Clinical Experience of Sirolimus-Eluting Stents in Patients with Coronary Artery Disease at Bangkok Heart Institute

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Abstract

Drug eluting stents represent one of the fastest growing fields in interventional cardiology today. From a recent study, the sirolimus eluting stent (SES) (CYPHER, Cordis, Johnson & Johnson) appear to demonstrate a remarkable efficacy and safety in preventing restenosis.

From the present study, the authors reported clinical experience of SES in 40 consecutive patients with coronary artery disease (CAD) between 25th June and 11th October, 2002. The mean age was 59 ± 12.16 years (mean ± SD) and 80 per cent of the patients were male. The majority of the patients had chronic stable angina and most percutaneous coronary interventions were performed by elective procedure (85%). Thirty-five per cent of the patients had single vessel disease and 42.5 per cent of the patients had double vessel disease. The authors successfully implanted 52 (69.3%) SES in 75 target lesions revascularization. Twenty-four (60%) of the patients had more than 1 vessel intervention. Twenty-seven (67.5%) of the patients had complete revascularization by percutaneous coronary intervention (PCI) and only 16 of 27 patients (59.3%) who had complete revascularization with SES. The SES were usually implanted at middle part of the left anterior descending artery (MLAD) (11 lesions), proximal part of the left anterior descending artery (PLAD) (8 lesions), middle part of the right coronary artery (MRCA) (8 lesions) and middle part of the left circumflex artery (MLCX) (6 lesions). The authors had to cover plaque entirely with SES, so SES implantation usually took longer than the bare stent (BS). The authors followed the initial clinical outcome of the patients within 1 month after discharge. Few adverse clinical events were found during 1 month follow-up because SES have a very low rate of restenosis in the short-term so, we have to follow-up the patients over a longer period and will report the clinical outcome in the next study.

Key word : Sirolimus Eluting-Stents, Clinical Experience, Outcome, Coronary Artery Disease

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The main limitation of the percutaneous coronary intervention remains the phenomenon of restenosis, which is an exaggerated healing response to the vessel wall injury that occurs as a result of mechanical dilatation. The 3 processes involved in restenosis are immediate elastic recoil, late constrictive remodeling, and neointimal hyperplasia. The stent can control the first 2 processes but lead to an increase in neointimal hyperplasia[1]. Uncontrolled neointimal hyperplasia shows some parallels to tumor growth, thus the use of antitumorous strategies seems to be a logical consequence. Numerous pharmacological agents with antiproliferative properties have been given systematically but can not inhibit restenotic process may be from insufficient concentrations in injured arteries. Local drug administration offers advantages. The active drug is applied to the vessel at the precise site and at the time of vessel injury. The new concept of local drug delivery *via* coated stents couples the biological and mechanical solutions are able to achieve higher tissue concentrations of the drug. Systemic release is minimal and may reduce the risk of remote systemic toxicity[2]. To date, the most popular antiproliferative and antimigratory agent that used in eluting stent is sirolimus (rapamycin). A small fractional dose of sirolimus is incorporated into a polymer matrix surrounding a balloon-expandable metallic stent (CYPHER, Cordis, Johnson & Johnson) suppresses smooth muscle cell (SMC) proliferation and inflammatory cell activity by virtue of cell cycle inhibition. These stents appear to demonstrate a remarkable efficacy and safety in preventing restenosis.

From the randomized study de novo native coronary artery leision (RAVEL)[3], comparing a bare metal stent with the rapamycin coated Bx velocity balloon expandable stent in the treatment of patients with denovo lesions in native coronary arteries. Two hundred and twenty patients were randomized to a single rapamycin coated stent (140 $\mu g/cm^2$) *versus* a bare metal Bx velocity stent. At six months' follow-up, the restenosis rate of the treated group was zero, the loss in minimal lumen diameter was zero, there was no target lesion reintervention, and the event-free survival was 96.5 per cent. From the present study this may be the new era of interventional cardiology for treating coronary artery disease.

On the basis of a previous study, the authors would like to report the clinical experience of sirolimus-eluting stents (SES) and short-term follow-up in our institute.

METHOD

Patients and stent implantation

The design of the study was a case series. The authors included the first 40 consecutive patients who underwent percutaneous coronary angioplasty with sirolimus-eluting stents between 25th June, 2002 and 11th October, 2002. All the patients had to fulfill the indications for percutaneous coronary intervention, received detailed information about the potential risks and benefits of the procedure, and signed informed consent to accept percutaneous coronary intervention in our institue.

