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Short-Term Clinical Benefit of Sirolimus-Eluting Stents Compared to Bare Metal Stents for Patients with Acute Myocardial Infarction

Sang Hoon Lee, M.D.[1], Kwon Bae Kim, M.D.[2], Chang Wook Nam, M.D.[2], Seung Ho Hur, M.D.[2], Yun Kyeong Cho, M.D.[2], Seong Wook Han, M.D.[2], Yoon Nyun Kim, M.D.[2], Young Soo Lee, M.D.[3], Kee Sik Kim, M.D.[3]

Department of Internal Medicine, Pohang Christianity Hospital, Pohang, Korea[1],
Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea[2],
Department of Internal Medicine, Catholic University School of Medicine, Daegu, Korea[3]

Abstract : Sirolimus-eluting stents (SES) have been recently proven to reduce restenosis and reintervention compared with bare metal stents (BMS). However, the effectiveness of SES in acute myocardial infarction (AMI) remains uncertain. The aim of this study was to evaluate the efficacy of SES implantation in patients with AMI compared with that of BMS. From January 2003 to April 2004, angioplasty with SES was performed in 76 patients (82 lesions) with AMI and the result was compared with that of 106 patients (113 lesions) treated with BMS. The incidence of major adverse cardiac events (death, nonfatal myocardial infarction, and target lesion revascularization) and binary angiographic restenosis were evaluated. Antiplatelet therapies included aspirin with clopidogrel, or cilostazole. follow-up angiography was performed at sixth month. Baseline demographic characteristics and the incidence of short term adverse events were similar between both SES and BMS groups. At follow-up angiography, SES group showed the significantly lower incidences in adverse events (8.2% vs. 39.3%, $p<0.01$). late loss (0.38 ± 0.54 mm vs 1.34 ± 0.96 mm, $p<0.01$) and restenosis (5.9% vs. 35.6%, $p<0.01$) comparing to BMS group. Therefore, SES implantation could be a safe and effective strategy for the treatment in patients with AMI.

Key Words : Acute myocardial infarction, Angioplasty, Sirolimus-eluting stent

Introduction

Despite of improvements in stent technology and implantation technique, intimal hyperplasia after stent implantation and the subsequent restenosis have limited the efficacy of coronary stenting, and remain problems to intervention cardiologists. In past decade, stents coated with antiproliferative agents have been the focus of considerable research. In many studies, sirolimus-eluting stents (SES, Cypher™, Cordis/Johnson and Johnson, Miami, FL) showed promise to reduce the incidence of restenosis[1-5]. Some clinical trials reported that SES implantation in patients with acute myocardial infarction (AMI) was safe and associated with extremely low incidence of in-stent restenosis[6]. However, the clinical benefit of SES implantation in comparison to conventional bare metal stents (BMS) in patients with AMI remains currently uncertain. This study was performed to evaluate the clinical outcomes of patients with acute myocardial infarction treated with SES compared with that with BMS.

Materials & Methods

From January 2003 to April 2004, a total of 182 consecutive patients with AMI which was resulted from significant atherosclerosis have been treated with coronary angioplasty. Patients with cardiogenic shock, left main disease, chronic renal failure, or previous stroke history were excluded.

Standard angioplasty and stent implantation were performed. Lesions were predilated with balloon. According to the reference vessel diameter, we determine the size of stents. The stents were dilated to nominal pressure at least.

We prescribed aspirin and clopidogrel before the procedure. Heparin (unfractionated or low molecular weight) was administered during the procedure. After stent implantation, in addition to aspirin, clopidogrel were recommended for six months. If allergic reaction to the clopidogrel was developed, cilostazole was administered in the lieu of clopidogrel. Angiographic follow-up was performed at six months.

