Comparison With Conventional Therapies of Repeated Sirolimus-Eluting Stent Implantation for the Treatment of Drug-Eluting Coronary Stent Restenosis

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This study compared the safety and efficacy of repeat percutaneous coronary intervention (PCI) using sirolimus-eluting stents (SESs) with conventional therapies for restenosis after drug-eluting stent placement. Fifty-five consecutive patients with 58 restenotic lesions (31 treated with SESs and 27 treated with paclitaxel-eluting stents) underwent PCI using SESs (33 lesions) or conventional therapies comprising cutting balloon angioplasty alone (11 lesions) or intracoronary brachytherapy (14 lesions). Baseline characteristics were similar for the 2 groups, except for greater edge involvement (75.8% vs 36.0%, p = 0.002) and less stent expansion (0.74 ± 0.17 vs 0.95 ± 0.21, p = 0.006) in the SES group than in the conventional group. The SES group achieved a greater postprocedural luminal gain than the conventional group (1.98 ± 0.50 vs 1.22 ± 0.48 mm, p <0.001). Follow-up angiography showed that late luminal loss (0.27 ± 0.56 vs 0.76 ± 0.84 mm, p = 0.021) and recurrent angiographic restenosis rate (3.6% vs 35.0%, p = 0.006) were lower in the SES group than in the conventional group. The repeated target lesion revascularization-free survival rates at 1 year were 96.7 ± 3.2% for the SES group and 91.7 ± 5.6% for the conventional group (p = 0.399). In conclusion, use of SESs was associated with a lower recurrent restenosis rate compared with conventional therapies. **(Am J Cardiol 2006;98:1451–1454)**

The present study compared the clinical, angiographic, and intravascular ultrasound (IVUS) outcomes after implantation of sirolimus-eluting stents (SESs; Cypher, Cordis Corporation, Miami Lakes, Florida) with those of conventional percutaneous coronary intervention (PCI) therapies, such as cutting balloon angioplasty and intracoronary brachytherapy, in the treatment of restenosis after initial stenting with SESs or paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts).

Methods

This study involved 55 consecutive patients who underwent repeat PCI for the treatment of 58 restenotic lesions after initial SES (27 lesions) or paclitaxel-eluting stent (31 lesions) implantation between March 2003 and February 2005. During the study, follow-up angiography identified restenosis in the analysis segment of 134 of 1,513 drug-eluting stent (DES)-implanted lesions (8.9%). The study was approved by the institutional review board, and informed written consent was obtained from all patients in accordance with the Declaration of Helsinki.

Cutting balloon angioplasty alone, intracoronary brachytherapy, and repeat SES implantation were used for the treatment of DES restenosis at the operator's discretion. Because large randomized studies have shown that late luminal loss using SESs has been consistently lower than when using a paclitaxel-eluting stent, SES was used as the default DES in the treatment of DES restenosis.[1–6] On the basis of visual angiographic estimations, focal (≤10 mm) restenotic lesions were treated with cutting balloon angioplasty alone (11 lesions) or repeat SES implantation (18 lesions). Repeat SES implantation for focal lesions was performed in patients with suboptimal results, serious dissection after cutting balloon angioplasty, or significant edge involvement. Diffuse (>10 mm) restenotic lesions were treated with intracoronary brachytherapy (14 lesions) or repeat SES implantation (15 lesions). Three patients who had 2 lesions of DES restenosis in each patient received SESs (2 patients) and brachytherapy (1 patient).

Intracoronary brachytherapy was used only in the early study period up to October 2004. As a pretreatment, cutting balloon angioplasty was also performed before SES implantation (n = 7) or all brachytherapies. The method of intracoronary brachytherapy has been previously described.[7,8] The delivery system was a rhenium-188 MAG_3-filled angioplasty balloon. The irradiation time was calculated to deliver 20 Gy at 1.0 mm deep into the vessel wall from the balloon/artery interface. Before and after the procedure, all

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Table 1
Clinical characteristics

Variable	SES Group (n = 31)	Conventional Group (n = 24)	p Value
Age (yrs)	56.3 ± 11.3	60.7 ± 9.6	0.135
Men	20 (65%)	16 (67%)	0.868
Diabetes mellitus	8 (26%)	7 (29%)	0.781
Total cholesterol >200 mg/dl	2 (7%)	5 (21%)	0.220
Smoker	6 (19%)	8 (33%)	0.238
Hypertension	18 (58%)	14 (58%)	0.984
Previous coronary bypass surgery	1 (3%)	0	1.000
Left ventricular ejection fraction (%)	58 ± 8	59 ± 8	0.818
Acute coronary syndrome	7 (23%)	8 (33%)	0.375

