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Original article

Potent effect of prasugrel on acute phase resolution of intra-stent athero-thrombotic burden after percutaneous intervention to acute coronary syndrome

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ABSTRACT

Background: Recent studies suggested protruding thrombus and atheroma after stent placement could be a substrate for subsequent adverse ischemic events. Although protruded atherothrombotic burden can be assessed as intra-stent tissue (IST) by optical coherence tomography (OCT), the effects of potent antiplatelet therapy on the acute phase resolution of IST in patients with acute coronary syndrome (ACS) was unknown.

Methods: Ninety-six consecutive ACS patients with multi-vessel disease were enrolled in this prospective registry. In combination with aspirin, either clopidogrel or prasugrel was selected according to the date of enrolment. OCT examination was done immediately after percutaneous coronary intervention (post-PCI) and 10 days after index PCI (follow-up acute phase) to calculate averaged IST score as semi-quantitative measures of IST. High residual platelet reactivity (HRPR) was defined as platelet reactivity units (PRU) $\geq$ 240 by VerifyNow P2Y12 assay (Accumetrics Inc., San Diego, CA, USA).

Results: Thirty two patients (38 stents) were enrolled in the prasugrel group and sixty four patients (72 stents) in the clopidogrel group. Averaged IST scores post-PCI were similar between the two groups (0.68 ± 0.41 vs. 0.68 ± 0.40, $p = 0.99$), which decreased in all of the prasugrel group and in 87.5% of the clopidogrel group ($p = 0.02$). Consequently, changes in averaged IST score (delta averaged IST score) were significantly greater in the prasugrel group compared to those in the clopidogrel group (-0.411 ± 0.288 vs. -0.299 ± 0.270, $p = 0.045$). The frequency of HRPR was significantly lower in the prasugrel group (10.0% vs 32.4%, $p = 0.028$).

Conclusions: Prasugrel plus aspirin achieved greater acute phase reduction of IST than clopidogrel plus aspirin, which might underlie the clinical benefit of potent antiplatelet therapy in ACS.

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Introduction

Recent advances in percutaneous coronary intervention (PCI) have improved clinical outcomes for patients with acute coronary syndrome (ACS). However, early stent thrombosis remains a critical issue, with an incidence of 1.4% after PCI for ACS in Japan even with contemporary drug-eluting stents (DES) [1]. Although the precise mechanisms of early stent thrombosis have not been fully elucidated, recent autopsy analysis highlighted protruding thrombus burden and presence of necrotic core prolapse within the deployed stent as triggers of early stent thrombosis [2].

Optical coherence tomography (OCT) clearly visualizes atherothrombotic burden before and after primary PCI in ACS patients [3,4], and potentially enables us to monitor acute phase changes of

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intra-stent tissue (IST) including thrombus and plaque protrusion following initial treatment [5].

To reduce the risk of stent thrombosis, dual antiplatelet therapy with a P2Y12 receptor inhibitor in combination with aspirin has been a standard care after stent placement [6]. Clopidogrel has been the treatment of choice for its safety profile and capability of loading administration. However, delayed onset and inter-patient response variability are considered drawbacks [7–9]. Resistance to clopidogrel has been reported to be a potential risk for adverse cardiac events [10,11]. Thus, a new-generation P2Y12 receptor inhibitor, prasugrel, with rapid onset and potent, consistent platelet inhibitory action has been developed [12]. Superiority of prasugrel over clopidogrel in ACS patients has been confirmed in terms of decreased incidence of recurrent infarction and stent thrombosis [13]. However, the precise mode of action of its antiplatelet effects on IST in comparison with clopidogrel has not been elucidated.

The aim of this study was to compare the effect of prasugrel and clopidogrel on acute phase IST changes by serial OCT evaluation in patients with ACS treated by stent placement.

Methods

Study population

Consecutive ACS patients with multivessel disease undergoing primary PCI with successful stent implantation to culprit lesion under OCT guidance from August 2012 to October 2015 at Osaka Saiseikai Nakatsu Hospital were enrolled in this prospective registry. Exclusion criteria were cardiopulmonary arrest, cardiogenic shock or use of intra-aortic balloon counter-pulsation (IABP), severe heart failure or renal failure without hemodialysis, failure to obtain final Thrombolysis in Myocardial Infarction grade 3 (TIMI3) flow, PCI without stent implantation, and patients with in-stent restenosis (ISR) or stent occlusion, use of oral anticoagulants or other anti-platelet agents. Patients who had taken prasugrel or clopidogrel before the onset of ACS were also excluded.