The primary end point of this study was in-stent minimal lumen diameter (MLD) at six month determined by quantitative coronary angiography. Secondary end points included 1) all-cause death, 2) nonfatal myocardial infarction, 3) target lesion revascularization (TLR). Reinfarction was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with re-elevation of the creatine kinase (CK) and creatine kinase muscle-brain fraction (CK-MB) level above 3 times the upper normal range within 24 hours after percutaneous coronary intervention (PCI). TLR was defined as a repeat intervention driven by lesion of previous implanted stents at the index procedure. Thrombotic stent occlusion was angiographically documented as a complex occlusion (thrombolysis in myocardial infarction (TIMI flow grade 0) or a flow-limiting thrombus (TIMI flow grade 1 or 2) of a previously successfully treated artery.

Quantitative coronary angiographic analysis was performed for standard quantitative characteristics such as lumen diameter, including proximal and distal references, and the MLD before and after the

procedure and at follow-up.

In some cases, automatic pullback images were obtained by intravascular ultrasound before and after stent placement and at follow-up. Imaging extended up to 5 mm distally and 5 mm proximally in most patients.

Effects across both SES and BMS groups were analyzed by analysis of variables. Continuous variables represented as means ± standard deviations, and comparisons were performed with an independent samples t-test. Dichotomous variables represented as percentages and comparisons were performed with a chi-square test.

Results

Baseline characteristics were similar between both groups (Table 1), except by higher primary PCI rate in BMS group (39.6% vs. 10.7%, $p<0.01$). In SES group, lesion length (23.6 ± 11.3 mm vs. 19.8 ± 10.5 mm, $p>0.05$) and stent length (26.9 ± 10.4 mm vs. 23.8 ± 11.1 mm, $p>0.05$) are longer, and stent size (3.04 ± 0.30 mm vs. 3.50 ±0.46 mm, $p<0.01$) is smaller than BMS group (Table 2). Pre-MLD is similar on quantitative coronary angiography between both groups. Although acute gain (2.55 ± 0.39 mm vs. 2.94 ± 0.48 mm, $p<0.01$) is significantly

Table 1. Baseline Clinical Characteristics

	BMS (n=106)	SES (n=76)	P value
Age (year)	60.7 ± 10.1	60.7 ± 11.3	NS
Male (%)	77 (72.6%)	58 (76.3%)	NS
Hypertension (%)	37 (34.9%)	32 (42.1%)	NS
Smoking (%)	72 (67.9%)	49 (64.5%)	NS
Diabetes (%)	19 (17.9%)	19 (25.0%)	NS
Hypercholesterolemia (%)	37 (34.9%)	27 (35.5%)	NS
Previous myocardial infarction (%)	5 (4.7%)	4 (5.3%)	NS
Previous PCI (%)	6 (5.7%)	6 (7.9%)	NS
STEMI (%)	81 (76.4%)	51 (67.1%)	NS
Primary PCI (%)	42 (39.6%)	8 (10.7%)	<0.001
Number of vessel			NS
1	51 (48.1%)	29 (38.2%)	
2	27 (25.5%)	25 (32.9%)	
3	28 (26.4%)	22 (28.9%)	

BMS: bare metal stent; SES: sirolimus-eluting stent; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; NS: not significant.

Table 2. Baseline Lesion Characteristics

	BMS	SES	P value
Number of lesion	113	82	
TIMI flow			
0/1	40 (35.4%)	20 (24.4%)	NS
2/3	73 (64.6%)	62 (75.6%)	NS
Lesion length (mm)	19.8 ± 10.5	23.6 ± 11.3	NS
Stent length (mm)	23.8 ± 11.1	26.9 ± 10.4	NS
Stent size (mm)	3.50 ± 0.46	3.04 ± 0.30	<0.001
Treated vessel			
LAD (%)	58 (51.3%)	40 (48.8%)	
LCX (%)	15 (13.3%)	12 (14.6%)	
RCA (%)	40 (35.4%)	30 (36.6%)	

BMS: bare metal stent; SES: sirolimus-eluting stent; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; NS: not significant.