Table 2
Lesion characteristics at the index procedure

Variable	SES Group (n = 33)	Conventional Group (n = 25)	p Value
Chronic total occlusion (>3 mo)	1 (3%)	1 (4%)	1.000
In-stent restenosis of bare metal stent	4 (12%)	2 (8%)	0.690
Ostial lesion	5 (15%)	1 (4%)	0.222
Bifurcation stenting in parent and side branches	2 (6%)	4 (16%)	0.387
Primary angioplasty of infarct-related artery	2 (6%)	0	0.501
Use of SES	14 (42%)	13 (52%)	0.596
Coronary artery			0.801
Left main	2 (6%)	1 (4%)	
Left anterior descending	23 (70%)	15 (60%)	
Left circumflex	1 (3%)	1 (4%)	
Right	7 (21%)	8 (32%)	
Total stent length (mm)	32.2 ± 15.6	40.2 ± 20.4	0.107

Table 3
Angiographic characteristics

Variable	SES Group (n = 33)	Conventional Group (n = 25)	p Value
Mehran classification			
Type I	18 (55%)	9 (36%)	0.161
Type II	5 (15%)	8 (32%)	0.203
Type III	7 (21%)	7 (28%)	0.550
Type IV	3 (9%)	1 (4%)	0.627
Edge involvement	25 (76%)	9 (36%)	0.002
Lesion length (mm)	14.0 ± 8.2	15.3 ± 10.8	0.606
Reference diameter (mm)	2.92 ± 0.45	2.81 ± 0.34	0.300
Minimal luminal diameter (mm)			
Before procedure	0.95 ± 0.43	0.98 ± 0.42	0.800
After procedure	2.93 ± 0.45	2.21 ± 0.31	<0.001
At follow-up	2.70 ± 0.65	1.51 ± 0.76	<0.001
Diameter stenosis (%)			
Before procedure	66.8 ± 14.9	64.0 ± 17.7	0.526
After procedure	0.1 ± 12.4	20.9 ± 9.0	<0.001
At follow-up	9.5 ± 17.9	46.9 ± 26.4	<0.001
Acute gain (mm)	1.98 ± 0.50	1.22 ± 0.48	<0.001
Late luminal loss (mm)	0.27 ± 0.56	0.76 ± 0.84	0.021
Recurrent angiographic restenosis	1/28 (4%)	7/20 (35%)	0.006
Type I	0	4 (20%)	
Types II–IV	1 (4%)	3 (15%)	

patients received aspirin (200 mg/day). Patients treated with brachytherapy and SES received clopidogrel (a loading dose of 300 mg 24 hours before the procedure and then 75 mg/day for 6 months) and cilostazol (a loading dose of 200 mg just after the procedure and then 100 mg 2 times daily for 1 month).[9] Intravenous glycoprotein IIb/IIIa inhibitors were used in 1 patient with an SES implant at the operator's discretion.

Coronary angiograms were obtained before the procedure, after the procedure, and at follow-up and were analyzed by 2 independent angiographers. Quantitative measurements included reference diameter, lesion length, and minimal luminal diameter before and after the procedure and at follow-up. Late luminal loss was defined as the difference in minimal luminal diameter between postprocedure and follow-up measurements. Quantitative angiographic measurements were performed in the analysis segment, including the treated segment and the margins 5 mm proximal and distal to the treated segment. Angiographic restenosis was defined as a >50% diameter stenosis and classified as previously described.[10]

IVUS imaging was performed after intracoronary administration of 0.2 mg of nitroglycerin using a motorized transducer pullback (0.5 mm/s) and a commercial scanner (SCIMED, Freemont, California) consisting of a 30-MHz transducer within a 3.2Fr imaging sheath. Serial quantitative IVUS measurements before and after the procedure and at follow-up were successfully performed according to the American College of Cardiology clinical expert consensus document.[11] Measurements included external elastic membrane, stent, lumen, plaque and media (external elastic membrane minus lumen), and intimal hyperplasia (stent minus lumen) areas. The lesion site selected for analysis was the image slice with the smallest lumen area. The proximal and distal reference segments selected for analysis were the most normal-looking sites within 10 mm proximal or distal to the lesion. Stent expansion at the target lesion was minimal stent area/reference lumen area. Late stent malapposition was defined as separation of ≥1 stent strut from the intimal surface of the arterial wall that was not overlapping a side branch, was not present immediately after stent implantation, and had evidence of blood flow (speckling) behind the strut.[12]