Study procedures

After coronary angiograms were done, the interventionist chose the patients who were suitable for only balloon dilatation, uncoated bare stent (BS) or implant of a sirolimus-eluting Bx velocity balloon-expandable stent (CYPHER, Cordis Corp, Johnson & Johnson) (SES) size between 2.25-3.00 mm and length 8.00-33.00 mm. All drug-eluting Bx velocity stents contained 140 μg sirolimus/cm^2 ($\pm$10%). Post dilatation was performed as necessary to achieve a residual stenosis below 20 per cent with a TIMI grade III flow. In the case of multivessel diseases, dissection or of incomplete coverage of the lesion, additional balloon dilatation, BS or SES were used as necessary. Heparin was administered in intravenous boluses to maintain an activated clotting time over 250 seconds for the duration of the procedure and was discontinued after the end of the procedural. Aspirin, at least 75 mg, was administered 12 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered before the procedure, followed by 75 mg once daily for 4 weeks. Alternatively, ticlopidine 250 mg twice daily was begun 1 day before the procedure and continued for 4 weeks.

Angiographic analysis and clinical outcome

Coronary angiograms were obtained in multiple views. Per cent of coronary stenosis were analyzed pre- and post procedural by an interventional cardiologist who performed the procedural.

Clinical outcome of patients as well as major adverse cardiac events were evaluated during in hospital care and 1 month follow-up by telephone or at the out patient clinic.

Statistical analysis

Statistical analysis was performed on a personal computer using the SPSS software package

Table 1. Baseline clinical characteristics.

Variable	N	%
Patients	40	
Mean age (year-old)	59.85 ± 12.16	
Age < 45	3	7.5
Age 45-60	18	45
Age > 60	19	47.5
Male sex	32	80
Coronary artery risks		
Diabetes	14	35
Hypercholesterolemia	27	67.5
Hypertension	25	62.5
Current smoker	6	15
Family history of CAD	3	7.5
Ageing	35	87.5
Diagnosis		
Chronic stable angina	29	72.5
Unstable angina	1	2.5
NSTEMI	3	7.5
STEMI	1	2.5
Previous CABG	1	2.5
Previous PCI	5	12.5
Old MI	3	7.5
Post MI angina	2	5
Syncope	3	7.5
Renal disease	3	7.5
History of stroke	1	2.5
Indication for PCI		
Elective	34	85
Early invasive	5	12.5
Primary	1	2.5

CAD = coronary artery disease, NSTEMI = non-ST elevation myocardial infarction, STEMI = ST elevation myocardial infarction, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, MI = myocardial infarction.

* Data are presented as number of relative percentages or mean value ± SD

Table 2. Number of vessel diseases and target lesions revascularization.

Variable	N	%
Total patients	40	
Number of vessel diseases		
SVD	14	35
DVD	17	42.5
TVD	8	20
TVD with LM	1	2.5
Total lesions revascularization	75	100
By sirolimus-eluting stents	52	69.3
By bare stents	19	25.3
By balloon dilatation	4	5.3
Multivessel intervention	24	60
Sirolimus-eluting (stent/case)	1.3	
Completed revascularization by PCI	27	67.5
Completed revascularization with SES	16/27	59.3

SVD = single vessel disease, DVD = double vessel disease, TVD, triple vessel disease, LM = left main artery, PCI = percutaneous coronary intervention.

version 10.0.7. Data are presented as nominal number, mean ± SD or proportions.

