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Sirolimus- vs. paclitaxel-eluting stent to coronary intervention in dialysis patients ☆

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ABSTRACT

Background: Patients on maintenance hemodialysis (HD) are at high risk for restenosis after percutaneous coronary intervention (PCI) even if treated with a sirolimus-eluting stent (SES). The aim of this study was to compare the effects of SES and paclitaxel-eluting stent (PES) in preventing restenosis in HD patients with coronary artery disease.
Methods: A total of 100 consecutive patients on HD who underwent PCI were enrolled into the study. They were randomly assigned to receive either SES or PES. We compared follow-up angiographic outcomes between the SES and PES groups at 8-month follow-up.
Results: The angiographical restenosis rate, defined as % diameter stenosis>50% at 8-month follow-up, was 19.7% in the SES group and 20.0% in the PES group ($p=0.97$). Late loss was also similar between the two groups (0.49 ± 0.70 mm vs. 0.48 ± 0.91 mm, $P=0.94$). There were no significant differences in the rates of all-cause death, non-fatal myocardial infarction, or TLR due to stent restenosis-induced ischemia between the two groups (2.0% vs. 4.0%, $p=0.56$, 2.0% vs. 4.0%, $p=0.56$, and 16.0% vs. 12.0%, $p=0.57$, respectively).
Conclusions: There was no significant difference in angiographical outcome at 8-month follow-up between HD patients treated with SES and PES. Even if treated with DES including SES and PES, patients on HD are at high risk of restenosis after PCI.

1. Introduction

It has been reported that cardiovascular disease is the main reason for morbidity and mortality in patients requiring hemodialysis (HD) [1,2]. Compared to non-HD patients, patients on HD have more complex lesions, such as coronary calcification of coronary lesions and multi-vessel disease [3]. Recently, percutaneous coronary intervention (PCI) has become an effective therapy for ischemic heart disease in such patients [4,5]. However, due to in-stent hyperplasia, a relatively higher restenosis rate had been a clinical limitation after PCI in patients on HD before drug-eluting stent (DES) era [6-8].

DES has dramatically reduced the risk of restenosis after PCI in many cases [9-13]. Thus, DES is one of the most exploited strategies for ischemic heart disease in patients on HD. Recent reports suggest that the restenosis rate during the follow-up period after PCI has been even higher in patients on HD, even if treated with the sirolimus-eluting stent (SES) [14,15]. It has been reported that paclitaxel inhibits smooth muscle cell proliferation and migration even in hyperglycemia and insulin resistance conditions [16]. Because many patients on HD have diabetes and impaired glucose metabolism, we hypothesized that implantation with PES would have a beneficial effect on preventing MACE, including restenosis, after PCI compared to that with SES. However, until now, there have been limited data concerning the effects of the paclitaxel-eluting stent (PES) in HD patients undergoing PCI. Thus, we investigated whether PES was superior to SES in preventing restenosis in HD patients with coronary artery disease.

2. Materials and methods

2.1. Study population

Between May 2007 and February 2008, we conducted a prospective, randomized, open-label study in 100 consecutive patients on maintenance HD, who underwent PCI for native coronary lesions with stable angina pectoris at Nagoya Kyoritsu Hospital. They were randomized into two groups: those who received an implantation of SES (Cypher™, Cordis Corp, Johnson & Johnson, Miami Lakes, FL, USA) and those who received an implantation of PES (Taxus Express™, Boston Scientific, Natick, MA, USA). Patients with a multi-vessel disease and/or a left main trunk lesion were excluded

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from the study. Thus, all enrolled patients had a single-vessel disease. In advance, we excluded patients who had a contraindication for the use of aspirin and/or thienopyridine, low left ventricular function (ejection fraction <45%), and/or were >85 years of age. For all patients, dual anti-platelet therapy with aspirin and thienopyridine was given orally for at least a month before PCI. Dual anti-platelet therapy was continued for at least 1 year. The physicians determined the method and device for PCI except for stent types. Basically, implantation of stent was recommended under intravascular ultrasound technique after rotational atherectomy and/or plain old balloon angioplasty.

The study protocol was approved by the institutional review board, and the physicians obtained written informed consent from each patient prior to PCI.

2.2. End points

The angiographic follow-up was scheduled for 8 months after PCI. The primary endpoint of the study was to compare the follow-up angiographic outcomes between the SES and PES groups. Clinical follow-up data up to 1 year after the PCI procedure, including death, nonfatal myocardial infarction, and target lesion revascularization (TLR) due to stent restenosis-induced ischemia, were also obtained.