All patients were evaluated clinically by office visits or telephone interviews at regular intervals during the follow-up period (21.4 ± 4.0 months). Repeat coronary angiography was routinely recommended 6 months after the procedure or sooner if indicated by clinical symptoms or evidence of myocardial ischemia. Angiographic success was defined as a final diameter stenosis <30% with Thrombolysis In Myocardial Infarction grade 3 flow in the target lesion after the procedure. Q-wave myocardial infarction was defined by the postprocedural presence of new Q waves >0.04 second in 2 contiguous leads. Non–Q-wave myocardial infarction was defined as a creatine kinase-MB level >3 times the normal upper limit. Repeat target lesion revascularization was performed in patients who had restenoses at target lesions and evidence of recurrent myocardial ischemia as assessed by symptoms or myocardial stress tests.

Table 4
Intravascular ultrasound characteristics

Variable	SES Group	Conventional Group	p Value
No. of lesions before procedure	17	16	
EEM area (mm^2)	14.64 ± 4.65	13.76 ± 3.70	0.554
Stent area (mm^2)	6.67 ± 1.88	6.81 ± 2.26	0.839
Lumen area (mm^2)	1.92 ± 1.15	2.04 ± 0.43	0.299
P&M area (mm^2)	12.73 ± 4.66	11.73 ± 3.60	0.499
Stent malapposition	3 (18%)	1 (6%)	0.601
Stent expansion	0.74 ± 0.17	0.95 ± 0.21	0.006
Radial stent symmetry	0.89 ± 0.06	0.89 ± 0.04	0.962
No. of lesions after procedure	17	16	
EEM area (mm^2)	16.34 ± 4.69	14.92 ± 3.64	0.351
Stent area (mm^2)	7.82 ± 1.88	7.79 ± 2.42	0.967
Lumen area (mm^2)	7.82 ± 1.88	5.64 ± 1.49	0.057
P&M area (mm^2)	8.97 ± 3.08	8.98 ± 2.78	0.992
No. of lesions at follow-up	14	8	
EEM area (mm^2)	17.58 ± 4.99	16.67 ± 4.74	0.680
Stent area (mm^2)	7.94 ± 2.08	8.60 ± 2.52	0.514
Lumen area (mm^2)	6.90 ± 2.57	5.40 ± 1.94	0.168
P&M area (mm^2)	10.67 ± 3.55	11.27 ± 3.43	0.706
Intimal hyperplasia area (mm^2)	1.03 ± 1.28	3.20 ± 1.98	0.005
New stent malapposition	0	0	1.000

EEM = external elastic membrane; P&M = plaque and media.

Continuous variables are presented as mean ± SD. Categorical variables are presented as counts or proportions (percentages). Differences between variables for patients treated with SES (SES group) and conventional therapies, including cutting balloon angioplasty or brachytherapy (conventional group), were compared using chi-square or Fisher's exact tests for categorical variables and Student's *t* test for continuous variables as appropriate. Repeat target lesion revascularization-free survival distributions were estimated according to the Kaplan-Meier method and were compared using log-rank tests. A p value <0.05 was considered to indicate a significant difference.

Results

The SES and conventional groups had similar clinical and lesion characteristics at the index procedure and before the repeat procedure, except for more edge involvement and less preprocedural stent expansion in the SES group (Tables 1 to 4).

Total treated segments of SES and brachytherapy were 22.2 ± 10.3 and 29.5 ± 17.4 mm, respectively. Additional stent implantation with SESs after brachytherapy was performed in 1 lesion (7.1%) for treatment of serious dissection. No deaths, stent thromboses, Q-wave myocardial infarctions, or target lesion revascularizations occurred during hospitalization. Angiographic success rates were 97% (32 lesions) in the SES group and 92% (23 lesions) in the conventional group (p = 0.572). The 3 lesions without angiographic success had <40% diameter stenosis. Periprocedural creatine kinase-MB increase >3 times normal occurred in 1 patient in the SES group (3.2%) and in no patient in the conventional group (p = 1.0). After the procedure, postprocedural minimal luminal diameter was greater in the SES group than in the conventional group due to greater acute luminal gain (Table 3). In the conventional group, the 2 groups treated with cutting balloon angioplasty alone and with brachytherapy had similar quantitative angiographic measurements at baseline and after the procedure. The brachytherapy group had a tendency of longer lesions than the cutting balloon alone group (18.1 ± 13.2 vs 11.9 ± 5.8 mm, p = 0.163), which did not reach statistical significance.

