Hemodialysis is an Independent Predictor of Coronary In-stent Restenosis after Paclitaxel Eluting Stent Implantation

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Abstract

Objective A drug eluting stent is often used for high-risk patients with complications such as diabetes mellitus (DM) and hemodialysis (HD), however the factors to predict restenosis after paclitaxel-eluting stent (PES) placement have not been reported to date.

Methods Between May 2007 and August 2009, 165 consecutive patients (231 stents) received PES in our hospital. Stent diameter and length were determined by the use of intravascular ultrasound (IVUS). All patients continued to take 2 types of anti-platelet agents (aspirin and Clopidogrel or Ticlopidine). Ninety percent of the subjects received a follow-up coronary angiogram 6 months later.

Results Underlying diseases were hypertension in 75%, hyperlipidemia in 78% and DM in 60% (15% on insulin), and 14% of the subjects received HD. Eighty-three percent of the patients had orally taken Statin, 85% ACE/ARB and 68% had beta blockers. Mean length and diameter of PES were 21.6 ± 7.2 mm and 2.9 ± 0.3 mm, respectively. Target lesion revascularization (TLR) rate 6 months after PES placement was 14.6% overall. In HD patients TLR was 43%, hypertension 15.0%, hyperlipemia 12.4%, DM with oral medication 12.5%, DM with insulin 12.0%, respectively. In multivariate analysis, HD was an independent risk factor for TLR ($p=0.0001$, OR: 6.61, 95% C.I.: 2.34-18.6).

Conclusion HD had the greatest influence on TLR after PES even though risk factors were well controlled. It is necessary to develop new PCI techniques and stents that are useful for HD patients.

Key words: drug-eluting stent, in-stent restenosis, percutaneous coronary intervention, hemodialysis

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Introduction

A conventionally-used bare metal stent (BMS) has the major problem of a high restenosis rate. It is reported that the restenosis rate with a drug eluting stent (DES) is lower than that with BMS (1, 2). Consequently, DES is more frequently used for high-risk patients with complications such as diabetes mellitus (DM) and hemodialysis (HD) (3). Com-

pared with Western countries, percutaneous coronary intervention (PCI) is overwhelmingly more popular than coronary artery bypass graft surgery (CABG) in Japan (4). The j-Cypher registry (5) conducted in Japan shows that, among the patients to whom the Cypher sirolimus-eluting stent (SES) is used, 41% have DM and 5.5% receive HD as complications. On the other hand, in studies of Taxus- IV, V, VI, about 23% have DM (the frequency of patients on HD is not shown) (6). These results indicate that DES is more fre-

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Table 1. Baseline Characteristics of PES Patients

Age(years)	66.0±9.9
Males	141 (85%)
Body Mass Index(kg/m ²)	24±3.6
PES patients	165
PES/patient	1.40/pt
Number of coronary risk factors	
Hypertension	127 (77%)
Hyperlipidemia	132 (80%)
Diabetes mellitus	102 (62%)
insulin usage	25 (15%)
Smoking	
Current	15 (9%)
Ex-smoker	96 (58%)
None	54 (33%)
Hemodialysis	23 (14%)
Family history	26 (16%)

PES, paclitaxel-eluting stent; VLST, very late stent thrombosis
CABG, coronary artery bypass grafting

Table 2. Clinical Events

Cardiac Death	0
Non-Cardiac death	0
SAT	2(1.21%)
VLST	0
TLR	24(14.5%)
CABG	0

SAT, Sub Acute Thrombosis;

quently used in patients with high risk in Japan. However, not many investigators have reported about the outcome of DES in high-risk patients. In particular, the factors to predict restenosis and target lesion revascularization (TLR) after paclitaxel-eluting stent (PES) placement have not been reported to date.

Methods

Study population

Subjects were 165 consecutive patients who received PES at our facility between May 2007 and August 2009 (the total number of PES was 231). All of the patients and their family gave written informed consent for PCI treatment before the procedure. During the study period we alternatively used PES and SES in order to avoid the influence of lesion morphology or operators' individual thoughts on the study results. PES placement was not performed for the myocardial infarction patients with ST elevation or the patients who were going to undergo surgery.

PCI procedure

Before the operation, 100 mg aspirin and 75 mg clopidogrel, or 100 mg aspirin and 200 mg ticlopidine were administered. After confirming there were no side effects such as hepatic impairment and thrombocytopenia, PES was placed.