Patients received intracoronary administration of isosorbide dinitrate before the initial, final, and follow-up angiographies, to achieve maximal vasodilatation. A contour detection minimum cost algorithm (QCA-CMS Version 3.0, MEDIS, Leiden, The Netherlands) was used for quantitative coronary angiography analysis. The reference vessel diameter and minimal lumen diameter were determined from the single worst view. Lesion length was determined before the PCI from quantitative coronary angiography measurements. Acute lumen gain was defined as the difference in the minimal lumen diameter before and after PCI. Late lumen loss was defined as the difference between minimal lumen diameter immediately after PCI and at the follow-up angiography. Types of lesions were characterized according to the American Heart Association/American College of Cardiology classification [17]. All angiographical analyses were performed by an experienced technician who was blinded to the assignment of the groups.

2.3. Statistical analysis

All statistical analyses were performed using SPSS (SPSS, Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation values. Univariate analysis of differences between the SES and PES groups was performed with the two-tailed unpaired *t*-test for continuous outcome variables and by chi-square or Fisher exact tests for discrete outcome variables. The event-free survival rates for each clinical event between the SES and PES groups were examined with the Kaplan-Meier method, and the differences in survival rates between the two groups were compared using the log-rank test. Differences were considered significant at $p < 0.05$.

3. Results

3.1. Baseline characteristics

For all patients, PCI was performed without a major complication (death, Q-wave myocardial infarction, or coronary artery bypass graft). The baseline characteristics of the SES and PES groups were well matched (Table 1). Twenty-four (48.0%) patients in the SES group and 19 (38.0%) patients in the PES group were treated with implantation of multiple stents because of a long lesion or other reason.

Complete follow-up coronary angiography was obtained from 48 patients (96.0%) with 71 stents (95.4%) in the SES group and 47 patients (94.0%) with 65 stents (94.2%) in the PES group. One patient in the SES group and one in the PES group died before follow-up angiography, and one patient in the SES group and two in the PES group experienced acute myocardial infarction before follow-up angiography.

3.2. Primary endpoint

Table 2 shows angiographic results in patients who obtained follow-up angiography. Quantitative coronary angiography data before the PCI procedure were similar for both groups. No significant difference was detected in the follow-up quantitative coronary angiography data (Table 2 and Fig. 1). Restenosis, defined as a diameter stenosis ≥50% at follow-up angiography, was also comparable between the two groups (19.7% vs. 20.0%, p = 0.97, Table 3 and Fig. 2). When including patients treated with both SES and PES, the restenosis rate after PCI was 19.8%.

Table 1
Baseline characteristics.

	SES (n = 50)	PES (n = 50)	p value
Male (%)	78.0	70.0	0.49
Age (years)	65 ± 9	64 ± 9	0.44
Diabetes (%)	48.0	54.0	0.54
Insulin treatment (%)	22.0	28.0	0.49
Hypertension (%)	64.0	66.0	0.93
Dyslipidemia (%)	12.0	6.0	0.29
Multiple stent implantation (%)	48.0	38.0	0.31
No. of implanted stent	74	69	
Lesion location (%)			0.70
Right coronary artery	28.4	34.8	
Left anterior descending artery	51.4	47.8	
Left circumflex artery	20.2	17.4	
AHA/ACC type (%)			0.47
A	4.1	8.7	
B1	8.1	4.4	
B2	64.9	59.4	
C	22.9	27.5	
Calcified lesion (%)	59.5	55.1	0.60
Diffuse lesion (%)	39.2	37.7	0.85
Bifurcation (%)	18.9	15.9	0.64
Balloon to artery ratio	1.11 ± 0.18	1.14 ± 0.22	0.36
Rotational atherectomy use (%)	9.5	8.7	0.87
Max inflation pressure (atm)	15.2 ± 3.1	13.6 ± 2.9	0.0020
Stent diameter (mm)	3.0 ± 0.4	3.0 ± 0.4	0.80
Stent length (mm)	19.3 ± 5.3	17.9 ± 6.1	0.18

SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; AHA: American Heart Association; ACC: American College of Cardiology.

We performed sub-analysis with reference to prevalence of diabetes (Table 3). In patients with diabetes, the angiographical restenosis rate at follow-up was 21.2% in the SES group and 21.1% in the PES group (p = 0.99). The restenosis rate was also similar in patients without diabetes (18.4% vs. 18.5%, p = 0.99).

