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Concomitant nitrates enhance clopidogrel response during dual anti-platelet therapy

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ABSTRACT

Background: Despite advances in modern anti-platelet strategies, clopidogrel still remains the cornerstone of dual anti-platelet therapy (DAPT) in patients undergoing percutaneous coronary interventions (PCI). There is some inconclusive evidence that response after clopidogrel may be impacted by concomitant medications, potentially affecting clinical outcomes. Sustained released nitrates (SRN) are commonly used together with clopidogrel in post-PCI setting for mild vasodilatation and nitric oxide-induced platelet inhibition.
Methods: We prospectively enrolled 458 patients (64.5 ± 9.6 years old, and 73.4% males) following PCI undergoing DAPT with clopidogrel and aspirin. Platelet reactivity was assessed by the VerifyNow™ P_2Y12 assay at the maintenance outpatient setting.
Results: Concomitant SRN (n = 266) significantly (p = 0.008) enhanced platelet inhibition after DAPT (251.6 ± 80.9 PRU) when compared (232.1 ± 73.5 PRU) to the SRN-free (n = 192) patients. Multivariate logistic regression analysis with the cut-off value of 253 PRU for defining heightened platelet reactivity confirmed independent correlation of more potent platelet inhibition during DAPT and use of SRN (Relative risk = 1.675; Odds ratio [1.059–2.648]; p = 0.027). In contrast, statins, calcium-channel blockers, beta blockers, angiotensin receptor blockers, ACE-inhibitors, diuretics, and anti-diabetic agents did not significantly impact platelet inhibition following DAPT.
Conclusion: The synergic ability of SRN to enhance response during DAPT may have important clinical implications with regard to better cardiovascular protection, but extra bleeding risks, requiring further confirmation in a large randomized study.

1. Introduction

Clopidogrel, which is still a cornerstone of modern dual anti-platelet therapy (DAPT) has several potential pitfalls including late onset of action, and inter-patient response variability [1–3]. The diminished responsiveness to clopidogrel, may be associated with recurrent thrombotic cardiovascular events [2], although the randomized data remain inconclusive. There are several factors, which may impact the ability of clopidogrel to exert potent anti-platelet activity. In addition to genetic variability of drug metabolism such as CYP2C19 polymorphism, drug–drug interactions have been suggested as one of the potential causes of clopidogrel lower responsiveness [4,5]. Such threat is especially true for the patients with coronary artery disease, considering the increasing number of concomitant medications, since many drugs share similar pharmacokinetic profiles and/or metabolic pathways. Aside from DAPT, nitrates are known to inhibit platelet activity, which have been consistently shown in numerous in vitro and ex vivo studies (e.g. [6–9]). Importantly, mild platelet inhibition, and vasodilatation has been universally regarded as favorable, and physicians do not hesitate to broadly prescribe nitrates [10]. As a result, there are common clinical scenarios when patients are treated with clopidogrel and nitrates simultaneously.

The purpose of this study was to investigate whether or not concomitant nitrates may influence platelet inhibition in patients after percutaneous coronary intervention (PCI) undergoing DAPT with clopidogrel and aspirin.

2. Methods

2.1. Patients

The study was approved by the Institutional Review Board of Dong-A University Hospital (Busan, Korea), and all enrolled patients provided

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written informed consent. Patients between 18 and 80 years of age with implanted drug eluting stent following PCI were screened. Asymptomatic patients receiving DAPT with aspirin 100 mg/day and clopidogrel 75 mg/day for more than 1 month were eligible. Patients with uncontrolled symptomatic ischemic heart disease (New York Heart Association classification ≥2), left ventricular systolic dysfunction (ejection fraction <40%), administration of unidentifiable medicine including over-the-counter drug and herbal medicine, combination of 3 or more anti-platelet agents, concurrent anti-coagulation therapy, those with recent admission from any cause within 1 month and those who omitted administration of clopidogrel or aspirin twice of more for the last 1 week were excluded. Thrombocytopenia of less than 100,000/μL and anemia defined as hemoglobin of less than 9.0 g/dL were not eligible either. However, the laboratory tests for anemia or thrombocytopenia were not mandatory unless the patient had any associated symptoms.

2.2. Study design

The present study was designed as a prospective observational study evaluating the pharmacodynamic efficacy of clopidogrel with or without concomitant nitrates. Enrolled patients provided detailed information about demographics, previous medical history, and all kinds of administered medications. Platelet function was assessed with VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA). Blood for platelet function test was sampled between 4 h to 12 h after last administration of routine drugs including clopidogrel, aspirin, and nitrates. After the assessment of platelet function, enrolled patients were not regularly followed up, but medical records were retrospectively reviewed for clinical outcomes and major adverse events. Primary outcome of the index study was the difference in platelet inhibition in patients on DAPT dependent on concomitant administration of nitrates.