All patients received loading dose of oral aspirin 200 mg once daily (od) and a P2Y12 receptor inhibitor at the emergency room. A P2Y12 receptor inhibitor was selected according to date of enrollment. Between August 2012 and July 2014, patients were prescribed clopidogrel 300 mg loading dose followed by 75 mg od maintenance dose. Between August 2014 and October 2015, prasugrel 20 mg loading dose followed by 3.75 mg od maintenance dose was prescribed. Prasugrel dosage was one third of that used in other countries, which adjustment was approved by the Japanese Health, Labor and Welfare Ministry to fit the Japanese population.

This study was approved by the ethics committee of Osaka Saiseikai Nakatsu Hospital and performed according to the guidelines of the Declaration of Helsinki. All enrolled study patients provided written informed consent to participate in the study.

PCI procedure and OCT examination

All patients received 100 U/kg unfractionated heparin intravenously before PCI. Direct stenting or pre-dilatation and pre-stent thrombus aspiration were allowed at the discretion of the operator. Full lesion coverage with stent was ensured by implantation of one or more stents. OCT imaging was performed using a frequency-domain OCT system (Dragonfly ILUMIEN Optis™, St. Jude Medical, St. Paul, MN, USA) immediately after index PCI with stent placement (post-PCI) under TIMI 3 reflow. An OCT catheter (Dragonfly JP™, St. Jude Medical) was advanced to the distal end of the target lesion. The entire length of lesion was scanned using the integrated automated pullback device at a speed of 40 mm/s during contrast injection either manually or by automatic injector.

Patients received PCI to the residual significant lesion and simultaneously OCT examination was done to the site of index stent placement at 10 days after index PCI for serial OCT examination (follow-up acute phase).

OCT analysis

All images were digitally stored and submitted to a core laboratory for independent evaluation (Kobe Cardiovascular Core Laboratory, Kobe University Graduate School of Medicine, Kobe, Japan) and subsequent analysis using proprietary software (ILUMIEN™, St. Jude Medical). OCT cross-sectional images were evaluated every 1 mm for the whole stented segment and proximal/distal reference area. For image quality assessment, lesions were defined as analyzable when more than 270 degrees of each cross-section and three quarters of the whole cross-section within the stented segment were visible. Reference lumen area (within 5 mm of the proximal and distal edges) and minimal stent area were measured. Percent expansion was calculated as minimal stent area divided by averaged reference lumen area × 100.

Since clear discrimination between intra-stent thrombus and plaque protrusion is difficult [14,15], we defined mass protruding beyond the stent strut into the lumen as intra-stent tissue (IST), representative of atherothrombotic burden within the stent. IST occupancy was graded according to the quadrant degree occupied in cross-sectional OCT images (grade 0 for no IST, grade 1 for IST $<$90-degree, grade 2 for $\geq$90 and $<$180-degree, grade 3 for $\geq$180 and $<$270-degree, and grade 4 for $\geq$270 degree). IST was evaluated at every 1-mm interval and IST score was calculated as the summation of the grade for each cross section [14]. Averaged IST score was defined as IST score divided by number of cross sections. Delta averaged IST score was defined as averaged IST score at follow-up acute phase minus post-PCI (Fig. 1). We also evaluated proportion of lesions with increased, unchanged, or decreased averaged IST score 10 days after index PCI.

Every flame analysis was performed to detect maximum IST within the stented segment. Maximum IST area was measured at both time points. To determine the equivalent IST at post-PCI and follow-up acute phase, the distance from both distal and proximal stent edges was used.

All OCT images were analyzed by two independent investigators blinded to patient information (Y.T. and K.Y.). For disagreement in IST score between investigators, a consensus reading was obtained from a third independent investigator (T.S.).

Platelet function test

We obtained blood samples from the arterial sheath at the time of acute phase follow-up angiography. Residual platelet reactivity was assessed by VerifyNow® point-of-care P2Y12 assay (Accumetrics Inc, San Diego, CA, USA). High residual platelet reactivity (HRPR) was defined as platelet reactivity units (PRU) $\geq$ 240 [16].

Study endpoints

The primary endpoint of the study was delta averaged IST score which was compared between clopidogrel and prasugrel groups. Secondary endpoints included the reduction of maximum IST area.

In-hospital cardiovascular death, myocardial infarction [increase in creatinine kinase (CK) MB ($>$1.5-fold the previous value) following transient decrease [17]], stent thrombosis (definite or probable according to Academic Research Consortium criteria), and target vessel revascularization were recorded. Frequencies of major and minor bleeding according to TIMI criteria were

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