The stenosis site was identified by coronary angiography (CAG), and the presence of calcification and the vascular diameter in the lesion were examined by intravascular ultrasound (IVUS). In principle, PES was placed after predilatation. IVUS was performed again after the placement to confirm the compression bonding of the stent to the vascular wall. When insufficient dilatation was observed, post dilatation using a balloon was performed as appropriate. Ninety percent of the subjects received follow-up CAG 6 months after PES placement. The other patients who did not receive CAG attended our out-patient department every two months. They had no chest symptom and no change of electrocardio-

gram and ultrasonic echocardiography. There was no patient death, myocardial infarction nor stent thrombosis. As a general rule, the subjects continued to take 2 types of antiplatelet agents (aspirin, and clopidogrel or ticlopidine) till follow-up CAG.

CAG was multidirectionally taken after injection of nitroglycerin into the coronary artery. Coronary arteries were evaluated by quantitative coronary angiography (QCA). The minimum luminal diameter (MLD) and the length of lesion were measured, and the percent diameter stenosis (%DS) was calculated. A lesion of not less than 50%DS observed on follow-up CAG was defined as restenosis. PCI for TLR was performed again for the patients who had both restenosis and chest symptoms, or who was positive for myocardial ischemia on single photon emission computed tomography (SPECT).

Major adverse cardiac event (MACE)

All cause mortality, Q-wave myocardial infarction, TLR and stent thrombosis were defined as MACE.

Statistical analysis

Quantitative data were expressed as rates or mean ± SD. Student's t test was used to analyze metric variables, and chi-square test for categorical variables. Multivariate analysis was performed on parameters found to be significant in univariate analysis. P values of less than 0.05 were considered to be statistically significant. Statistical analysis was performed using commercially available software (SPSS for Windows, version 11.5, SPSS Inc, Chicago, IL, USA).

Results

PES placement was performed in 165 consecutive patients at our facility between May 2007 and August 2009, and the total number of PES was 231. The average number of PES per patient was 1.4.

Baseline characteristics

Average age of patients was 66 years, and 85% were males. Approximately 80% of the patients had hypertension and hyperlipidemia as underlying diseases. In addition, 62% had DM and 15% used insulin. Twenty-three patients (14%) received HD (Table 1).

Clinical events

As shown in Table 2, neither cardiac death nor non-cardiac death was observed within 6 months after PES

Table 3. Comparison of Patient Characteristics between TLR(-) and TLR(+)

	TLR(-) (n=141)	TLR(+) (n=24)	p value
Age(years)	66.6±10.3	68.4±7.2	
Males	118 (84%)	23(96%)	0.206
Height(cm)	160.9±9.1	161.8±6.5	0.674
Weight(kg)	63.4±12.4	59.7±9.9	0.180
BMI (kg/m ²)	24.3±3.7	22.7±2.7	0.040
Waist(cm)	85.4±10.8	81.2±8.6	0.076
Number of coronary risk factors			
Hypertension	105 (92%)	15 (63%)	0.800
Hyperlipidemia	112 (79%)	16 (67%)	0.188
Diabetes mellitus	86 (61%)	14 (58%)	0.824
insulin usage	22 (16%)	3 (13%)	0.695
Smoking			
Current	13(9%)	2 (8%)	
Ex-smoker	82 (58%)	14 (58%)	0.990
None	46 (33%)	8 (33%)	
Hemodialysis	13 (9%)	10 (42%)	0.0001
Family history	21 (15%)	5 (21%)	0.460

TLR, Target lesion revascularization; BMI, body mass index;

Table 4. Oral Medication and Laboratory Data at Follow-up CAG

	TLR(-) (n=141)	TLR(+) (n=24)	p value
Aspirin	141 (100%)	24 (100%)	
Clopidogrel	66 (47%)	12 (50%)	0.772
Ticlopidine	68 (48%)	11(46%)	0.828
Warfarin	21 (15%)	2 (8%)	0.391
Statin	120 (85%)	18 (75%)	0.216
ACE inhibitor/ARB	123 (87%)	17 (71%)	0.038
Beta blocker	97 (69%)	15 (63%)	0.542
Calcium blocker	70 (50%)	15 (63%)	0.244
Total-cholesterol(mg/dL)	163±32	148±26	0.033
TG(mg/dL)	154±110	136±86	0.455
HDL(mg/dL)	53±17	52±15	0.813
LDL(mg/dL)	92±28	81±20	0.068
HbA1c(%)	6.15±1.13	6.17±0.87	0.938
Creatinine(mg/dL)	1.39±1.56	1.65±2.39	0.492

CAG, coronary angiography; ACE,Angiotensin Converting Enzyme Inhibitor;

ARB, angiotensin receptor blocker;

TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein

placement. Two patients developed sub-acute thrombosis: One patient had discontinued anti-platelet agents by himself. In the other patient, ticlopidine was changed to cilostazol due to an allergy to ticlopidine. The catheter was performed urgently in both patients at the time of SAT onset. In both patients, new stent placement was not performed, and blood flow was improved only by thrombus suction and temporary IABP support. Both patients recovered and were discharged. These 2 patients continued to take antiplatelet agents after discharge, and no restenosis was observed on 6-month follow-up CAG. Therefore, SAT observed in these 2 patients was thought to be caused by discontinuation of antiplatelet agents.