Table 3. Quantitative Coronary Angiographic Results at 6-month Follow-up

	BMS (n=106)	SES (n=76)	P value
Pre-MLD (mm)	0.39 ± 0.33	0.39 ± 0.27	0.022
Pre-DS (%)	87.3 ± 10.0	86.6 ± 9.0	NS
Post-stent MLD (mm)	3.33 ± 0.48	2.94 ± 0.35	<0.001
Post-stent DS (%)	7.6 ± 3.7	7.9 ± 3.8	NS
Acute gain (mm)	2.94 ± 0.48	2.55 ± 0.39	0.005
Follow-up MLD (mm)	2.04 ± 1.09	2.54 ± 0.64	<0.001
Follow-up DS (%)	41.5 ± 27.0	18.9 ± 14.3	<0.001
Late loss (mm)	1.34 ± 0.96	0.38 ± 0.54	<0.001
Net gain (mm)	1.64 ± 1.04	2.10 ± 0.69	<0.001

BMS: bare metal stent; SES: sirolimus-eluting stent; Acute gain: difference between MLD after procedure and MLD before procedure; Late loss: difference between MLD at sixth month and MLD after procedure; Net gain: difference between acute gain and late loss; MLD: minimal lumen diameter; DS: diameter stenosis; NS: not significant.

Table 4. In-Hospital and 6-month Outcomes

	BMS (n=106)	SES (n=76)	P value
In-hospital			
Acute thrombosis (%)	0	0	NS
Subacute thrombosis (%)/TLR (%)	0	1 (1.3%)/1	NS
Nonfatal MI (%)	9 (15.3%)	(1.3%)	NS
Death (%)	0	9 (13.2%)	NS
Follow-up @ 6 month		0	
TLR (%)	15 (22.1%)	3 (6.5%)	0.021
Nonfatal MI (%)	4 (3.8%)	1 (1.3%)	NS
Death (%)	1 (0.9%)	0	NS
MACE (%)	17 (16.0%)	4 (5.3%)	0.019

BMS: bare metal stent; SES: sirolimus-eluting stent; TLR: target lesion revascularization; MI: myocardial infarction; MACE: major adverse cardiac events; NS: not significant.

smaller in SES group, late loss (0.38 ± 0.54 mm vs. 1.34 ± 0.96 mm, $p<0.01$) on six-month follow-up angiography is also significantly smaller in SES group (Table 3). The In-stent restenosis (ISR) rate is lower (5.9% vs. 35.6%, $p<0.01$) in SES group. Death, acute thrombosis and stroke event were not happened during hospitalization. Nonfatal myocardial infarction rate is similar between both groups. Subacute thrombosis was diagnosed in one patient in SES group and was not detected in the BMS group.

During 6 months follow-up, one cardiac death was happened in BMS group due to acute myocardial infarction. Nonfatal myocardial infarction rate is similar between groups. However, TLR rate (6.5% vs. 22.1%, $p<0.05$) and major adverse cardiac events (MACE) (5.3% vs. 16.0%, $p<0.05$) is lower in SES group (Table 4).

Discussion

Routine stent implantation has been advocated for patients with acute myocardial infarction referred for primary angioplasty, with superior results compared to balloon dilation[7-8]. But, intimal hyperplasia after stent placement and the resultant restenosis are still hampered, the need for repeat intervention emerged. Conventional coronary stenting for the treatment of acute myocardial infarction has been limited by the need of late repeat intervention ranging from 3.6% to 22.7%[7-8].

Sirolimus, a natural macrocyclic lactone, is a potent immunosuppressive agent. It binds to an intracellular receptor protein and elevates p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes and induces cell-cycle arrest in the late G1

phase. Due to the effect above mentioned, it inhibits the proliferation of smooth muscle cells[9-10] and reduces intimal thickening[11]. Since FIM (First-In-Man) study reported in 2001 by Sousa *et al.*[12-13], many studies showed that SES implantation clearly had a reduced risk of reintervention compared with BMS implantation[14-15].

Lemos *et al.*[16] evaluated the early outcomes of patients with acute coronary syndromes treated with SES[16]. Compared with BMS implanted patients, patients treated with SES had more primary angioplasty, more bifurcating stenting, less previous myocardial infarction and less glycoprotein IIb/IIIa inhibitor use. This registry provides information that SES utilization had no influence on major adverse cardiac events and safe in patients with acute coronary syndrome. However, with the focus on a 30-day endpoint it cannot and does not provide information that SES implantation is superior to BMS implantation in terms of reducing restenosis.

