Coronary Heart Disease

Single-Center Experience with Overlapping Paclitaxel-Eluting Stent for Diffuse Coronary Lesions

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Background: Treatment of long, de novo coronary lesions with single drug-eluting stent is associated with very low rate of target lesion revascularization and other major adverse cardiac events. However, safety and efficacy of using multiple overlapping drug-eluting stents in patients with diffuse coronary artery lesions remain unclear. We reported the clinical and angiographic outcomes of overlapping paclitaxel-eluting stents at 9 months post-implantation in our institution.

Methods: From April 2004 to November 2007, we evaluated fifty-one consecutive patients who required overlapping paclitaxel-eluting stents for diffuse, de novo coronary lesions (> 20 mm). A retrospective chart review was conducted at the end of 9 months to identify any major adverse cardiac events during the 9-month period after the procedure.

Result: The study population consisted of fifty-one patients and included 60.8% of the cases with diabetes mellitus (60.8%) and 32 cases with triple-vessel disease (62.7%). The number of stents implanted per patient was 2.1 ± 0.3, and the mean total stent length was 56.5 ± 12.1 mm. Procedural success was achieved in 100% of the cases. No patients had in-hospital Q-wave myocardial infarction, intraprocedural stent thrombosis or death. Forty-five patients (88%) were available for clinical follow-up, and 28 patients (54.9%) had an angiographic follow-up during the 9-month period. One patient died of non-cardiac cause, three patients underwent target lesion revascularization (6.7%) and four patients (8.9%) underwent target vessel revascularization after 9-month clinical follow up. The rate of major adverse cardiac events at 9 months was 8.9%.

Conclusion: Overlapping paclitaxel-eluting stents are relatively safe and associated with good midterm clinical outcomes in patients with diffuse coronary lesions.

Key Words: Angioplasty • Coronary heart disease • Drug eluting stent

INTRODUCTION

Several studies have reported that drug eluting stents (DESs) are more effective than bare metal stents in reducing repeat revascularization.[1,2] Treatment of long de novo coronary lesions with paclitaxel-eluting stents (PESs) in TAXUS VI is associated with lower risks of target lesion revascularization compared to bare-metal stents.[3] However, many patients have severe long diffuse coronary lesions, and currently there is no proven treatment available for them. Severe diffuse coronary artery lesions may present to intervention cardiologists a significant therapeutic challenge. Multiple overlapping stents are often required to treat severe diffuse lesions, but treatment of diffuse coronary artery stenosis with multiple bare-metal stents is associated with very high restenosis rates and poorer clinical outcome.[4,5] Recently,

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there have been findings suggesting that overlapping sirolimus-eluting stents (SESs) may be safe and effective for the treatment of severe diffuse coronary lesions and PESs may have a higher rate of in-stent restenosis compared with SESs.[6,7] At the present time there is limited information about the safety and efficacy of overlapping PESs in treating patients with severe diffuse coronary lesions. In this retrospective study, we evaluated the safety and efficacy of using multiple overlapping PESs by examining a consecutive series of patients who had undergone overlapping PESs for diffuse coronary lesions in our hospital.

METHODS

Study patients

Patients with diffuse de novo coronary disease (> 20 mm) undergoing implantation of overlapping paclitaxel-eluting stents (PESs) at Hualien Budhist Tzu Chi General Hospital were studied. The patient population consisted of a consecutive series of 51 patients (52 lesions) who had been treated with overlapping PESs (Taxus, Boston Scientific, Natick, MA) from April 2004 to November 2007. All these patients were treated by an experienced operator. Angiographic and clinical follow-up were left to the discretion of the physician, who decided based on clinical grounds. Angiograms were arranged either because of typical symptoms or ischemia shown by nuclear scan and treadmill test. For every coronary angiography, quantitative coronary analysis (QCA) was performed. A retrospective chart review was conducted at the end of 9 months to identify rates of target lesion revascularization (TLR) and target vessel revascularization (TVR). Major adverse cardiac events (MACEs), defined as death, Q-wave myocardial infarction or symptom-driven revascularization, were also calculated during the 9-month follow-up period.