RESULTS

Between 25th June and 11th October, 2002, 40 consecutive patients underwent percutaneous coronary angioplasty with sirolimus-eluting stents implantation. The baseline clinical characteristics are reported in Table 1. The mean age was 59 ± 12.16 years (mean ± SD) and 80 per cent of the patients were male. The prevalence of hypercholesterolemia, hypertension and diabetes in the patients was 67.5 per cent, 62.5 per cent and 35 per cent, respectively. The majority of the patients had chronic stable angina and most percutaneous coronary interventions were performed by elective procedure (85%). The number of vessels diseased and type of stents implantation are presented in Table 2. Thirty-five per cent of the patients had single vessel disease and 42.5 per cent of the patients had double vessel disease. The type B lesions were the majority lesions of the patients (Table 3). The authors included 1 patient with non-ST elevation myocardial infarction (NSTEMI) and cardiogenic shock. The coronary angiogram of this patient had left main with triple vessel disease and PCI was undertaken because her family refused to allow her to undergo coronary artery bypass graft (CABG). The authors implanted 52 (69.3%) of SES in 75 target lesions revascularization. The mean of SES per case was 1.3. Twenty-four (60%) of the patients had more than 1 vessel intervention. Twenty-seven (67.5%) of the patients had complete revascularization by PCI and only 16 of 27 patients (59.3%) who had complete revascularization with SES. The type of stents implantation at target lesions are shown in Table 4. The SES was usually implanted at the middle part of the left anterior descending artery (MLAD) (11 lesions), proximal part of the left anterior descending artery (PLAD) (8 lesions), middle part of the right coronary artery (MRCA) (8 lesions) and middle part of the left circumflex artery (MLCX) (6 lesions). The authors implanted SES in 2 lesions of saphenous vein grafts (SVG) and 2 lesions of In-Stent Restenosis (ISR). The size and length of SES are presented in Table 5. The authors usually implanted SES size 2.75 mm (30.8%) or 3.00 mm

Table 3. Lesion type and target lesions revascularization.

Lesion type (AHA/ACC)	SES	BS	Balloon
Type A	8	1	1
Type B	32	14	2
Type C	12	4	1
Total	52	19	4

AHA/ACC = American Heart Association/American College of Cardiology classification, SES = sirolimus-eluting stent, BS = bare stent.

Table 4. Target lesions revascularization.

Target lesion	SES	BS	Balloon
Left main trunk	1		
Left anterior descending			
PLAD	8	2	
MLAD	11	5	1
DLAD	1		
Diagonal		2	
Left circumflex			
PLCX	2		
MLCX	6	1	2
DLCX	1		1
Obtuse Marginal	4	1	
Right coronary			
PRCA	3	2	
MRCA	8	3	
DRCA	3	2	
Posterior Descending	1		
SVG	2		
ISR	2		
Total	52	19	4

SES = sirolimus-eluting stent, BS = bare stent,
PLAD = proximal left anterior descending,
MLAD = middle left anterior descending, DLAD = distal left anterior descending,
PLCX = proximal left circumflex, MLCX = middle left circumflex,
DLCX = distal left circumflex, PRCA = proximal right coronary artery,
MRCA = middle right coronary artery, DRCA = distal right coronary artery,
SVG = saphenous vein graft, ISR = in-stent restenosis.

(44.2%) and SES length 18 mm (53.8%) or 33 mm (44.2%) in the patients. The clinical outcomes during in-hospital and within one month after discharge are reported in Table 6. One patient was lost during hospitalization; she was implanted with 3.0 x 8 mm SES at the left main coronary artery. She had left main with triple vessel disease and very tortuous coronary arteries and could not completely revascularize her coronary vessels. She also had severe peripheral vascular disease. She died after having limb ischemia due to prolonged use of intra-aortic balloon pump, hyperkalemia and severe sepsis. The clinical outcome of the patients was followed within 1 month after discharge by telephone call or follow-up at the outpatient clinic. Four patients (10.3%) were lost to follow-up because they were all foreigners and did not live in Thailand. During that period, none of the patients had recurrent acute coronary syndrome or death. The authors found 4 patients (10.3%) who had recurrent chest pain; 1 patient had typical angina with triple vessel disease and he did not get complete revascularization, the others had atypical angina with

Table 5. Procedural angiographic data and sirolimus-eluting stent profiles.

Target vessel	SES	%
Procedural angiographic data		
Initial stenosis		
Minimum		55
Maximum		100
Mean		81.90 ± 12.56
Residual stenosis		
Minimum		0
Maximum		5
Mean		0.096 ± 0.69
Sirolimus-eluting stent profiles		
Stent size		
2.25 mm	2	3.8
2.50 mm	11	21.2
2.75 mm	16	30.8
3.00 mm	23	44.2
Stent length		
8.00 mm	1	1.9
18.00 mm	28	53.8
33.00 mm	23	44.2

* Data are presented as number of relative percentages or mean value ± SD

Table 6. Clinical outcome while in hospital and within one month after discharge.

	In-Hospital		Within one month	
	Case	%	Case	%
Death	1	2.5	0	
Q-MI	0		0	
Non-Q MI	0		0	
Unstable angina	0		0	
Repeated PCI	0		0	
CABG	0		0	
Recurrent chest pain	0		4	10.3
Loss follow-up	0		4	10.3

single vessel disease and had complete revascularization. All of them had normal result of physical examination and cardiac investigations and their chest pain could be controlled by medication.