CABG was performed for no patient within 6 months after PES placement. Twenty-four patients (14.5%) had re-PCI for TLR 6 months after the placement.

Comparison between patients with and without TLR

Table 3 shows the comparison between the patients with (n=24) and without (n=141) TLR (TLR(+) and TLR(-) groups, respectively). The mean age of TLR(+) group (68 years) was similar to that of TLR(-) group (66 years). There

was no significant difference in the gender distribution. No difference was observed in height or abdominal girth, but the TLR(+) group had a significantly lower body mass index (BMI) than the TLR(-) group (p=0.04). Concerning complications, there was no difference in the frequency of diabetes mellitus, or the frequency of insulin usage. TLR(+) group received hemodialysis significantly more than TLR(-) group (p=0.0001).

Aspirin was orally taken by all patients, and also either clopidogrel or ticlopidine was orally taken at the time of 6-month follow-up. Statin was orally taken by 85% of the patients even in TLR(-) group. Beta blocker was orally administered to not less than 60% of both TLR(+) and TLR(-) groups. Angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blockers (ARB) was orally taken significantly less by TLR(+) group than TLR(-) group (p=0.038) (Table 4).

And also, Table 4 shows blood test results at the time of 6-month follow-up CAG. Low-density lipoprotein (LDL) cholesterol was controlled well by statins in both TLR(+) and TLR(-) groups. The total cholesterol level tended to be lower in TLR(+) group (p=0.033). Table 5 shows the com-

Table 5. Comparison of Lesion Characteristics between TLR(-) and TLR(+)

	TLR(-) (n=141)	TLR(+) (n=24)	p value
Clinical diagnosis			
eAP	76 (54%)	14 (58%)	0.754
uAP(non-STEMI)	12 (9%)	1 (4%)	
OMI	53 (38%)	9 (38%)	
Lesion characteristics			
de novo	103 (73%)	16 (67%)	0.255
CTO	7 (5%)	3 (13%)	
Cypher ISR	14 (9.9%)	4 (17%)	
BMS ISR	7 (5%)	1 (4%)	
Bifurcation	21 (15%)	1 (25%)	0.216

eAP,effort angina pectoris; uAP, unstable angina pectoris

STEMI,ST-segment elevation myocardial infarction; OMI, old myocardial infarction

CTO,Chronic Total Occlusion; ISR, in stent restenosis; BMS,bare metal stent

Table 6. PCI Procedure

	TLR(-) (n=141)	TLR(+) (n=24)	p value
Stent length(mm)	21±7	20±7	0.503
Stent size(mm)	2.9±0.3	2.8±0.2	0.248
Stent/Lesion ratio	1.3±0.4	1.2±0.4	0.345
Post dilatation	120 (85%)	20 (83%)	0.765
Final balloon size(mm)	3.24±0.44	3.04±0.34	0.672

Table 7. Comparison of QCA and IVUS Findings between TLR(-) and TLR(+)

	TLR(-) (n=141)	TLR(+) (n=24)	p value
Pre			
MLD	1.04±0.73	0.81±0.56	0.540
%DS	74.3±33.0	68.2±24	0.280
Post			
MLD	2.51±0.36	2.62±0.60	0.110
%DS	12.5±9.26	8.64±11.5	0.167
MSA	5.4±1.9	5.1±1.7	0.092

QCA, quantitative coronary angiography; IVUS, intravascular ultrasound imaging

MLD, minimal lumen diameter; DS, diameter stenosis; MSA, minimal stent area

Table 8. Multivariate Logistic Regression Analysis for Prediction of TLR

	OR	95%CI	p value
Hemodialysis	6.608	2.34-18.64	0.0001
Total-cholesterol(mg/dL)	0.98	0.962-0.999	0.038
ACEinhibitor/ARB	0.252	0.082-0.776	0.016
BMI(kg/m ²)			0.330

parison of lesion morphology and other comparisons between TLR(+) and TLR(-) groups. There was no difference in the frequency of angina or old myocardial infarction (OMI). Furthermore, no difference in the incidence of *de novo* lesion, chronic total occlusion (CTO), or restenosis in the stent was observed between the two groups.