Angiographic analysis

All the angiographic analyses were performed with an automated edge-detection algorithm with the contrast-filled catheter as the calibration standard. An experienced angiographer performed QCA by using an online QCA software (Centricity Cardiology CA1000, GE Healthcare) to measure the reference diameter, minimal lumen diameter and percentage of diameter stenosis before and after the stenting procedure, and at follow-up.

Statistical analysis

Data are expressed as means ± SDs for continuous variables and as frequencies for categorical variables. The Kaplan-Meier method was used to analyze the occurrence of clinical events during follow-up.

RESULTS

Baseline clinical and angiographic characteristics

The baseline clinical and angiographic characteristics of the patients are listed in Tables 1 and 2. Mean patient age was 62.9 ± 10.1 years (range 39 to 85). 60.8% of the study population had diabetes, and 62.7% had tri-

Table 1. Baseline clinical characteristics

Characteristic	n = 51
No. of coronary lesions	52
Age (yrs)	62.92 ± 10.1
Men	80.4% (41/51)
Current smoker	19.6% (10/51)
Former smoker	27.5% (14/51)
Diabetes mellitus	60.8% (31/51)
Diabetes mellitus insulin	11.8% (6/51)
Diabete mellitus oral hypoglycemic agent	49.0% (25/51)
Dyslipidemia	66.7% (34/51)
Hypertension	60.8% (31/51)
Clinical presentation	
Stable angina pectoris	60.8% (31/51)
Unstable angina pectoris	19.6% (10/51)
Non ST elevation myocardial infarction	17.6% (9/51)
ST elevation myocardial infarction	2.0% (1/51)
Previous myocardial infarction	27.5% (14/51)
Previous percutaneous coronary intervention	27.5% (14/51)
Previous congestive heart failure	27.5% (14/51)
Previous CABG	11.8% (6/51)
Chronic renal failure (Non HD)	15.7% (8/51)
Chronic renal failure (HD)	3.9% (2/51)
Triple-vessel coronary disease	61.5% (32/52)
Two-vessel coronary disease	25.0% (13/52)
Single-vessel coronary disease	13.4% (7/52)

Values are percentages or mean ± SD.
* Total cholesterol > 200 mg/dL, HDL < 35, LDL > 200 or receiving lipid-lowering treatment, TG > 150.

ple-vessel coronary artery disease. The mean dual antiplatelet therapy duration was 232 ± 77 days for patients with clinical follow-up. The average number of stent overlaps per lesion was 2.1 ± 0.3 (range 2 to 3) and the total stented length 56.5 ± 12.1 mm (range 28 to 88).

Angiographic and clinical outcomes

Angiographic follow-up data were available for 28 patients (angiographic follow-up rate of 54.9%). Target lesion revascularizations were documented in 3 patients (10.7%). All of the in-stent restenosis patterns were diffuse proliferative. QCA data from follow-up angiogram are shown in Table 2. Forty-five patients (88%) were available for clinical follow-up, and the clinical events are listed in Table 3. Seventeen patients were not indicated for angiogram because of either no symptoms or negative stress tests. During follow-up, there was 1 death (non-cardiac) and there were no Q-wave myocardial infarctions. Three target lesion revascularizations (TLR of 6.7%) and four target vessel failures (TVR of 8.9%) occurred. No definite late stent thrombosis occurred, and the event-free survival rate for death/Q-wave myocardial infarction was 97.8% (Figure 1). The cumulative probability of survival without major adverse cardiac events was 91.1% after 9 months.

