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Original article

Reduction of in-stent thrombus immediately after percutaneous coronary intervention by pretreatment with prasugrel compared with clopidogrel: An optical coherence tomography study

Takashi Kubo (MD, PhD, FJCC)*, Yasushi Ino (MD, PhD), Yoshiki Matsuo (MD, PhD), Yasutsugu Shiono (MD, PhD), Takeyoshi Kameyama (MD, PhD), Takashi Yamano (MD, PhD), Yosuke Katayama (MD), Akira Taruya (MD), Tsuyoshi Nishiguchi (MD), Keisuke Satogami (MD), Kuninobu Kashiyama (MD, PhD), Makoto Orii (MD, PhD), Akio Kuroi (MD, PhD), Tomoyuki Yamaguchi (MD), Atsushi Tanaka (MD, PhD), Takeshi Hozumi (MD, PhD), Takashi Akasaka (MD, PhD, FJCC)

Department of Cardiovascular Medicine, Wakayama Medical University, Wakayama, Japan

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ABSTRACT

Background: Prasugrel is a new-generation thienopyridine antiplatelet agent that provides more consistent and prompt platelet inhibition than clopidogrel. The aim of this study was to compare in-stent thrombus inhibition effect of pretreatment with prasugrel and clopidogrel by using optical coherence tomography (OCT) immediately after percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS).

Methods: We performed OCT immediately after PCI in 108 ACS patients pretreated with either prasugrel ($n = 51$) or clopidogrel ($n = 57$). OCT detected thrombus/plaque protrusion in all stented segments.

Results: Although stent volume (190.4 ± 119.1 mm^3 vs. 189.4 ± 95.8 mm^3, $p = 0.961$), mean stent area (6.9 ± 2.9 mm^2 vs. 7.1 ± 2.0 mm^2, $p = 0.772$), and minimum stent area (5.6 ± 2.7 mm^2 vs. 5.4 ± 1.7 mm^2, $p = 0.554$) were not different between the two groups, in-stent thrombus/plaque protrusion volume (1.8 ± 2.9 mm^3 vs. 4.5 ± 5.3 mm^3, $p = 0.002$), mean in-stent thrombus/plaque protrusion area (0.1 ± 0.1 mm^2 vs. 0.2 ± 0.2 mm^2, $p = 0.005$), and maximum in-stent thrombus/plaque protrusion area (0.5 ± 0.7 mm^2 vs. 0.8 ± 0.6 mm^2, $p = 0.007$) were significantly smaller in the prasugrel group compared with the clopidogrel group.

Conclusions: Pretreatment with prasugrel was associated with significantly reduced in-stent thrombus/plaque protrusion immediately after PCI for ACS compared with that with clopidogrel.

Introduction

Dual antiplatelet therapy consisting of aspirin and a thienopyridine is recommended in patients undergoing percutaneous coronary intervention (PCI) to prevent stent thrombosis. Clopidogrel is the most widely used thienopyridine, with abundant evidence of benefit in PCI [1]. However, clopidogrel has some suboptimal characteristics as an antithrombotic agent. Clopidogrel exhibits pharmacodynamics variability between individuals mainly due to genetic variations in cytochrome P450 (CYP) 2C19, and 20–40% of patients are non-responders, poor-responders, or resistant [2]. In addition, clopidogrel shows a delayed onset of action, which is observed 4–5 days after daily administration of clopidogrel [3].

Prasugrel is a new-generation thienopyridine antiplatelet agent that provides more consistent and prompt platelet inhibition than clopidogrel [4]. Prasugrel is converted into its active metabolite with less influence of the CYP genotype. The active metabolite of prasugrel appears in circulating blood within 15 min of dosing, which reaches maximal plasma concentration at ≈30 min [3]. Therefore, a more beneficial effect for preventing stent thrombosis is expected in prasugrel compared with clopidogrel.

* Corresponding author at: Department of Cardiovascular Medicine, Wakayama Medical University, 811-1, Kimiidera, Wakayama 641-8510, Japan.
Tel.: +81 73 441 0621; fax: +81 73 446 0631.
E-mail address: takakubo@wakayama-med.ac.jp (T. Kubo).

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Optical coherence tomography (OCT) is a high-resolution (10–20 μm) intravascular imaging technique that uses near infra-red light to create images. Compared with conventional intravascular imaging techniques, OCT allows more accurate assessment of intracoronary thrombus [5]. In the present study, we aim to compare in-stent thrombus inhibition effect of pretreatment with prasugrel and clopidogrel by using OCT immediately after PCI for acute coronary syndrome (ACS).

Methods

Study population

The present study retrospectively investigated 108 patients who met all of the following enrollment criteria: (1) PCI for ACS caused by de novo native coronary artery lesions between September 2013 and August 2015; (2) pretreatment with prasugrel or clopidogrel; (3) successful stent implantation; and (4) OCT before and immediately after PCI. In the present study, ACS included unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI). UA/NSTEMI is defined by the presence of ischemic chest pain (new-onset, progressive, or rest angina), the notable absence of ST segment elevation on electrocardiography, and the presence of either ST segment depression or T-wave inversion on electrocardiography and/or abnormal cardiac biomarkers [6]. Culprit lesion of ACS was determined as the lesion with the most severe stenosis or with thrombus on coronary angiography. Clopidogrel was used in consecutive patients undergoing PCI between September 2013 and August 2014, and prasugrel was used in consecutive patients undergoing PCI between September 2014 and August 2015 in our institution. Patients who received prasugrel or clopidogrel since before the onset of ACS were excluded from analysis. General exclusion criteria of OCT imaging were cardiogenic shock, chronic renal failure without hemodialysis, or extremely tortuous vessels. The present study was approved by the institutional review board, and written informed consent was obtained from all patients.