Concerning PCI procedures (Table 6), there was no difference in mean stent length or diameter. No difference was observed in the presence of post-dilatation or balloon size between TLR(+) and TLR(-) groups. In addition, there was no difference in MLD observed by QCA or MSA by IVUS between the two groups (Table 7).

Prediction of TLR

Among the investigated factors, HD, total cholesterol,

treatment with ACE inhibitors/ARB and BMI showed significant differences between TLR(+) and TLR(-) groups. Multivariate logistic regression analysis was performed for these factors. Consequently, hemodialysis was the most significant factor to predict TLR for PES (p=0.0001, OR: 6.608, 95% C.I.: 2.34-18.64) (Table 8).

Discussion

DES in high-risk patients

Since DES is reported to demonstrate a markedly reduced restenosis rate compared to BMS, it is coming to be used more for high-risk patients (1, 2).

Some studies have reported the results of SES in high-

risk patients (7-11) but few reports discuss the outcomes when using PES in high-risk patients. In our study, the factors to influence TLR for PES in patients with very high risks (i.e., 77% had hypertension, 80% hyperlipidemia and 62% DM; 15% used insulin; and 14% received HD) were investigated. Approximately 80% of the patients with hyperlipidemia were administered statin, and it was controlled very well [LDL-cholesterol: 92 ± 28 mg/dL in TLR(+) group, and 81 ± 20 mg/dL in TLR(-) group]. Mean blood pressure was 124 mmHg (data not shown) even in TLR(+) group. Seventy percent of all patients received ACE inhibitors/ARB and 60% beta blockers, and blood pressure was well-controlled in both TLR(+) and TLR(-) groups.

Our study subjects included numerous high-risk patients with complications, but they were well treated and favorably controlled. However, the rate of TLR was high. Therefore, we investigated which factor had the greatest influence on TLR. Consequently, the most important factor to predict TLR was the presence of HD, but not DM or usage of insulin. Stent restenosis in HD patients is still a major issue (12). Our study results indicated that they still had a higher restenosis rate even when using PES.

In Japan, new DESs (e.g., ZES; zotarolimus eluting stent, and EES; everolimus eluting stent) have become available. However, how to select the appropriate DES in Japanese patients has not been clarified yet. We should evaluate new DESs in HD patients, whose restenosis rate could not be lowered by PES, in order to confirm whether they are effective even for HD patients.

Hemodialysis patients

According to NIH, the most frequent cause of death in HD patients is cardiovascular-related diseases (45%) (13). The HD patients have better long-term survival after CABG than PCI (14). But recent reports from the BMS era showed comparable long-term survival after percutaneous and surgical coronary revascularization procedures in renal transplant recipients (15), the invasiveness of surgical methods contributes to an increased rate of in-hospital death and post-operative stroke (16).

It is reported that, when using BMS, the rate of TLR is higher in HD patients than in non-HD patients (17). Causes of restenosis in hemodialysis patients include chronic vascular inflammation, poor dilation (18) due to calcification (19-21), and complications of not only cardiac dysfunction but other organ dysfunctions. However, in our study, there was no difference in post-MSA measured by IVUS, or post-MLD analyzed by QCA between TLR(+) and TLR(-) groups. Therefore, technical factors such as poor dilation of the vessels were not the causes of the high TLR rate in HD patients. The incidence of restenosis in HD patients is high and stent restenosis is still a major issue (12). The reason for this might be that the mechanism of restenosis in HD patients is highly related to vessel shrinkage and neointimal hyperplasia (22).

In this study, multivariate analysis showed that the factors

to predict TLR in high-risk patients were BMI, the presence of hemodialysis, low cholesterol level, and administration of ACE inhibitors/ARB. HD had the greatest influence on TLR after PES. It is necessary to develop new PCI techniques and stents that are useful for HD patients in the near future.

Conclusion

The incidence of restenosis was high when using PES in HD patients. We should investigate stent placement techniques, oral medicines, and outcomes of new DESs in HD patients in order to confirm whether they were effective even for HD patients.

Study limitations

Our study limitation was that this was a retrospective investigation, and not a randomized comparative study. Consequently, it was realized that even PES had limitations in HD patients. If stents and techniques that are useful for HD patients are developed, we should perform prospective studies on such patients in the future.

In addition, the number of subjects in this study (165 consecutive patients) was not sufficiently large. We wish to undertake a study with a larger number of subjects.

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