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Original Article

Clinical Outcomes of Sirolimus with Eluting Stent Implantation in Coronary Artery Disease

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Abstract

Objective: To evaluate the immediate post procedure, thirty-days, and six-months clinical outcomes of sirolimus-eluting stents (SES) implantation in patients with single and multivessel coronary artery disease (CAD).

Methods: A case series of all consecutive patients undergoing percutaneous coronary interventions (PCI) with SES implantation at Shifa International Hospital, Islamabad, were evaluated at early post-procedure, 30-days and six-months clinical follow-up for the incidence of major adverse cardiac event (MACE). This included death, nonfatal myocardial infarction (MI) and repeat revascularization.

Results: Out of 206 consecutive patients, 324 had SES implanted. Cumulative MACE rate was 2.93% and 6% at 30-days and six-months follow-ups respectively. Five patients developed ST-segment elevation MI (STEMI). One patient developed non-STEMI. Emergency Coronary Artery Bypass Grafting (CABG) was done in two patients. Repeat (PCI) was carried in three (1.46%) patients for acute in-stent thrombosis. Diabetes Mellitus and multivessel stenting were found to be the independent predictors for acute in-stent thrombosis (P-value <0.02 and 0.05 respectively).

Conclusion: SES implantation in coronary artery disease can be safe and effective MACE at one and six months follow-ups (JPMA 58:449;2008).

Introduction

Drug-eluting stents have been a major advance in percutaneous coronary revascularization. Widespread use of these stents has been spurred by substantial reductions in restenosis rates when compared with bare metal stents.[1-3]

Although the use of stents has reduced the rate of restenosis as compared to balloon angioplasties, the rate of in-stent restenosis (ISR) still continues to be between 15-30%.[1] Randomized trials such as RAVEL and SIRIUS have shown the efficacy of SES over bare metal stents to reduce angiographic restenosis and repeat revascularizations, in selective patients with relatively simple lesions.[4,5] In reported randomized studies, treatment of stenotic lesions in native coronary arteries by the implantation of the SES or paclitaxel-eluting stent, showed a low percentage of angiographic restenosis and additional revascularization.[6]

To the best of our knowledge we could not find any study that has evaluated the safety and effectiveness of SES implantation in coronary artery diseases in Pakistan. In this study, early and mid-term clinical outcome of SES implantation in CAD patients in our country was evaluated.

Patietns and Methods

It was a case series of all consecutive patients from April 2002 till February 2005, who underwent PCI with SES at Shifa International Hospital, Islamabad. Patients medical records were reviewed for the intra and immediate post-procedure events, in-hospital, one-month and six-months post-procedure outcomes.

All procedures were performed according to standard intervention techniques. All patients were started on aspirin 300 mg and clopidogrel 300 mg bolus at least four hours prior to the procedure. During the procedure intravenous heparin (70 micrograms/kg) was given to achieve an activated clotting time of at least 250 seconds. Glycoprotein IIb/IIIa inhibitors (eptifibatide, abciximab, and tirofiban) were administered at the discretion of the operator. Baseline clinical, procedural information and in-hospital complications were recorded. Patient cohort included all the patients who had stable angina (exercise tolerance test [ETT] or thallium scan suggestive of myocardial ischaemia) and acute coronary syndrome (ACS). Procedures performed within first 24 hours of an acute MI were classified as rescue or primary angioplasty, regardless of any preceding failed thrombolysis. Patients treated after 24 hours of an acute episode of MI were classified as post MI unstable angina (Braunwald classification C). Stent implantation was performed with lesion predilatation or direct stenting according to the evaluation of the operator. MACE was defined as occurrence of 1) death, 2) non fatal MI, and 3) repeat revascularization of the target lesion. Definite diagnosis of an MI required a significant rise in plasma levels of cardiac

enzymes (troponins I or creatinine kinase MB) together with ischaemic symptoms or dynamic electrocardiographic (ECG) changes. Post procedure cardiac enzymes were not done routinely. They were only done in patients who either had symptoms or dynamic ECG changes suggestive of an acute cardiac event. Target lesion revascularization (TLR) was defined as any surgical or percutaneous re-intervention done as a result of significant luminal narrowing within the stent or 5mm distal or proximal peri-stent segment.[3,6] Target vessel revascularization (TVR) was defined as any re-intervention driven by lesions located in treated vessel beyond the target lesion limits.[3,6] Angiographic success of angioplasty procedure was defined as restoration of TIMI flow grade 3 and less than 30% in-lesion stenosis after stent placement.[2,5] In the study protocol, stent thrombosis was defined as acute if it occurred within 24 hours after an index procedure, subacute if it occurred between 1 and 30 days after the procedure, and late if it occurred more than 30 days after the procedure. Acute and subacute stent thrombosis was classified on the basis of vessel occlusion on angiography, any recurrent Q-wave MI in an area irrigated by the stented vessel, or death from cardiac causes. Late stent thrombosis was diagnosed on the basis of any recurrent MI with vessel occlusion on angiography.[7]

