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Original article

Comparison of peri-procedural platelet inhibition with prasugrel versus adjunctive cilostazol to dual anti-platelet therapy in patients with ST segment elevation myocardial infarction

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ABSTRACT

Background: It has been well known that the inhibition of platelet aggregation (IPA) by anti-platelet agents was important to reduce the thrombo-embolic events in patients with ST segment elevation myocardial infarction (STEMI). However, the peri-procedural IPA by anti-platelet agents was not well known.
Methods: We compared the peri-procedural IPA between prasugrel and adjunctive cilostazol to dual anti-platelet therapy (triple anti-platelet therapy; TAP) in patients with STEMI undergoing primary percutaneous coronary intervention (PCI). We prospectively randomized 70 consecutive clopidogrel-naive patients with STEMI planned PCI to either prasugrel [loading dose (LD) 60 mg; 37 patients] or TAP (LD aspirin 300 mg, clopidogrel 600 mg, and cilostazol 200 mg; 33 patients). Primary end points of the study were the platelet reactivity unit (PRU) or % inhibition by the VerifyNow $P2Y_{12}$ assay at pre-PCI and pre-discharge.
Results: The drug loading to pre-PCI time was similar between prasugrel and TAP groups (25.4 ± 10.42 min vs. 25.5 ± 10.56 min, $p = 0.957$). PRU at pre-PCI was significantly lower in prasugrel than in TAP (269.1 ± 71.69 vs. 306.5 ± 48.67, $p = 0.012$). The lower PRU and greater % inhibition also observed in prasugrel than in TAP at pre-discharge (108.2 ± 60.51 vs. 238.1 ± 73.40; $63.6 \pm 18.51\%$ vs. $16.8 \pm 17.91\%$, $p < 0.001$ respectively). No differences in in-hospital bleeding complications between the two groups were observed.
Conclusion: Our study demonstrates that prasugrel could produce a significantly greater peri-procedural as well as in-hospital IPA compared with TAP in patients with STEMI undergoing primary PCI.

Introduction

Even though the treatments for patients with ST-segment elevation myocardial infarction (STEMI) have improved over the past decades, it remains the most common cause of death and is mainly caused by thrombotic occlusion. For reduction of infarct size and mortality, the optimal inhibition of platelet aggregation (IPA) by anti-platelet agents and primary percutaneous coronary intervention (PCI) should be performed as soon as possible. European Society of Cardiology (ESC) Guidelines for the management of patients with STEMI recommended that if the patient presents early, with a large amount of myocardium at risk or directly to a PCI-capable hospital, primary PCI should be performed within 60 min of first medical contact [1]. Therefore, the faster PCI patients undergo treatment, the faster onset of anti-platelet effect patients should be needed to achieve.

The ADP receptor inhibitor prasugrel has a faster and more potent IPA than clopidogrel by a different primary metabolic pathway [2]. The addition of cilostazol to aspirin and clopidogrel (triple anti-platelet therapy; TAP) also has a significantly greater IPA and better clinical outcomes compared with dual anti-platelet agents in patients with acute myocardial infarction [3]. However, peri-procedural IPA by prasugrel and TAP have not been studied in patients with STEMI. Therefore, the purpose of this study was to compare the peri-procedural and in-hospital IPA between prasugrel and TAP in patients with STEMI undergoing primary PCI.

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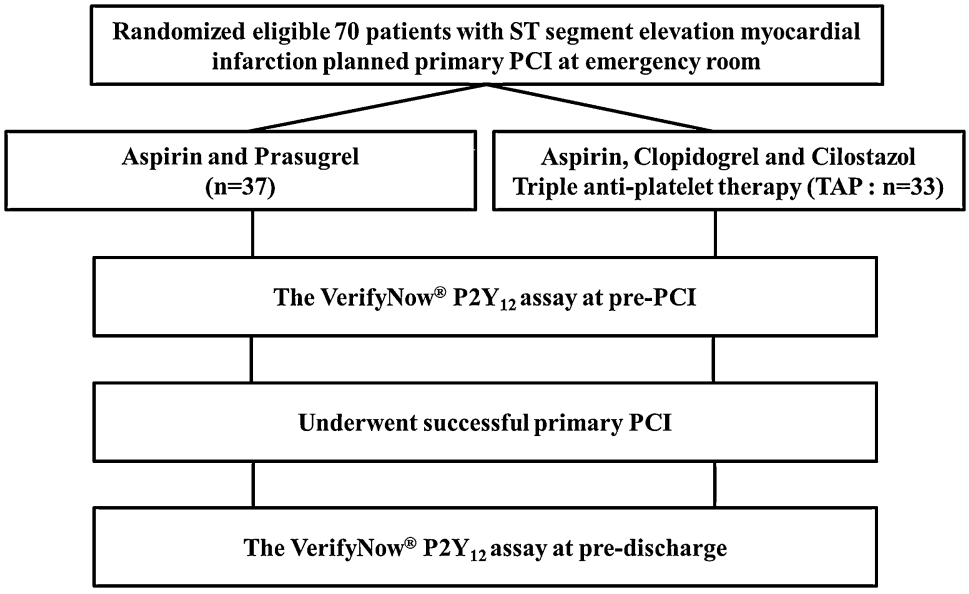

Fig. 1. The flow chart of the study. PCI, percutaneous coronary intervention.