3.3. Clinical follow-up data

We obtained 1-year clinical follow-up data for all patients. Table 4 summarizes the incidences of adverse events during the 1-year follow-up period. There were no significant differences in the rates of all-cause death, nonfatal myocardial infarction, and TLR due to stent restenosis-induced ischemia between the SES and PES groups (2.0% vs. 4.0%, p = 0.56, 2.0% vs. 4.0%, p = 0.56, and 16.0% vs. 12.0%, p = 0.57, respectively). During the 1-year follow-up period, there were no events related to in-stent thrombosis in either group. In all patients who experienced acute myocardial infarction, the stent-treated vessel was not the infarct-related artery.

Table 2
Results of quantitative coronary angiography.

	SES (n = 71)	PES (n = 65)	p value
Reference (mm)	2.71 ± 0.43	2.69 ± 0.58	0.79
Lesion length (mm)	19.17 ± 5.85	17.81 ± 5.97	0.12
Minimal lumen diameter (mm)			
Pre	1.00 ± 0.38	0.98 ± 0.37	0.77
Post	2.62 ± 0.43	2.65 ± 0.48	0.66
Follow up	2.13 ± 0.75	2.13 ± 0.77	0.99
Late loss	0.49 ± 0.70	0.48 ± 0.91	0.94
% diameter stenosis (%)			
Pre	62.7 ± 14.6	63.3 ± 12.3	0.82
Post	10.2 ± 10.4	11.3 ± 8.6	0.53
Follow up	23.6 ± 22.4	22.5 ± 25.3	0.79

SES: sirolimus-eluting stent ; PES: paclitaxel-eluting stent.

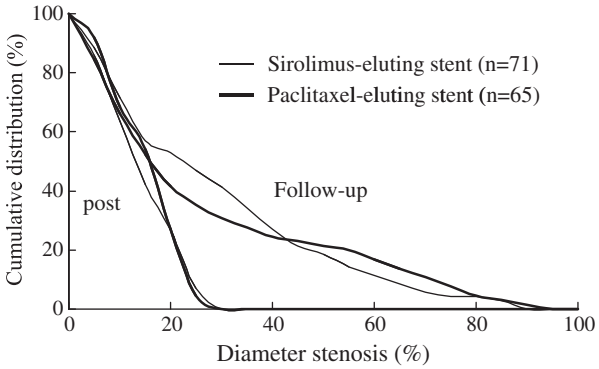

Fig. 1. Cumulative distribution curves of diameter stenosis from angiography immediately after procedure and at 8-month follow-up. Diameter stenosis at follow-up was similar among the SES and BMS groups (p = 0.79).

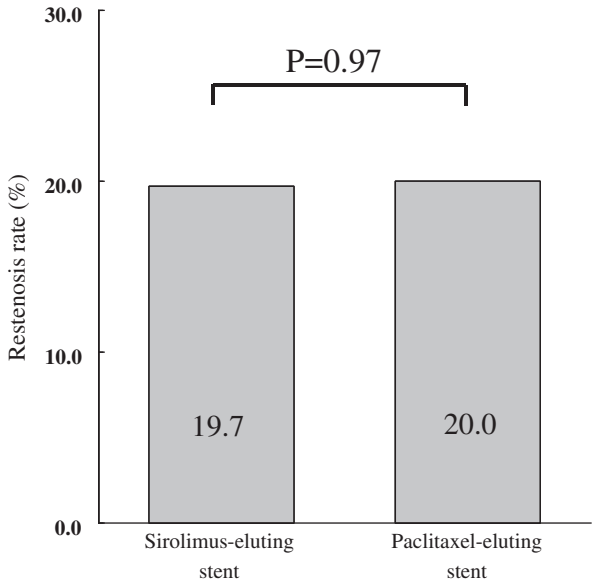

Fig. 2. Restenosis rate at 8 months after stent implantation: Rate of restenosis, defined as a diameter stenosis ≥50% at follow-up angiography, was 19.7% after implantation of sirolimus-eluting stent and 20.0% after implantation of paclitaxel-eluting stent (p = 0.97).

4. Discussion

In the present study, we found that angiographic data at 8-month follow-up after PCI were similar between HD patients treated with SES and those treated with PES. In addition, the restenosis rate after PCI was relatively high in patients on maintenance HD even if treated with DES, including SES and PES. From this point of view, PCI is still considered to be a challenge for patients on HD.