Results were presented as frequencies, percentages or mean with standard deviation (SD). For comparison between groups with categorical data, chi square test was used. P-values of less than 0.05 were considered statistical significant. Cox regression analysis was used to identify independent predictors of MACE. Data was entered and analyzed using SPSS version 13.

Results

A total of 282 lesions were treated with 324 SES implantations in 206 patients (79% males and 21% females) with the mean of 1.37±0.64 lesions per patient, median and mode of 2. Mean age at presentation was 56.03 ± 10.17 years. Forty two percent of the patients were hypertensive, 37% were smokers and 35% diabetics. Hundred and seven (60%) patients had unstable angina, 4 (2%) had STEMI and 30 (14.6%) had an NSTEMI. Hundred and eight (52%) patients had single vessel disease, 67 (33%) had two-vessel disease while the remaining 31 (15%) patients had three-vessel disease. Maximum number of lesions were located in left anterior descending artery 134(47.5%). Most lesions stented were either located proximally (49.6%) or in mid segment of the vessels (31.2%). Fifty-five (19.5%) lesions were located in small vessels of less than 2.5mm in diameter. More than half (53.2%) of the lesions were directly stented. Overlap stenting was done in 27.7 % of the lesions and maximum stented length was 79 mm. Bifurcation stenting was done in 3.5% of the lesions. Post stent dilatation was done in 3.5% of the lesions. In 0.71% same delivery balloon was used and in 2.84% of lesions different delivery balloon was used. In all the cases post stent dilatation was done for stent under expansion (Table 1).

All patients received aspirin and clopidogrel at least four hours prior to the procedure. Glycoprotein IIb/IIIa

Table 1. Procedural characteristics of the patients.

Procedural findings	Frequency	Percent
Target Vessel		
LAD	134	47.5
Lcx	43	15.2
RCA	100	35.5
LIMA-anastomosis	4	1.4
CABG	1	0.4
Location in Vessel		
Ostial	36	12.8
Proximal	140	49.6
Mid	88	31.2
Distal	18	6.4
Bifurcation	16	5.7
De novo lesions	273	96.8
In-stent restenosis	9	3.2
Lesion thrombosis	21	7.4
Total occlusions		
> 3 months	2	0.7
< 3 months	3	1.1
Direct Stenting	150	53.2
Balloon dilatation (prior to stenting)	132	46.8
Post Stent Dilatation	10	3.5
Same delivery Balloon	2	0.7
Different delivery balloon	8	2.84
Overlap stenting	92	27.7

Key: LAD: Left anterior descending, Lcx: Left circumflex, RCA: Right coronary artery, LIMA: Left internal mammary artery, CABG: Coronary artery bypass graft

Table 2. In-hospital and 30 days incidence of major adverse cardiac events.

Events	In-Hospital Mace (frequency and percent)	30 Days Mace (frequency and percent)	Composite 30 Days Mace (frequency and percent)
Death	1 (0.49%)	0	1 (0.49%)
Nstemi	0	1 (0.49%)	1 (0.49%)
Stemi	3 (1.46%)	1 (0.49%)	4 (1.95%)
Total mace	4 (1.94%)	2 (0.98%)	6 (2.93%)
Repeat PCI	3 (1.46%)	0	3 (1.46%)
Emergent cabg	0	2 (0.98%)	2 (0.98%)

Key: MACE: Major adverse cardiac events, NSTEMI: Non ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft

Table 3. Six-months clinical outcomes.