Table 2. Angiographic and procedural characteristics

Total overlapping PES Lesions	n = 52
Lesion characteristics	
Target vessel	
Left anterior descending	59.6% (31/52)
Left circumflex artery	25.0% (13/52)
Right coronary artery	13.4% (7/52)
Graft	1.9% (1/52)
Chronic total occlusion	13.5% (7/52)
Procedural characteristics	
Stent length per lesion (mm)	56.46 ± 12.13
Stents per lesion	2.1 ± 0.3
Rotational atherectomy	9.6% (5/52)
Mean inflation pressure	12.58 ± 2.32
Post stent balloon dilatation	42.3% (22/52)
Mean post stent balloon dilatation pressure	16.17 ± 3.24
Quantitative coronary angiography	n = 28
Before intervention	
Lesion length (mm)	45.73 ± 9.95
Reference vessel diameter (mm)	3.15 ± 0.44
Minimal lumen diameter (mm)	0.42 ± 0.28
Diameter stenosis (%)	86.4 ± 9.1
After intervention	
Reference vessel diameter (mm)	3.24 ± 0.37
Minimal lumen diameter (mm)	3.10 ± 0.45
Diameter stenosis (%)	4.39 ± 4.17
Follow-up	n = 28
Minimal lumen diameter (mm)	1.81 ± 0.83
Diameter stenosis (%)	28.2 ± 22
Acute gain (mm)	3.02 ± 0.37
Late loss (mm)	1.49 ± 0.87
Late loss index (mm)	0.50 ± 0.28

PES, paclitaxel-eluting stent.

DISCUSSION

In this report, we describe the angiographic and clinical outcomes of a small consecutive series of patients

Table 3. Major clinical events during hospitalization and at follow-up

Clinical events	In hospital (n = 51)	Follow-up (n = 45)
Death		
Cardiac death	0 (0%)	0 (0%)
No cardiac death	0 (0%)	1 (2.2%)
Q myocardial infarction	0 (0%)	0 (0%)
MACEs	0 (0%)	4 (8.9%)
TLR	0 (0%)	3 (6.7%)
TVR	0 (0%)	4 (8.9%)
Repeat intervention	0 (0%)	3 (6.7%)
CABG	0 (0%)	1 (2.2%)

CABG, coronary artery bypass graft surgery; MACEs, major adverse cardiac events; TLR, target lesion revascularization; TVR, target vessel revascularization.

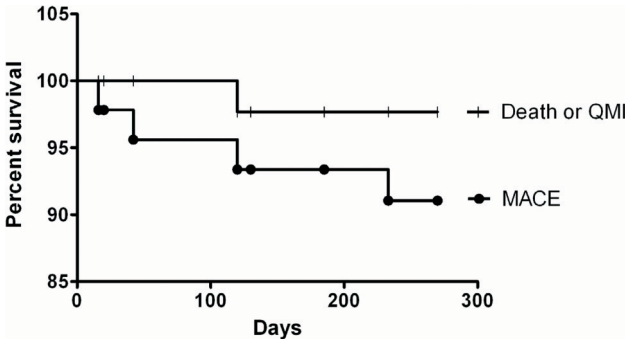

Figure 1. *Kaplan-Meier estimates of cumulative survival free from major adverse cardiac events and free from death or Q-wave myocardial infarction (QMI).*

treated with overlapping paclitaxel-eluting stents. Concerns were raised with overlapped bare-metal stents when previous study showed an increased incidence of major adverse events in patients with a longer stent length.[5,8] There are also concerns that multiple stents placement may be associated with an increased in-stent restenosis and cardiac events because prolonged intracoronary manipulation can result a higher degree of vascular injury.[9] Single DES implantation has demonstrated clinical effectiveness in reducing restenosis for long coronary lesions. However, overlapped DESs for diffuse coronary lesions may potentially interfere with long-term vascular healing and increase risk of MACEs. As paclitaxel is cytotoxic whereas sirolimus is cytostatic, the risk of overlapping PESs may be higher than that using SESs.[6] Currently there is lack of clinical trial data to support this claim. In our study, percutaneous treatment of diffuse coronary disease with multiple overlapping PESs was associated with low rate of MACEs in the midterm follow-up. PESs were apparently safe, with a relatively low incidence of major adverse cardiac events (8.9%) in our study. The mean lesion length in our study was 45.73 mm, with a mean stent length of 56.46 mm, whereas the mean lesion in previous TAXUS VI study was 20.94 mm, with a mean stent length of 33.7 mm. The stent length and lesion length in our study were much longer than observed in TAXUS VI. In contrast, our TVR of 8.9% was lower than the TVR of 9.1% in the TAXUS IV study. Although there are concerns about the increased probability of stent thrombosis in overlapping drug-eluting stents, we did not observe any acute, subacute or late stent thrombotic events.