DISCUSSION

Drug eluting stents represent one of the fastest growing fields in interventional cardiology today so our institute started early to implant the SES in patients with coronary artery disease. Many studies reported SES implantation can prevent neointimal proliferation and late lumen loss irrespective of the vessel diameter such as The First-In-Man (FIM) study performed in Sao Paulo and Rotterdam[4-6]. It was a small pilot trial involving 45 patients with de novo coronary lesions of length < 18 mm and vessel diameter 3.0-3.5 mm. All patients were treated with an 18 mm long sirolimus-eluting stent. At four months' follow-up, there was minimal neointimal hyperplasia in both groups as assessed by intravenous ultrasound (IVUS) and quantitative coronary angiography. Neither in-stent or edge restenosis nor major clinical events (stent thrombosis, repeat revascularisation, myocardial infarction (MI), and death) had occurred by 12 months and from the randomized double-blind study with the sirolimus-eluting Bx velocity balloon expandable stent in the treatment of patients with de novo native coronary artery leision (RAVEL)[7,8] involved 238 patients from 19 centers. One hundred and twenty patients received the SES while 118 patients received the BS as control. At 6 months, there was 0 per cent restenosis rate in the sirolimus arm as opposed to 26 per cent in the control arm ($p < 0.0001$). At 12 months, target lesion revascularization (TLR) rate was 0 per cent in the sirolimus group. These phenomena have never been reported in the past. These evidence based studies, convinced our institute to use the SES early. If coated stent can really prevent restenosis we will witness the onset of a new era in interventional cardiology and the revolution of catheter based intervention and coronary bypass surgery.

The present study was a case series aimed to report the experience of sirolimus-eluting stents (SES) in patients with coronary artery disease. The SES implantations in our institute were limited by the cost, size and length of stents. Implanted SES in patients who could afford it and tried to select the best size and length of SES for covering the lesions. Because the authors had only 3 lengths of SES (8.0, 18.0, and 33.0 mm), some SES were much longer than the target lesions. Recently, a few evidence based studies for implanted SES to treat in-stent restenosis or SVG stenosis such as the pivotal RAVEL[7,8] and sirolimus eluting stents and intravascular ultrasound follow-up (SIRIUS) trials[9,10], feasibility studies are ongoing to assess efficacy of rapamycin coated stents in more complex lesion subsets such as in-stent restenosis. From the present study, the authors succeeded in implanting SES in 2 lesions of saphenous vein grafts (SVG) and 2 lesions of In-Stent Restenosis (ISR) without immediate complication.

The clinical outcome during hospitalization and within 1 month after discharge was reported because implant SES was started in June and the last patient was implanted in early October. Few adverse clinical events were found during 1 month follow-up because SES have a very low rate of restenosis in a short time, therefore patients should be followed-up for a longer period and will be reported the clinical outcome later. Because of the higher initial cost, such stents can markedly reduce the need of repeated revascularization procedure (and potential complications) so patients who would get the most benefit from SES and should get completely revascularization by PCI should be selected. Ideally, two groups of patients will benefit most from using the drug eluting stents: patients at high risk of coronary artery restenosis like diabetes, small coronary vessel and long diffuse lesions; and patients with a high clinical risk due to restenosis such as those with poor ventricular function and artery supplying a large proportion of remaining viable myocardium. In fact from the present study, many patients did not have complete revascularization so the long-term clinical outcome may be not satisfactory and may have a high rate of repeat revascularization.

Recently, from IVUS findings in a multicenter, randomized, double-blind RAVEL trial very few adverse clinical events in an SES group at 12 months was reported, so long-term follow-up for 2-3 years is required to elucidate if the drug permanently inhibits neointimal growth or simply delays the formation of neointimal hyperplasia[1]. Furthermore, the multicenter trials will help to answer some of the most important clinical questions and determine whether this really reflects the "new era" or just a "new fashion" in interventional cardiology.

SUMMARY

Drug eluting stents represent one of the fastest growing fields in interventional cardiology today so our institute started early to implant the SES in patients with coronary artery disease. From the present study, initial clinical experience of SES in 40 patients with coronary artery disease was reported. The authors found a few adverse clinical events during 1 month follow-up because SES have a very low rate of restenosis in the short-term so, the patients should be followed-up for longer period and the clinical will be reported later.

