Journal of Cardiology 64 (2014) 25–31

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Impact of hemodialysis on local vessel healing and thrombus formation after drug-eluting stent implantation

Akihide Konishi (MD)[a], Toshiro Shinke (MD, FJCC)[a,*], Hiromasa Otake (MD)[a], Daisaku Nakatani (MD)[b], Masayuki Nakagawa (MD)[a], Takumi Inoue (MD)[a], Hirotoshi Hariki (MD)[a], Tsuyoshi Osue (MD)[a], Yu Taniguchi (MD)[a], Masamichi Iwasaki (MD)[a], Ryo Nishio (MD)[a], Noritoshi Hiranuma (MD)[a], Hiroto Kinutani (MD)[a], Masaru Kuroda (MD)[a], Junya Shite (MD, FJCC)[a], Ken-ichi Hirata (MD)[a]

[a] Kobe University Graduate School of Medicine, Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe, Hyogo, Japan
[b] Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

ARTICLE INFO

Article history:
Received 7 August 2013
Received in revised form 4 October 2013
Accepted 29 October 2013
Available online 27 December 2013

Keywords:
Drug-eluting stents
Thrombus
Hemodialysis

ABSTRACT

Background: Although hemodialysis (HD) is a suggested risk factor for stent thrombosis, its contribution to local vessel healing after drug-eluting stent (DES) implantation is unclear.
Methods: A total of 121 patients (152 lesions treated with DES) who underwent 8-month follow-up coronary angiography with optical coherence tomography (OCT) were enrolled, and the findings were compared between patients with and without HD. To match baseline differences, mid-term OCT findings of 42 propensity score-matched lesions (21 non-HD vs. 21 HD) were compared. Effects of HD on the efficacy of antiplatelet therapy were also evaluated by VerifyNow assay (Accumetrics, San Diego, CA, USA).
Results: Patients with HD had a significantly higher rate of thrombus formation than those without (64% vs. 33%, $p=0.007$), although the baseline parameters and lesion characteristics differed between the groups. Multivariate logistic regression analysis revealed that HD was associated with an increased risk of thrombus formation (odds ratio 5.991, 95% confidence interval: 1.972–18.199, $p=0.002$). Even after propensity-matching for patient background and balancing of angiographic and OCT variables, the risk of thrombus formation remained significantly higher in HD patients. The P2Y12-reaction unit was significantly increased after HD (Pre HD: 211 ± 75 vs. Post HD: 262 ± 59, $p=0.01$), but patients without HD showed no increase during the same elapsed time (221 ± 88 vs. 212 ± 96, $p=0.19$).
Conclusions: HD is a potential risk factor for subclinical thrombus attachment after DES therapy. Systemic problems, such as residual platelet reactivity, associated with HD as well as local vessel features in HD patients might contribute to the increased incidence of thrombus attachment and subsequent onset of thrombotic event after DES implantation.

Introduction

Although implantation of drug-eluting stents (DES) significantly reduces restenosis compared with bare-metal stents in a wide range of patient populations [1], hemodialysis (HD) continues to be associated with an increased risk of restenosis and an unfavorable clinical outcome after DES deployment [2–5]. Because the detailed vessel response after DES implantation in patients undergoing HD therapy has not been fully elucidated, the mechanisms of such interactions remain unclear. In the present study, we assessed the relationship between HD and local vessel conditions before and after DES deployment using a large-scale single center optical coherence tomography (OCT) database pooled in the Kobe University OCT Registry. Also, to assess the possible impact of HD treatment on the efficacy of antiplatelet therapy, responsiveness to antiplatelet therapy was also evaluated using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA, USA).

* Corresponding author at: Kobe University Graduate School of Medicine, Department of Cardiology, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. Tel.: +81 78 382 5846; fax: +81 78 382 5859.
E-mail addresses: shinke@med.kobe-u.ac.jp, shinke820@aol.com (T. Shinke).

0914-5087/$ – see front matter © 2013 Published by Elsevier Ltd on behalf of Japanese College of Cardiology.
http://dx.doi.org/10.1016/j.jjcc.2013.10.020

Materials and methods

Study population and methods

Between April 2006 and April 2010, a total of 516 patients underwent elective percutaneous coronary intervention (PCI) with DES (Cypher, Cordis Corp., Miami Lakes, FL, USA; TAXUS®, Boston Scientific, Natick, MA, USA; and XIENCE V™, Abbott Vascular, Inc., Santa Clara, CA, USA) for de novo native coronary lesions (822 DES). Of those, 342 patients underwent prospectively scheduled follow-up angiography as a routine angiographic follow-up widely performed in Japan. To ensure patient safety during OCT, patients with left main trunk disease ($n = 28$), severe tortuous lesions, and severely calcified vessels ($n = 41$) were also excluded due to anticipated difficulties advancing the OCT catheters. In addition, patients with vessels greater than 4.0 mm in diameter on angiography ($n = 34$) were excluded, because these vessels might be too large to occlude blood flow. Therefore, 239 patients became candidates of the follow-up OCT registry and were asked to undergo follow-up OCT. Among these candidates, 192 patients agreed to undergo OCT at the follow-up angiography and were enrolled into the OCT registry. Furthermore, patients who did not take clopidogrel at the time of the follow-up angiography ($n = 38$) and patients who did not agree to genetic analysis ($n = 21$) were excluded from the study. A total of 133 patients (171 DES) who underwent an 8-month follow-up coronary angiography with OCT as well as genetic analysis were enrolled and the OCT findings of the lesions were compared between patients with and without HD treatment. Also, to match the potential differences in patients, lesions, and procedural characteristics, 42 propensity-score-matched lesions (21 non-HD vs. 21 HD) were queried from the overall patient population and the mid-term OCT findings were compared between patients with and without HD treatment.