There are limited published data on the target lesion restenosis rate of multiple overlapping drug-eluting stents. Previously, Lee et al. reported an in-stent restenosis rate of 12.4% for multiple overlapping drug-eluting stents in patients with follow-up coronary angiography.[6] A major finding of Lee's study was that patients treated with PESs had a higher restenosis rate compared to those with SESs (22.2% vs. 11.1%). They concluded that the use of PESs may be a predictor of in-stent restenosis. Another study from Tsagalou et al. also reported a binary restenosis of 19.6% for multiple overlapping DESs in treating diffuse left coronary artery disease.[7] Our study demonstrated a better angiographic outcome, with an in-stent restenosis rate of 10.7% in patients with follow-up coronary angiography. Clinical follow-up at 9 months showed a TLR of 6.7%. Table 4 summarizes the overall outcome data of this study in comparison with previous trials.[6,7,10] Although the number of diabetic patients was greater in our study, the in-stent restenosis rate was lower. The reason may be that the lesion length was shorter and the number of stents implanted were fewer (2.1) than in the studies of Lee et al. and Tsagalou et al. (2.5 and 2.8, respectively).[6,7]

Regarding the angiographic pattern of restenosis, all of the in-stent retenoses in our patients were diffusely proliferative (Class III). On the contrary, previous study examining the angiographic patterns of in-stent restenosis for DESs has shown that focal in-stent restenosis accounts for 51.3% of the in-stent restenosis in PESs.[11] One possible reason is that since IVUS was not routinely used in our study, the incomplete lesion coverage and inappropriate stent expansion may be the mechanism for the diffuse proliferative in-stent restenosis. Another explanation is that our study not only had higher percentage of diabetic patients (60.8%) but also has more patients with chronic renal failure and triple-vessel coro-

Table 4. One year TLR or TVR and MACE rate in this study, comparing data from patients with long-length or multiple bare metal stenting

Trial	# of DES	DES types SES/PES	DM (%)	Multiple vessels (%)	Stent length (mm)	Lesion length (mm)	Follow-up (months)	TLR/TVR	Cumulative MACE free 12 months (%)
Tsagakiy et al.	66	39/27	29	29	84 ± 22	64 ± 18	9 ± 4.6	NA/15%	71.21
Lee et al.	347	264/83	36.3	74	71.9 ± 13.7	55.8 ± 12.9	16.6 ± 6.9	3.8%/NA	95.4
Aoki et al.	122	81/41	19	70	79 (64 - 168)*	NA	12	NA/7.5%	92.0
Our study	51	0/51	60.8	88	56.46 ± 12.1	45.73 ± 9.9	9	6.7%/8.9%	91.1

* Median with range; DM, diabetes mellitus; NA, not available; PES, paclitaxel-eluting stents; SES, sirolimus-eluting stents.

nary disease. Diffuse coronary artery lesions may be precipitated by the underlying systemic disease, which may promote diffuse in-stent restenosis.

STUDY LIMITATIONS

Our study had some potential limitations. First, the risk of non-ST segment elevation myocardial infarction was not evaluated. Because long overlapping stent may compromise coronary flow in the small branches, the incidence of non-ST segment elevation myocardial infarction may increase in patients with multiple overlapping stents.[11] However, the clinical significance of non-ST segment elevation myocardial infarction in this setting has not been elucidated. Another limitation of this study is the lack of a control group treated with bare-metal stents. However, multiple overlapping bare-metal stents have been associated with poor outcome and are not recommended for treatment of diffuse coronary disease unless under special circumstances. Furthermore, the number of patients included in this study was small and follow-up time may not have been long enough. Any possible risk of late thrombosis may require a longer follow-up time to evaluate because of low incidence. Finally the TLR in this study was clinically driven either by symptoms or positive stress test. Only 28 patients were followed by coronary angiogram in our study, and lower angiographic follow-up rate may have lead to a low TLR.

CONCLUSION

Overlapping paclitaxel-eluting stents are relatively safe and associated with good midterm clinical outcomes in patients with diffuse coronary artery lesions.

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