Event	Frequency	Percent
Death	3	2
NSTEMI	1	0.66
STEMI	5	3.33
Cumulative MACE	9	6
TLR	5	3.33
PCI	3	2
CABG	2	1.33
TVR	1	0.67
PCI	1	0.67
CABG	0	0

Key: NSTEMI: Non ST-segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, MACE: Major adverse cardiac events, TLR: Target lesion revascularization, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft, TVR: Target vessel revascularization

inhibitor was given to 42.8% of the patients intra and post procedurally, out of which 13% were diabetics. Beta-blockers were prescribed to 182 (88.3%) patients. In 22 (11%) patients beta-blockers were withheld due to asthma and low blood pressure at the time of discharge. Statins were prescribed to 202 (98.1%) patients on discharge. Angiotensin converting enzyme inhibitors (ACE-I) were given to 188 (91.3%) patients on discharge. In 10 (5%) patients ACE-I were changed to angiotensin receptor blocking agents (ARBs) at 1-month follow up because of intractable cough associated with the ACE-I.

As stated in Table 2, one patient went into ventricular fibrillation and had sudden cardiac arrest during the procedure. About 1-hour post procedure, 2 patients developed severe chest pain and dynamic ECG changes. Re-angiography showed acute periprocedure instent thrombosis. After restenting and adjunctive therapy with glycoprotein 2b3a receptor inhibitor, final TIMI flow grade 3 was restored. One patient developed NSTEMI 8 hours after the index procedure despite being on glycoprotein 2b3a receptor inhibitor peri and post procedure. Repeat PCI was done for acute instent thrombosis, glycoprotien 2b3a receptor inhibitors and low molecular weight heparin in full therapeutic dose was given till 3 days after the procedure. All these patients who developed acute in stent thrombosis were diabetics. At 30 days clinical follow up 2 patients underwent coronary artery bypass grafting. No patient developed major haematoma requiring tranfusion, pseudoaneurysm or need for vascular repair.

Six months clinical follow-ups of 156 patients were reviewed out of 206 patients. Table 3 reports the adverse events at 6 months follow-up. Cumulative MACE incidence was 9 (6%), with 3 (2%) deaths, 6 (4%) MIs and 6 (4%) repeat revascularization. One patient had sudden cardiac arrest three months after the index procedure and died. The other patient, insulin-dependant type-2 diabetic, presented with unstable angina 5 months after the procedure. No independent predictors of MACE, TLR free survival and TVR free survival were found. Variables included in this model were ACS, diabetes mellitus and multivessel stenting. In addition predictors of acute instent thrombosis were identified. Diabetes mellitus and multivessel stenting were significantly associated with acute in-stent thrombosis (P <0.02 and <0.02 respectively).

Discussion

In-stent restenosis (ISR) remains a challenge for interventional cardiologists. The exceedingly encouraging data from randomized trials of drug-eluting stents with selected simple lesions and an unselected cohort of patients have shown that SES implantations are related to decrease incidence of ISR and repeat revascularization.[8-10] Previous data has uncovered that the degree of neointimal proliferation, manifested as the mean (+/-SD) late luminal loss, was significantly lower in the sirolimus-stent group (-0.01+/-0.33 mm) than in the standard-stent group (0.80+/-0.53 mm, P<0.001). None of the patients in the sirolimus-stent group, as compared with 26.6% of those in the standard-stent group, had restenosis of 50% or more of the luminal diameter (P<0.001).[8]

In this study, only 3.2% of the patients had ISR as a complication of SES implantation, which is much lower, compared to bare metal stents and paclitaxel eluting stents.[10,11] In terms of ISR incidence, our results are encouraging and comparable to similar major studies conducted in developed countries.[6,12] The low incidence of ISR with SES implantation can be explained due to its cytostatic and anti-inflammatory properties. Sirolimous, a naturally occuring antibiotic, inhibit cell proliferation at the G-1 phase of the cell cycle, by targeting replicating smooth muscle cells. It also reduces local inflammatory cell activity in the vessel wall.[13-15]

In this study, MACE incidence and repeat revascularization turned out to be six and four percent respectively, despite the fact that most patients in the study had ACS with complex lesions and had very long lesions (maximum stented length of 79 mm), and direct stenting had been done in majority of the patients (54.2%). The figure of MACE incidence in this study was lower comparable to previous such studies conducted in developed countries (6% vs 13.8%).[3,5,12]

In this study, we found that most patients underwent repeat PCI rather than CABG for TLR and TVR. This is an important finding since majority of restenosis seen with SES is focal and can easily be treated with repeat PCI rather than CABG.[6]

Further more, diabetes mellitus and multivessel stenting are significant independent predictors of acute in-stent thrombosis. This necessitates a more liberal use of glycoprotien IIb/IIIa inhibitors in this subset of patients. However, long-term follow-up is needed to look for the impact of diabetes on MACE incidence and ISR.