2.3. Platelet activity

Platelet function was assessed one time using VerifyNow assay (Accumetrics, Inc., San Diego, CA, USA) is a cartridge-based optical detection system utilizing the whole blood. Blood was drawn into a Greiner Bio-One 3.2% citrate Vacuette tube. The channel contains fibrinogen-coated polystyrene beads and 20 μL adenosine diphosphate as a platelet agonist and contains 22 nmol/L prostaglandin E1 (PGE1), as a suppressor of intracellular free calcium levels to reduce the non-specific contribution of the adenosine diphosphate binding to $P2Y_1$ receptors. The degree of platelet function was numerically expressed in platelet reactive units (PRU).

2.4. Statistical analysis

Categorical variables are presented as frequencies, while continuous variables are presented as a mean ± standard deviation. The differences in PRU values according to clinical characteristics, comorbidities and concomitant medications were assessed using t-tests. Logistic regression was used to estimate the independent risk factors for heightened platelet reactivity. Variables with a p-value of ≤0.20 in univariate analyses were candidates for multivariable logistic regression model. A backward elimination process was used to develop the final multivariable models. Cox proportional hazards regression modeling was used to identify factors that were independently associated with MACE. All statistical comparisons were two-sided and statistical significance was defined as p-values of less than 0.05. Statistical analyses were conducted using Statistical Package for Social Science 20.0 (IBM, Chicago, IL, USA).

3. Results

The study enrolled 458 patients with implanted coronary drug-eluted stents treated with DAPT using aspirin and clopidogrel. Baseline clinical characteristics are presented in Table 1. Mean age was 64.5 ± 9.6 years old, and 336 patients (73.4%) were male. In addition to aspirin and clopidogrel, patients were treated with about 5 (mean 4.8 ± 1.7) additional medications. Statins were most commonly prescribed, followed by calcium-channel blockers (CCB), nitrates and beta blockers (BB) (Fig. 1).

Overall, mean platelet reactivity was 243.4 ± 78.4 PRU and the results dichotomized according to the clinical characteristics and concomitant medications are presented in Table 2. Platelet reactivity was significantly higher in females, hypertensive, and non-smokers, but, surprisingly, not in diabetics. With regard to medications, therapy with sustained released nitrates was associated with significantly higher platelet inhibition, in contrast to statins, CCB, BB, ACE-inhibitors, angiotensin receptor blockers, diuretics, and anti-diabetic agents, all of which showed no significant impact. Among statins, both rosuvastatin and atorvastatin did not affect response after clopidogrel despite different metabolism. There were no patients treated with proton pump inhibitors in our cohort.

Additional multivariate logistic regression analysis for HPR with a cut-off value of 253 PRU revealed that administration of sustained release nitrate agents has been independently affiliated with a greater degree of platelet inhibition (Relative risk = 1.675; Odds ratio [1.059–2.648]; p = 0.027) (Table 3). Seven different brands of nitrates (predominantly Angiobid® and Isotril®) were used in the study. Individual plots of PRU values dependent on a brand of nitrate used when compared with n0 nitrate DAPT patients is exhibited in Fig. 2. MACE developed in 20 patients (4.4%) during the follow-up (970 ± 333 days); while the PRU value of the patients with MACE (240 ± 75) compared with those without MACE (244 ± 79) showed no significant difference (p = 0.850). The MACE included (myocardial infarction (n = 9), urgent target vessel revascularization (n = 8), and strokes (n = 8). Five patients died, due to sudden cardiac deaths (n = 2), cardiogenic shock following stent thrombosis (n = 1), ischemic stroke (n = 1), and finally septic shock of unknown cause (n = 1). Some patients experienced multiple MACEs including deaths. Importantly, among clinical characteristics, only renal failure (RR = 33.921; OR [3.076–374.112]; p = 0.004) was associated with mortality during the follow-up.

4. Discussion

Although novel anti-platelet agents such as prasugrel and ticagrelor are broadly available, clopidogrel still remains the cornerstone of modern DAPT. In reality, however, post-PCI patients receive multiple concomitant pharmaceuticals on top of DAPT with aspirin and clopidogrel, but also beta blockers, lipid-lowering agents, anti-diabetic agents, and gastrointestinal protectants. Such poly-pharmacy obviously increases the risk of drug–drug interactions, which can also result in impaired response after clopidogrel. Some pharmaceuticals were reported to impact response after clopidogrel, with the most evidence available for atorvastatin [11], and omeprazole [12]. Since clopidogrel hyporesponsiveness may be associated with adverse cardiovascular events, assessment of possible drug interactions with clopidogrel and prevention of impaired response is indeed important. Although numerous studies assessed the drug interactions with clopidogrel, the majority of previous research

Table 1
Baseline clinical characteristics of enrolled patients.

Variables	Mean ± SD
Male gender, n(%)	336 (73.4%)
Age (years)	64.5 ± 9.6
Weight (kg)	66.3 ± 11.2
Hemoglobin (g/dL)	13.3 ± 1.7
Platelet (k/mL)	234 ± 70
GFR (mL/min/1.73 m^2)	69 ± 24
Additional medications	4.8 ± 1.7
Observation duration (months)	17.7 ± 8.1
Mean platelet reactivity (PRU)	243.4 ± 78.4