In a recently published study[6] performed by same group in Netherlands with SES in 186 consecutive acute myocardial infarction patients comparing with 183 patients treated with BMS, SES implantation reduced risk of reintervention. Postprocedural vessel patency, enzymatic release, and the incidence of short-term adverse events were similar in both SES and BMS. At 300 days, SES implantation was effective in reducing adverse events in patients with ST segment elevation myocardial infarction compared with BMS and the risk of subacute thrombosis did not appear higher compared with BMS.

Weber *et al.* reported[17] safety of SES in acute myocardial infarction. Fifty consecutive patients with acute myocardial infarction were subjected to acute primary coronary intervention with SES and compared to 50 matched control patients who received BMS. SES diameter was 3.0 ± 0.1 mm vs. 3.3 ± 0.5 mm with BMS, while the length of stented segment is shorter in SES than BMS. It is similar result of our study. Because of the lower rate of restenosis and target lesion revascularization, the major adverse cardiac events with SES is lower than BMS.

Summary

SES with conventional antiplatelet therapy effectively inhibit restenosis and intimal hyperplasia in coronary arteries. SES implantation for patients with acute myocardial infarction were markedly reduced the risk of major adverse cardiac events and repeated intervention. SES appeared to be an attractive strategy for patients admitted with acute myocardial infarction.

References

1. Schampaert E, Cohen EA, Schluter M, Reeves R, Traboulsi M, Title LM, *et al.* The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesion in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;**43**:1110-5.
2. Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, *et al*. Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusion. *J Am Coll Cardiol* 2004;**43**:1954-8.

3. Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, *et al*. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Eng J Med* 2003;**349**:1315-23.
4. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, *et al*. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization, *N Eng J Med* 2002;**346**:1773-80.
5. Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, *et al*. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesion in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;**362**:1093-9.
6. Lemos PA, Saia F, Hofma SH, Daemen J, Ong AT, Arampatzis CA, *et al.* Short- and long-term clinical benefit of sirolimus-eluting stents compared to conventional bare stents for patients with acute myocardial infarction. *J Am Coll Cardiol* 2004;**43**:704-8.
7. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, *et al*. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1999;**341**:1949-56.
8. Stone GW, Grines CL, Cox DA, Garcia E, Tcheng JE, Griffin JJ, *et al*. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med* 2002;**346**:957-66.
9. Marx SO, Jayaraman T, Go LO, Marks AR. Rapamycin-FKBP inhibits cell cycle regulators of proliferation in vascular smooth muscle cells. *Circ Res* 1995;**76**:412-7.
10. Poon M, Marx SO, Gallo R, Badimon JJ, Taubman MB, Marks AR. Rapamycin inhibits vascular smooth muscle cell migration. *J Clin Invest* 1996;**98**:2277-83.
11. Gallo R, Padurean A, Jayaraman T, Marx S, Roque M, Adelman S, *et al*. Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* 1999;**99**:2164-70.
12. Sousa JE, Costa MA, Abizaid A, Abizaid As, Feres F, Pinto IM, *et al*. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. *Circulation* 2001;**103**:192-5.
13. Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, *et al*. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;**104**:2007-11.
14. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, *et al*. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;**346**:1773-80.
15 Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shauhnessy C, *et al*. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;**349**:1315-23.
16. Lemos PA, Lee CH, Degertekin M, Saia F, Tanabe K, Arampatzis CA, *et al*. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndrome; insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (REAEARCH) registry. *J Am Coll Cardiol* 2003;**41**:2093-9.
17. Weber F, Schneider H, Schwarz C, Holzhausen C, Petzsch M, Nienaber CA. Sirolimus-eluting stents for percutaneous coronary intervention in acute myocardial infarction. Lesson from a case-controlled comparison of bare metal versus drug-eluting stents in thrombus-laden lesions. *Z Kardiol* 2004:**93**:938-43.