The safety of drug-eluting stents has been called into question by recent reports of increased stent thrombosis, myocardial infarction, and death. Stent thrombosis after one year was more common with both sirolimus-eluting stents and paclitaxel-eluting stents than with bare-metal stents.[15-20]

In this study, 156 patients out of 206 were reviewed for a period of six months. Smaller number of patients and short follow-ups were our limitations.

References

1. Moliterno DJ. Healing Achilles-siroliinus versus paclitaxel. N Engl .1 Med. 2005;353:724-27.
2. Ryan J, Cutlip DE, Cohen DJ, Pinto DS. Drug eluting stents for ST-elevation myocardial infarction: risk and benefit. J Thromb Thrombolysis. 2007 ;24:293-99. Epub 2007.
3. Mikhail Gw, Airoldi F, Tavano D, Chieffo A, Rogacka R, Carlino M. el al. The use of drug eluting stents in single and multivessel disease: results from a single centre experience. Heart 2004; 90: 990-94.
4. Van Hout BA, Serruys PW, Lemos PA, van den Brand MJBM, van Es G-A. et al. One year cost effectiveness of sirolimus eluting stents compared with bare metal stents in the treatment of single native de novo coronary olesions: an analysis from the RAVEE trial. Heart 2005; 91: 507-12.
5. Holmes DR Jr, Eeon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald P.I. et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis.Circulation. 2004; 109:634-40.
6. Orlic D, Bonizzoni E, Stankovic G, Airoldi F, Chieffo A, Corvaja N. et al. Treatment of multivessel coronary artery disease with sirolimus-eluting stent implantation: immediate and mid-term results. J Am Coll Cardioi. 2004; 43: 1154-60.
7. Hodgson JM, Stone GW, Lincoff AM, Klein L, Walpole H, Bottncr R. el al. Late stent thrombosis: considerations and practical advice for the use ot drug-eluting stents: a report from the Society for Cardiovascular Angiography and Interventions Drug-eluting Stent Task Force.Catheter Cardiovasc Interv. 2007; 69: 327-33.
8. Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M. et al. RAVEL Study Group. Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with cle Novo Native Coronary Artery Lesions.A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med. 2002; 346: 1773-80.
9. Moses JW, Leon MB, Popma JJ, Fitzgerald P.I, Holmes DR. O'Shaughnessy 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.
10. Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA. Hoye A. et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Flospital (RESEARCH) registry.Circulation. 2004 ; 109: 190-95. Epub 2003.
11. Li JJ, Xu B, Yang YJ, Ma WH, Chen JL, Qiao SB. et al. A comparison of angiographic and clinical outcomes after sirolimus-eluting versus paclitaxel-eluting stents for the treatment of in-stent restenosis.Chin Med J (Engl). 2006; 119: 1059-64.
12. 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 syndromes: insights from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. J Am Coll Cardiol. 2003; 41: 2093-99.
13. lakovou I, Ge L, Michev I, Sangiorgi GM, Montorfano M. et al. Clinical and angiographic outcome after sirolimus-eluting stent implantation in aorto-ostial lesions.J Am Coll Cardiol. 2004; 44: 967-71.
14. Schiihlen H, Kastrati A, Dirschinger J, Hausleiter J, Elezi S, Wehinger A. et al. Intracoronary Stenting and Risk for Major Adverse Cardiac Events During the First Month. Circulation. 1998; 98: 104-1 11.
15. Parry TJ, Brosius R, Thyagarajan R, Carter D, Argentieri D, Falotico R. et al. Drug-eluting stents: sirolimus and paclitaxel differentially affect cultured cells and injured arteries.Eur J Pharmacol. 2005; 524: 19-29. Epuh 2005.
16. Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC. et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N "Engl J Med. 2007; 356: 998-1008. Epub 2007.
17. Spaulding C, Daemen J, Boersma E, Cutlip DE, Serruys PW. A pooled analysis of data comparing siroliinus-eluting stents with bare-metal stents.N Engl J Med. 2007; 356: 989-97. Epub 2007.
18. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin E. et al. Eong-term outcomes with drug-eluting stents versus bare-metal stents in Sweden.N Engl J Med 2007; 356: 1009-19. Epub 2007.
19. Kastrati A, Mehilli J, Pache J, Kaiser C, Valgimigli M, Kelbaek H. et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. N Engl J Med. 2007 8; 356: 1030-9. Epub 2007.
20. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl JMed. 2007; 356: 1020-9. Epub 2007.