Angiographic follow-up was obtained for 28 SES-treated lesions (84.9%) and 20 conventionally treated lesions (80.0%, p = 0.731), with the latter comprising 9 cutting balloon-treated lesions (81.8%) and 11 brachytherapy-treated lesions (78.6%). Late luminal loss and recurrent angiographic restenosis rates were lower in the SES group than in the conventional group (Table 3). In the conventional group, late luminal loss was similar between the cutting balloon alone group (0.61 ± 0.68 mm) and the brachytherapy group (0.87 ± 0.96 mm, p = 0.526). The overall recurrent restenosis rate was 16.7% (8 lesions). Recurrent restenosis occurred in 2 lesions (8.7%) of 23 SES implantations and 6 lesions (24.0%) of 25 paclitaxel-eluting stent implantations at the index procedure (p = 0.249). One recurrent restenosis in the SES group occurred in a lesion treated with a paclitaxel-eluting stent. Of the 7 recurrent restenoses in the conventional group, 3 restenoses (33.3%) occurred in cutting balloon-treated lesions and 4 restenoses (36.4%) in brachytherapy-treated lesions (p = 1.0). IVUS analysis showed that the area of intimal hyperplasia was less in the SES than in the conventional group (Table 4). Clinical information was obtained for all patients. Follow-up durations were 20.7 ± 4.4 months for the SES group and 22.4 ± 3.2 months for the conventional group (p = 0.108). There were no incidents of death, stent thrombosis, or myocardial infarction during follow-up. Repeat target lesion revascularization was performed in 1 patient (3.2%) in the SES group and in 2 patients (8.3%) in the conventional group (p = 0.575). Repeat target lesion revascularization-free survival rates at 1 year were 96.7 ± 3.2% for the SES group and 91.7 ± 5.6% for the conventional group (p = 0.399).

Discussion

The major finding of the present study was that repeat PCI with currently available devices for the treatment of DES restenosis was safe. There was no incidence of death or stent thrombosis. In addition, this approach was feasible, with an acceptable incidence of recurrent angiographic restenosis and repeat target lesion revascularization. The study also found that SES implantation was more effective in decreasing the recurrent restenosis rate compared with conventional therapies.

DESs greatly decreased the incidence of restenosis and the need for target lesion revascularization.[1–6] Despite these improvements, 5% to 10% of patients are reported to undergo target lesion revascularization due to restenosis after DES implantation.[1–6,13–16] Due to the relatively low incidence of this condition, few studies have evaluated the long-term effectiveness of repeat PCI for DES restenosis.[17–20] In the present study, repeat PCI using SESs, cutting balloons, or brachytherapy was not associated with serious acute or long-term complications, such as stent thrombosis, angiographic aneurysmal change, or malapposition, which are caused by repeated vascular injury. This finding is in line with previous

studies showing that repeat PCI with DESs, bare metal stents, brachytherapy, or balloon angioplasty were safe and did not increase the rate of vascular complications.[17–20]

Long-term efficacy of available treatment strategies for DES restenosis has not been clearly elucidated. A pilot study evaluating clinical outcomes after repeat PCI in 27 SES restenoses using exclusively SESs (12 lesions) or paclitaxel-eluting stents (11 lesions) reported an overall recurrent restenosis rate of 42.9% (29.4% after repeat DES implantation).[17] Compared with the aforementioned study,[17] the lower recurrent restenosis rate in the present study may be related to greater involvement of simple type 1 and 2 restenoses (69% vs 14%) and large vessels (2.87 vs 2.49 mm). Nevertheless, the combined findings of the present and other recent studies[18–20] indicate that repeat SES implantation and conventional therapies are feasible in terms of acceptable recurrent restenosis and repeat revascularization rates.

There are no published data comparing the efficacy of repeat DES implantation with conventional therapies for DES restenosis. In the present study, SES was associated with a lower late luminal loss and recurrent restenosis rate than conventional therapies. The late luminal loss of 0.27 mm in the SES group was comparable to that in previous large studies using SESs for treatment of de novo lesions and in-stent restenosis after bare metal stent placement.[1,2,4–6] Lower intimal growth identified by IVUS examination in the present study supported the greater efficacy of repeated SES implantation. By multivariate analysis, repeat SES implantation was the only protective factor of angiographic restenosis, which was independent of the original DES, restenosis pattern, and quantitative angiographic variables.

The limitations of the present study should be addressed. Because the present study was retrospective, nonrandomized, and consisted of a relatively small population, significant biases might be introduced. More inclusion of edge involvement, inadequate stent expansion, and focal restenosis in the SES group might influence the outcomes. In addition, serial IVUS evaluation was performed in limited patients. Nevertheless, the findings of this study suggest that repeat DES implantation may be a feasible strategy for DES restenosis and highlight the need for another large randomized study.

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