Pretreatment with antiplatelet agents

Loading dose of prasugrel (20 mg) or clopidogrel (300 mg) was administered before PCI. On the day after the loading dose, maintenance dose of prasugrel (3.75 mg) or clopidogrel (75 mg) was administered once daily, and was to be continued for at least 12 months after stent implantation. Patients with a history of intracranial bleeding or ischemic stroke, predisposition to hemorrhagic disease, or poorly controlled hypertension were started on the maintenance dose of either drug, without the loading dose. Aspirin (200 mg for the first dose and 100 mg/day thereafter) was concomitantly administered with prasugrel or clopidogrel.

PCI

PCI was performed with standard techniques through the radial or the femoral approach using 6 Fr or 7 Fr sheaths and catheters. During PCI, patients received intravenous heparin (a bolus of 100 IU/kg and additional doses aimed at achieving an activated clotting time of 250–300 s). No patients received IIb/IIIa inhibitor, urokinase-type plasminogen activator, or tissue plasminogen activator. XIENCE everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA), PROMUS everolimus-eluting stent (Boston Scientific, Natick, MA, USA), NOBORI biolimus-eluting stent (Terumo, Tokyo, Japan), or KANAME bare-metal stent (Terumo) were used for PCI. Manual thrombus aspiration prior to stent implantation, pre-dilatation, and post-dilation were performed at the operator's discretion.

Angiographic analysis

Quantitative coronary angiographic analysis was performed using a validated automated edge detection algorithm (CAAS-5, Pie Medical, Maastricht, The Netherlands) by an experienced investigator (T.Y.) who was blinded to the clinical information, PCI procedure characteristics, and OCT findings. The reference lumen diameter, minimum lumen diameter, percent diameter stenosis [(1 − minimum lumen diameter/reference lumen diameter) × 100], and acute gain (minimum lumen diameter immediately after the index procedure − minimum lumen diameter before the index procedure) were calculated. Thrombolysis In Myocardial Infarction (TIMI) flow grade was assessed as described previously [7]. No-reflow phenomenon was defined as TIMI flow grade 0, 1, or 2 without mechanical obstruction on the angiogram immediately after stent implantation or post-dilatation [8]. Distal embolization was defined as the angiographic cutoff of the distal branch or vessel at any point during the PCI procedure [8].

OCT imaging and analysis

ILUMIEN OPTIS (St. Jude Medical, St. Paul, MN, USA) or LUNAWAVE (Terumo) was used in the present study. Following a zero calibration, an OCT image catheter was advanced distally to the coronary culprit lesion or stented segment over a 0.014-in. conventional angioplasty guidewire. If the OCT catheter failed to pass through the culprit lesion, dilatation with a small balloon of ≤2.0 mm in diameter was performed prior to the OCT imaging. After the catheter placement, preheated contrast media at 37 °C (Omnipaque 350 Injection, Daiichi Sankyo Co., Ltd., Tokyo, Japan) was flushed through the guiding catheter at a rate of 2–4 ml/s for approximately 3–6 s using an injector pump (Mark V; Medrad, Warrendale, PA, USA). When a blood-free image was observed, the OCT imaging core was withdrawn at a rate of 20–40 mm/s using the stand-alone electronic control of the pullback motor. The OCT images were stored digitally for subsequent analysis.

All OCT images were analyzed by an experienced investigator (Y.I.) who was blinded to the clinical information, PCI procedure characteristics, and angiographic findings. The OCT analysis was performed using a dedicated off-line review system with semi-automated contour-detection software (St. Jude Medical or Terumo).

The culprit lesion characteristics were evaluated in the OCT images acquired before PCI. Fibrous tissue was defined as homogeneous, signal-rich region; calcification as well-delineated, signal-poor region with sharp border; and lipid as signal-poor region with diffuse border [9]. Thrombus was defined as an intraluminal mass protruding from the surface of the vessel wall with significant signal attenuation [9]. Plaque rupture was identified by fibrous cap disruption and a cavity formation within the lipidic plaque; erosion by the presence of attached thrombus overlying an intact plaque; calcified nodule by fibrous cap disruption detected over a calcified plaque characterized by protruding superficial calcification; and others by tight stenosis without the aforementioned findings, spontaneous coronary artery dissection, or coronary spasm [10,11]. Minimum fibrous-cap thickness was measured at the thinnest portion throughout the entire lesion. Maximum lipid arc and maximum calcium were measured at the largest sites throughout the culprit lesion, respectively.

Stent, lumen, and thrombus/plaque protrusion were evaluated in the OCT images acquired immediately after PCI. Thrombus/plaque protrusion was defined as a tissue prolapse between stent struts extending inside a circular arc (Fig. 1) [5]. Cross-sectional areas of stent, intra-stent lumen, extra-stent lumen, and thrombus/plaque protrusion (defined as stent area minus intra-stent

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