Materials and methods

Study population and protocol

From March to November 2012, we enrolled consecutive clopidogrel-naive patients with STEMI-planned PCI at Chonnam National University Hospital. We excluded the patients who presented with cardiogenic shock at admission and with a history of previous PCI or bypass surgery, transient ischemic attack or cerebrovascular accidents (CVA), and a bleeding disorder. We immediately randomized the enrolled patients to either prasugrel or TAP in the emergency room. All patients received the loading dose (LD) of aspirin 300 mg followed by maintenance dose (MD) of 300 mg/day during hospitalization. Prasugrel was given as 60 mg LD followed by 10 mg/day or 5 mg/day MD when the patient was more than 75 years or less than 60 kg, whereas TAP group was administered a LD of 600 mg clopidogrel and 200 mg cilostazol followed by MD of clopidogrel 75 mg/day and cilostazol 200 mg/day. After administration of LD of anti-platelet agents in the emergency room, the patient was sent to the cardiac catheterization room as soon as possible, and received coronary angiography and PCI. The primary PCI was performed in a routine manner. The vascular access, manual aspiration thrombectomy, and the type of stents were determined based on the decision of operators. Glycoprotein IIb/IIIa inhibitors were used as an only bail-out therapy during the procedure in situations of large thrombi or no reflow. After the intervention, all patients took 300 mg of aspirin per day and the MD of the anti-platelet agents of the study group to which they belong during hospitalization. Other medical treatments were also used based on the standard treatment regimen for patients with STEMI in a non-restrictive manner. We performed the platelet function assay twice during hospitalization, at pre-PCI and pre-discharge. Pre-PCI was defined as the time just before wiring for target lesion during primary PCI and pre-discharge, as the hospital discharge day or commonly 5 days after primary PCI. A flow chart diagram of our study is shown in Fig. 1.

Platelet function assay

The first 2–4 ml of blood was discarded to avoid spontaneous platelet activation, and blood samples were collected in 2.7 mL BD Vacutainer® plastic whole blood tube with 3.2% sodium citrate (Becton, Dickinson & Co., Plymouth, UK). Then, platelet function test was performed immediately using the VerifyNow® (Accumetrics Inc., San Diego, CA, USA) point-of-care P2Y12 function assay. The results are expressed in $P2Y_{12}$ reaction units (PRU). The VerifyNow® $P2Y_{12}$ assay also determines the percentage of platelet inhibition (% PI) by the anti-platelet agents using PRU and baseline PRU values. It is well known that the VerifyNow® $P2Y_{12}$ assay correlated strongly with inhibition of $P2Y_{12}$ function, as measured with the "gold standard" of light transmission aggregometry (LTA) in patients treated with prasugrel or clopidogrel [4]. The high on-treatment platelet reactivity (HTPR) was considered as a value ≥235 PRU [5].

Endpoints

The primary endpoint was a PRU or % PI at pre-PCI and pre-discharge between the two groups. The secondary endpoint was a composite of cardiac death, non-fatal MI, CVA, and stent thrombosis. Stent thrombosis was defined according to the Academic Research Consortium definition. We also compared the incidence of thrombolysis in myocardial infarction (TIMI) major or minor bleeding during hospitalization in both groups [6].

Statistical analysis

Categorical variables were expressed as a frequency and continuous variables as mean ± SD (standard deviation). An analysis of categorical variables was performed using chi-square test or Fisher's exact test and that of continuous ones using Student's *t*-test. The mean PRU among 3 groups were compared by one-way ANOVA with post hoc analysis for multiple comparisons. All tests were 2-tailed and statistical significance was considered for *p*-values <0.05. All the statistical analyses were performed using SPSS (Statistical Package for Social Science, SPSS Inc., Chicago, IL, USA) for Windows, Version 18.0.

Sample size calculation

There were no available data about PRU at acute phase in both prasugrel and TAP. However, according to the results of ACCEL-AMI and TIMI 44 trial [3,7], we could hypothesize that prasugrel would