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ประสบการณ์การใช้ขดลวดเคลือบยา ไซโรลีมัส (Sirolimus) ในการรักษาผู้ป่วยโรคหลอดเลือดหัวใจตีบในศูนย์หัวใจกรุงเทพ

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ปัจจุบันการใช้ขดลวดเคลือบยา ไซโรลีมัส (Sirolimus) ในการรักษาผู้ป่วยโรคหลอดเลือดหัวใจตีบมีความก้าวหน้าไปมากและผลของการรักษาด้วยวิธีดังกล่าวนี้ได้ผลการรักษาที่ดี ปลอดภัยและสามารถยับยั้งการเกิดภาวะการตีบซ้ำของหลอดเลือดหัวใจหลังการรักษาได้ดี

จากการศึกษานี้เป็นการรายงานประสบการณ์การใช้ขดลวดเคลือบยา ไซโรลีมัส (Sirolimus) ในศูนย์โรคหัวใจกรุงเทพ ในการรักษาที่มีโรคหลอดเลือดหัวใจตีบ โดยรวบรวมผู้ป่วยทั้งหมด 40 ราย ตั้งแต่ 25 มิถุนายน ถึง 11 ตุลาคม พ.ศ. 2545 พบว่า อายุเฉลี่ยอยู่ที่ 59 ± 12.16 ปี และ ร้อยละ 80 เป็นผู้ชาย ผู้ป่วยที่มีส่วนใหญ่ในการศึกษานี้เป็นโรคหลอดเลือดหัวใจตีบแบบเรื้อรัง (Chronic stable angina) และได้รับการรักษาโดยการนัดมาขยายหลอดเลือดหัวใจ ถึง ร้อยละ 85 ในการศึกษานี้พบว่าร้อยละ 35 ของผู้ป่วยจะมีหลอดเลือดหัวใจตีบอยู่ 1 เส้น ร้อยละ 42.5 จะมีหลอดเลือดหัวใจตีบ 2 เส้น ในผู้ป่วยทั้งหมด 40 รายมีการใส่ขดลวดเคลือบยา ไซโรลีมัส (Sirolimus) ทั้งหมด 52 (ร้อยละ 69.3) ตำแหน่งในทั้งหมด 75 ตำแหน่งที่ได้รับการขยายหลอดเลือด ผู้ป่วย 24 ราย ในทั้งหมด 40 ราย ได้รับการขยายหลอดเลือดหัวใจมากกว่า 1 เส้นและผู้ป่วย 27 ราย (ร้อยละ 67.5) ในทั้งหมด 40 ราย ที่ได้รับการขยายหลอดเลือดหัวใจอย่างสมบูรณ์ ในทุกเส้นเลือดหัวใจที่มีปัญหาและมีเพียง 17 รายใน 27 ราย (ร้อยละ 59.3) ดังกล่าวที่ได้รับการใส่ขดลวดเคลือบยา ไซโรลีมัส (Sirolimus) ชนิดเดียวโดยไม่ได้ใช้ขดลวดชนิดอื่น ตำแหน่งที่ได้รับการขยายหลอดเลือดได้แก่ ส่วนกลางของ Left anterior descending artery (MLAD) ทั้งหมด 11 ตำแหน่ง ส่วนต้นของ Left anterior descending artery (PLAD) และ ส่วนกลางของ Right coronary artery (MRCA) อย่างละ 8 ตำแหน่ง และ ส่วนกลางของ Left circumflex artery (MLCX) 6 ตำแหน่ง

จากการติดตามผลการรักษาผู้ป่วยหลังจากการรักษาโดยการใส่ขดลวดเคลือบยา ไซโรลีมัส (Sirolimus) ในระยะสั้นเป็นเวลา 1 เดือน พบว่าอาการของผู้ป่วยหลังการรักษาเป็นที่หน้าพอใจและยังไม่พบการตีบซ้ำของหลอดเลือดหัวใจหลังการรักษาจากอาการแสดงของผู้ป่วยแต่อย่างใด คงจะต้องมีการติดตามผลการรักษาในระยะยาวต่อไปในอนาคต

คำสำคัญ : ขดลวดเคลือบยา ไซโรลีมัส, ประสบการณ์การใช้, ผลการรักษา, โรคหลอดเลือดหัวใจตีบ

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