Influence of Diabetes Mellitus and Cigarette Smoking on Variability of the Clopidogrel-Induced Antiplatelet Effect and Efficacy of Active Management of the Target P2Y12 Reaction Unit Range in Patients Undergoing Neurointerventional Procedures

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Background: Optimal antiplatelet inhibition is essential in patients undergoing neurointerventional procedures; however, variability in response to clopidogrel can contribute to thromboembolic and hemorrhagic complications. The present study evaluated the influence of diabetes mellitus and cigarette smoking on clopidogrel reactivity. *Methods:* Between 2011 and 2013, 71 consecutive patients underwent aneurysmal coil embolization (CE) or carotid artery stenting (CAS) and received clopidogrel (75 mg daily) and aspirin (100 mg daily) before the treatment. The patients were divided into 2 groups: CE (n = 31) and CAS (n = 40). The patients underwent prospective assessment of preoperative platelet function using VerifyNow assay and received adjunctive cilostazol (200 mg daily, triple antiplatelet therapy) in case of clopidogrel hyporesponse. Patients with clopidogrel hyper-response underwent clopidogrel dose reduction (clopidogrel, 12.5-50 mg daily). *Results:* Clopidogrel resistance was noted in 15 patients (37.5%) in the CAS group and in 4 patients (12.9%) in the CE group ($P = .031$). Clopidogrel hyper-response was noted in 2 patients (5%) in the CAS group and in 11 patients (54.8%) in the CE group ($P < .001$). There was a significant difference in the baseline clinical characteristics between the 2 groups. In the multivariate logistic regression analysis, diabetes and age were independent predictors of clopidogrel hyporesponse, whereas current smoker was an independent predictor of clopidogrel hyper-response. *Conclusions:* Significant differences in baseline clinical characteristics were present when comparing patients undergoing endovascular treatment of unruptured cerebral aneurysms and carotid artery stenosis. Diabetes mellitus and current smoker status were independent factors

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related to reactivity to clopidogrel. **Key Words:** Neurointervention—platelet reactivity—environmental factor—target P2Y12 reaction unit.

Introduction

Pretreatment with dual antiplatelet therapy is a standard strategy for patients undergoing carotid artery stenting (CAS) and coil embolization (CE).[1] Clopidogrel is widely used and plays a pivotal role in the prevention of ischemic complications. Clopidogrel is a prodrug that requires 2-step oxidation by cytochrome P450 (CYP) isoenzymes to generate an active metabolite that irreversibly inhibits the platelet P2Y12 receptor.[2] However, there is wide interindividual variation in the antiplatelet effect of clopidogrel. Numerous studies have reported periprocedural thromboembolic complications in patients with clopidogrel resistance who undergo neurovascular and cardiovascular stent placement.[3,4] Multiple factors are related to platelet inhibition induced by clopidogrel, including genetic and environmental factors modulating hepatic metabolism of clopidogrel.[5,6] The mechanism of clopidogrel resistance is thought to be secondary to variable absorption and to variable activation in the liver secondary to CYP polymorphisms. Recent investigations have shown that the addition of cilostazol to aspirin and clopidogrel results in greater inhibition of platelet aggregation in patients with acute coronary syndrome when compared with those receiving standard dual antiplatelet therapy[7,8] or high-dose clopidogrel (150 mg daily) plus aspirin treatment.[9] We previously demonstrated that adjunctive cilostazol in patients with clopidogrel hyporesponse suppresses the frequency of new cerebral ischemic lesions in patients undergoing CAS.[10]

Recent studies have also suggested that hyper-response to clopidogrel is associated with an increased risk of hemorrhagic complications. Patients with low on-treatment platelet reactivity had a significantly higher incidence of bleeding complications among those undergoing percutaneous coronary intervention[11] and neurointervention.[12] In addition, delayed conversion to a hyper-response to the standard 75 mg daily clopidogrel dose in follow-up was associated with an increased risk of major hemorrhagic complications in patients undergoing treatment of cerebral aneurysm with stent assistance or flow diverters.[13] However, there are no reliable data regarding hyper-responders to clopidogrel and the reduction of clopidogrel dosing needed to target levels of platelet activity. The aim of the present study was to assess the influence of diabetes mellitus and cigarette smoking on the variability of the clopidogrel-induced antiplatelet effect. Further, we investigated the impact of active management of antiplatelet reactivity, the adjunctive use of cilostazol for clopidogrel hyporesponders, and a reduction of clopidogrel dosing for clopidogrel hyper-responders among patients undergoing CE and CAS.

Patients and Methods

Inclusion Criteria

Consecutive patients undergoing CAS for carotid artery stenosis and CE for unruptured cerebral aneurysm at Nara Medical University from October 2011 to October 2013 were recruited. The criteria for CAS were stenosis greater than 80% for asymptomatic lesions or stenosis greater than 50% for symptomatic lesions, and patients who were at high risk of CEA according to the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy criteria.[14] The criteria for CE were dome size greater than 5 mm and age younger than 75 years referring to Unruptured Cerebral Aneurysm Study Japan.[15] The baseline clinical characteristics of the patients, including patient age, sex, past history related to atherosclerosis, and preoperative medical conditions, were recorded. Diabetes mellitus patients needed to have been on insulin or oral antidiabetic agents managed for at least 2 months without changes in hypoglycemic treatment regimen according to the World Health Organization Report.[16] Untreated diabetic patients were introduced to internal medicine and received antidiabetic treatment prior to CAS. Chronic kidney disease (CKD) patients were defined as those with glomerular filtration rate less than 60 mL/minute/1.73 m^2. Current smokers were defined as those who smoked at least 1 cigarette per day during the month before the treatment. All patients underwent preoperative magnetic resonance imaging (MRI)/angiography, followed by cerebral angiography. All patients underwent diffusion-weighted imaging (DWI) before and the day after the treatment to evaluate for the existence of new ipsilateral bright spots (i.e., a fresh embolic stroke due to the interventional procedure).

Antiplatelet Medications

The patients were divided into 2 groups: patients who underwent CE (CE group) and patients who underwent CAS (CAS group). The patients were given 2 antiplatelet agents, aspirin 100mg and clopidogrel 75 mg daily, starting 1 week before CE and starting more than 4 weeks before CAS. We prospectively subjected these patients to active management of antiplatelet medications before the procedure. Patients who were resistant to clopidogrel were given adjunctive cilostazol 200 mg daily 2 days before the procedure. Patients who were hyper-responsive to clopidogrel received reduced dosing of 50, 25, or 12.5 mg daily according to the results of follow-up P2Y12 reaction units (PRUs) at 7, 14, 30, and 90 days after the treatment. In detail, for PRU values greater than 95, we maintained the same dosage of clopidogrel. For PRU values between