Even in patients on HD, PCI with stent implantation has an ability to reach a high initial success rate by producing consistently large target-lesion lumens and reducing elastic recoil. However, neointimal growth after stenting is pronounced in such a population, resulting in a higher restenosis rate at the follow-up phase. Systemic atherosclerosis and higher inflammatory status also increase the risk of restenosis in patients on HD [18,19]. It is well known that patients on HD have more complex lesions, such as increased media thickness, massive calcification of coronary lesions, particularly intima and media calcification, and/or multi-vessel disease, compared to patients without HD [3,20]. Patients on HD also have abnormalities in platelet function and activate plasma coagulation factors [21,22]. These factors may be related to restenosis after PCI. In the bare metal stent era, the restenosis rate of the follow-up period was higher in patients on HD than in non-HD patients [5,7]. Studies have reported that markedly lower TLR after SES implantation in patients with chronic renal insufficiency, compared to BMS implantation [23,24]. Some studies investigated whether this extends to those receiving HD, that is, high-risk individuals. However, they have shown that patients on maintenance HD are related to high restenosis rates even after SES implantation [14,15]. In such situations, PES had been the device expected to reduce restenosis in patients on HD. Because data on the effects of preventing restenosis in HD patients treated with PES have been lacking, we tried to show the efficacy of PES. Unfortunately we found that PES was not superior to SES in preventing restenosis at 8-month follow-up in patients on HD. Recently, Otsuka and colleagues have shown that PES might be superior to SES in preventing restenosis in HD patients in their retrospective study. [25]. Coronary risk factors and lesion characteristics were comparable between their and our studies. In addition, the late loss in the PES group was similar between the two studies (0.55 ± 0.66 mm vs. 0.48 ± 0.91 mm). However, that in the SES group was different between the two studies (0.82 ± 0.93 mm vs. 0.49 ± 0.70 mm). The reasons to explain remain unclear. However, there were a few possible speculations. First, our study was a prospective. Second, study period was different. Particularly, duration of SES implantation was quite different. Third, there might be differences in medical treatments such as duration of dual anti-platelet therapy between the two studies.

It has been reported that paclitaxcel has a unique mechanism to inhibit smooth muscle cell proliferation and migration even in hyperglycemia and insulin resistance conditions [16]. In a clinical setting, PES has a similar low risk of restenosis for diabetic and non-diabetic patients with a limited number of maintenance HD, although major adverse cardiac events were significantly increased in diabetic patients compared to non-diabetic patients [26]. On the other hand, reports suggest that diabetes is a risk factor for restenosis in patients treated with SES [27,28]. However, restenosis rates were similar between PES and SES in diabetic patients on HD in a sub-analysis of the present study. Thus, risk factors might be different between diabetic patients with and without HD. Further investigations with a larger sample size are needed.

This study had several limitations. First, it enrolled only 100 patients and was performed at a single center. Thus, the problem of low statistical power might exist. Our sample size may be too small to make definite conclusion. Second, angiographical follow-up was performed at 8 months. We had no data for much longer duration. Third, although we could evaluate clinical follow-up data for all patients, we could not collect angiographical follow-up for all patients. Fourth, we used the Taxus Express ™ system in the present study. A recent study has shown that the Taxus Liberté ™ system is superior to the Taxus Express ™ system in reduction of restenosis [29]. In addition, maximal inflation pressure was significantly higher in the SES

Table 3
Restenosis rate at 8 months after stent implantation.

	SES (n = 71)	PES (n = 65)	p value
Overall	14 (19.7%)	13 (20.0)	0.97
Diabetes	7/33 (21.2)	8/38 (21.1)	0.99
Non-diabetes	7/38 (18.4)	5/27 (18.5)	0.99

SES: sirolimus-eluting stent ; PES: paclitaxel-eluting stent.

Table 4
One-year clinical outcome after stent implantation.

	SES (n = 50)	PES (n = 50)	p value
All-cause death	1 (2.0)	2 (4.0)	0.56
Non-fatal myocardial infarction	1 (2.0)	2 (4.0)	0.56
Target lesion revascularization	8 (16.0)	6 (12.0)	0.57

SES: sirolimus-eluting stent ; PES: paclitaxel-eluting stent.

group than in the PES group. The reason might be because recommended nominal pressure was 12 atmospheres for Cypher™ and 9 atmospheres for Taxus Express™. However, this may affect the results. Final, we intended to evaluate other DESs, such as zotarolimus eluting stent, everolimus-eluting stent, tacrolimus-eluting stent and so on, in a future study.

In conclusion, we showed that the restenosis rates were similarly high between implantation of PES and SES in patients on HD. Restenosis after PCI in such a population has remained a major clinical problem.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

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