The PCI procedure was performed with intravascular ultrasound guidance (Boston Scientific Corp. or Volcano Corporation, Rancho Cordova, CA, USA).

All patients were taking aspirin 100 mg/day. Clopidogrel 75 mg/day was additionally given for at least 12 months after DES implantation. This study was approved by the Ethics Committee of Kobe University and all enrolled study patients provided written informed consent. The study conformed to the tenets of the Declaration of Helsinki.

Coronary angiographic evaluation

As a qualitative angiographic evaluation, coronary calcification was defined as "readily apparent densities observed within the artery wall and site of lesion as an X-ray absorbing mass," and classified as none or mild (focal densities noted only at the margin of only one side of the arterial wall); moderate (i.e. not classified as mild or severe); or severe (bulky or circulatory densities observed on both sides of the arterial wall) [6].

Quantitative coronary angiographic evaluation (QCA) was performed for the target lesion before and after the PCI and at the time of angiographic follow-up using dedicated software (QCA-CMS 5.1, Medis, Leiden, The Netherlands). In-stent restenosis was defined as a diameter of stenosis (DS) > 50% within the stented segment. In-stent late luminal loss was defined as the minimal luminal diameter immediately after PCI minus that at 8 months.

OCT examination

OCT examination was performed 8 months after stenting. In this study, because frequency-domain OCT had not been approved for clinical use in Japan, time-domain OCT with coronary artery occlusion was used as previously reported [7]. The entire length of the stent was imaged with an automatic pullback device moving at 1 mm/s.

OCT analysis

All images were analyzed by an independent observer blinded to the clinical presentation and lesion characteristics. Cross-sectional OCT images were analyzed at 1-mm intervals (every 15 frames).

Neointimal thickness inside each stent strut was measured. Stent area and maximum and minimum stent diameter were measured manually. Struts with a measured neointimal thickness of 0 μm were defined as uncovered struts. A maximum distance of more than 170 μm for sirolimus-eluting stents (SES), more than 164 μm for paclitaxel-eluting stents (PES), and 108 μm for everolimus-eluting stents (EES) between the center reflection of the strut and the adjacent vessel surface was defined as incomplete strut apposition [7].

To assess for asymmetric stent expansion, a stent eccentricity index (SEI) was determined by the minimum stent diameter divided by the maximum stent diameter in each cross section. To assess the unevenness of neointimal thickness, a neointimal unevenness score (NUS) was calculated for each cross-section as maximum neointimal thickness in one cross-section divided by the mean neointimal thickness of the cross-section. Then, the mean SEI and NUS were calculated for each stent. Intra-stent thrombus was defined as a protruding mass beyond the stent strut into the lumen with significant attenuation behind the mass (Fig. 1). To differentiate thrombi from plaque protrusion or neointimal hyperplasia, we excluded protruding masses without remarkable signal attenuation and surface irregularity [8,9].

Blood sampling and genotyping methods

To assess the possible underlying mechanisms of subclinical thrombus formation in HD patients, we obtained blood samples from the arterial sheath at the time of follow-up angiography. Genomic DNA was extracted from whole blood using the commercially available QIAamp™ DNA Blood Mini kit (QIAGEN N.V., Venlo, The Netherlands) according to the manufacturer's instructions. CYP2C19*2 (681G > A) or *3 (636G > A) polymorphisms were

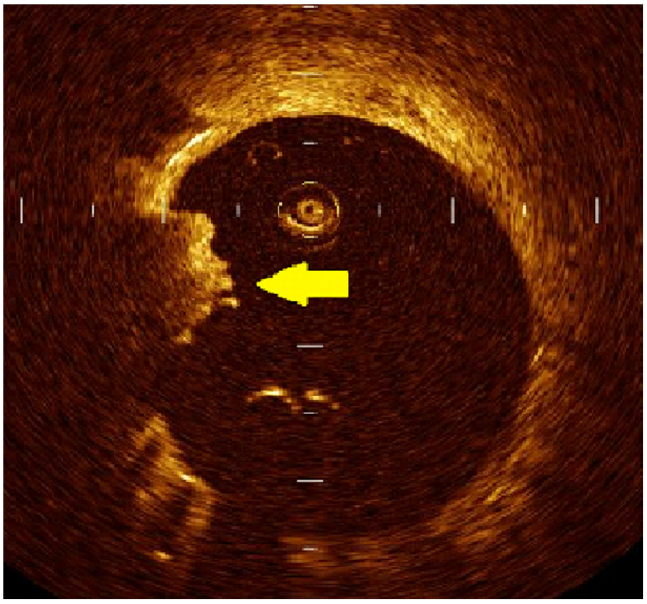

Fig. 1. Intra-stent thrombus was defined as a protruding mass beyond the stent strut into the lumen with significant attenuation behind the mass.