 75 mg/day in Japanese CAD patients. Platelet inhibition with a much lower LD of prasugrel (15 mg) exhibited similar effects to an LD of clopidogrel 300 mg. More recently, MD of prasugrel 5 mg/day in Korean CAD patients was shown to be more potent than clopidogrel 75 mg/day in Korean CAD patients. However, in regards of LD, a 600 mg LD of clopidogrel is known to be superior to 300 mg LD of clopidogrel, and is frequently used in many centers. Therefore, in the present study, we compared a 30 mg LD of prasugrel with a 600 mg LD of clopidogrel, a higher dose than previously studied. We decided to use 30 mg as LD of prasugrel because it is the same dose used in our previous study in healthy Korean subjects. We compared it with a conventional 60 mg prasugrel LD group, revealing a similar platelet inhibition in both groups in Korean CAD patients.

In our previous study, peak inhibition of platelet reactivity was achieved 2 hours after administration of LD prasugrel and 6 hours after the clopidogrel LD administration. Platelet reactivity remained at a steady state thereafter. Therefore, we did not serially measure the platelet reactivity, but measured at baseline, at 2 hours after prasugrel LD, and 6 hours after clopidogrel LD.

To determine HPR incidence, we used two cut-off values based on previous publications. However, they are higher than those used in other reports and the general consensus. This was in consideration of ethnic differences, which have reported higher cut-off values for patients of East Asian ethnicity. However, the results were consistent with lower cut-off values for HPR with a PRU of 220; HPR was detected in 13 patients (92.9%) in the clopidogrel 600 mg group and 2 patients (13.3%) in the prasugrel 30 mg group, while no incidences were detected in the prasugrel 60 mg group.

It has been demonstrated that LPR is associated with an increased risk of bleeding. Additionally, LPR arising from prasugrel treatment has specifically been linked with an increased risk of bleeding events. We defined LPR using the cut-off value in a recently adopted consensus report. The prasugrel 30 mg group showed a lower incidence of LPR than the prasugrel 60 mg group. There was no incidence of LPR in the clopidogrel group.

In terms of potency, consistency, and rapid onset, prasugrel is superior to clopidogrel. Although HPR was a major concern with the use of clopidogrel, prasugrel showed lower platelet reactivity and a reduced incidence rate of ischemic events. However, 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. The present randomized, controlled, open-label study comparing the pharmacodynamic effects of prasugrel 30 mg, with clopidogrel 600 mg and prasugrel 60 mg in Korean CAD patients undergoing elective coronary angiography revealed a significantly higher platelet inhibition in the 30 mg LD prasugrel group compared to the 600 mg LD clopidogrel group. The LD of prasugrel 30 mg was found to cause similar platelet inhibition to 60 mg LD prasugrel. Additionally, the incidence of HPR in the prasugrel 30 mg group did not increase, resulting in a lower overall incidence of LPR.
study evaluating the clinical outcomes of lower LD prasugrel with long-term observation is needed to confirm the clinical benefits of a lower prasugrel LD.

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