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SAFETY AND CLINICAL OUTCOMES OF LONG SIROLIMUS-ELUTING STENTS IN PATIENTS WITH CORONARY ARTERY DISEASE: PROSPECTIVE, SINGLE-CENTRE STUDY WITH ONE-YEAR OUTCOMES

Cardiology

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ABSTRACT

OBJECTIVE: In long coronary lesions, multiple stenting is associated with stent overlap, edge dissection, geographical miss and prolonged coronary intervention. In this regard, we evaluated clinical outcomes with implantation of single long sirolimus-eluting stents (SES) of lengths ≥38 mm in patients with coronary artery disease (CAD).

METHODS: This was a prospective, single-centre study of 34 CAD patients with long coronary lesions, who underwent implantation of sirolimus-eluting stents of length ≥38 mm at a tertiary-care centre in India. Primary endpoints were stent thrombosis (ST), in-stent restenosis (ISR), target vessel revascularization (TVR), myocardial infarction (MI) and death, assessed one year post implantation of the stents. Angiographic success, procedural success and clinical success were also assessed.

RESULTS: The study population comprised of 33 (97%) males, 26 (76.5%) smokers and 14 (41.2%) hypertensives. Mean age was 53.4±12.3 years. Stents of mean length 44.3±3.2 mm were implanted. Over the one year follow-up, acute ST in one (2.9%) patient, clinical ISR in one (2.9%) patient, angiographic ISR in four (11.8%) patients, TVR in two (5.9%) patients and no incidents of MI or death were reported.

CONCLUSION: In patients with CAD, management of long coronary lesions with SES ≥38 mm demonstrated favourable outcomes.

KEYWORDS

Antiplatelet agents; Coronary Artery Disease; Coronary restenosis; Drug Eluting Stents; Percutaneous Coronary Intervention

INTRODUCTION

While developing countries have observed a decline in cardiovascular mortality, India has experienced a rapid increase over a brief period of time [1]. Epidemiologic studies have estimated the prevalence of coronary heart disease in India to be between 7% and 13% in urban and 2% and 7% in rural populations with more than 30 million current cases [2]. With emergence of traditional risk factors for coronary artery disease (CAD) in the younger population, India appears to be experiencing an epidemiological transition [3].

Percutaneous coronary intervention (PCI) with the implantation of stents has become one of the most extensively adopted cardiovascular strategies for the treatment of CAD [4]. DES, through elution of high drug concentration and inhibition of multiple biological processes that promote restenosis, have attained reduction of restenosis [5]. In line with this evidence, numerous trials have identified sirolimus-eluting stents (SES) to be beneficial in the sudden reduction of restenosis and in-stent restenosis [6-8].

However, PCI for long coronary artery lesions have been synonymous with hazards such as stent deliverability, stent overlap, peri-procedural myocardial infarction (MI), stent thrombosis (ST) and restenosis. In addition, multiple stenting in long coronary lesions may culminate in geographical miss, intracoronary manipulation and stent overlap, paving way for arterial wall injury [9]. Twenty percent of PCI are comprised of long lesions. This has urged treatment through implantation of a single, long drug eluting stents (DES) [10]. Though clinical safety and efficacy of SES has been reported in real-world patients, limited data exists pertaining to a specific population of patients implanted with long SES. Thus, the aim of this study was to evaluate the one year clinical outcomes post implantation of long indigenously manufactured SES in patients with CAD.

MATERIALS AND METHODS

Study design and patient population

This prospective study was conducted at our tertiary-care centre in India. CAD patients who were admitted at the cardiology department with long coronary lesions between November 2011 and May 2014 were considered for enrolment.

Inclusion criteria were: (a) patients with CAD i.e. chronic stable angina, unstable angina, non ST-segment elevation MI, ST-segment elevation MI; (b) patients with angiographic eligibility for inclusion which consisted of a planned total stent length of ≥38 mm and; (c) those who gave consent.

Exclusion criteria were: (a) allergy to antiplatelet drugs, heparin, stainless steel, contrast agents, or sirolimus; (b) renal dysfunction (serum creatinine concentration ≥2.5mg/dL) or dependence on dialysis; (c) terminal illness; (d) elective surgery planned within 6 months after the procedure; (e) necessitation of antiplatelet agent discontinuation; (f) participation in a study of another device; or (g) inability to follow the protocol.

The study was approved by the ethics committee. Written informed consent was obtained from each patient that participated in the study.

Investigation

Stent implantation was performed according to standard techniques. All patients received standard premedication before stent deployment i.e. 325 mg aspirin and a 600 mg loading dose of clopidogrel. Heparin was administered throughout the procedure to maintain an activated clotting time of ≥250 seconds. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator, and patients who presented with acute coronary syndrome mostly received it. After the procedure, all patients received 150 mg/day aspirin indefinitely in addition to 75 mg clopidogrel twice a day for one month and then once daily for at least 12 months. Use of the standard post-intervention care was recommended.

Endpoints, definitions and follow-up

Primary endpoints were functional status, ST, in-stent restenosis (ISR), target vessel revascularization (TVR), MI and death. Angiographic success, procedural success and clinical success were also assessed.

ST was defined as the sudden occlusion of a stented coronary artery due to thrombus formation. ST may be classified according to the timing of occurrence i.e. acute (<24 hours), sub-acute (24 hours to 30 days), and late (30 days to one year). ISR was defined clinically or angiographically. Clinical ISR was defined as the presentation of recurrent angina or objective evidence of myocardial ischemia, whereas angiographic ISR was defined as the presence of >50% diameter stenosis in the stented segment. Angiographically, type I pattern included focal (≤10 mm in length) lesions, type II pattern included ISR >10mm within the stent, type III pattern included ISR >10mm extending outside the stent, and type IV pattern referred to totally occluded ISR. TVR was defined as repeat revascularization (either repeat PCI or CABG) of the treated vessel.

Angiographic success after PCI was defined as the attainment of residual diameter stenosis of less than 50%, generally associated with at least a 20% improvement in diameter stenosis and relief of ischemia.

Procedural success was defined as angiographic success without occurrence of major complications (death, MI, CABG) within 30 days of the procedure. Clinical success was defined as procedural success without the need for urgent repeat PCI or surgical revascularization within the first 30 days of the procedure.

Enrolled patients were followed up over the period of one year and were evaluated with routine investigations.

Statistical Analysis

Categorical variables are presented counts and percentages and continuous variables as mean ± standard deviation. All statistical analysis was done using Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 15.

RESULTS

Demographic profile

Enrolled patients' age ranged from 27 years to 88 years with an average of 53.4±12.3 years. One (2.9%) out of 34 enrolled patients was female. Diabetics represented 14.7% of the population, who were taking either OHA or insulin as an anti-diabetic measure. Hypertensives and smokers comprised of 41.2% and 76.5% of the population, respectively. More than half of the patients presented with STEMI (55.9%), 35.3% had inferior wall MI and 20.6% had anterior wall MI. The demographic details are shown in **Table 1**.

Angiographic and procedural characteristics

The percentages of single vessel disease, double vessel disease and triple vessel disease were 58.8%, 26.5% and 14.7%, respectively. A total of 39 long SES of mean length 44.3±3.2 mm were implanted in 39 coronary lesions. Majority of the SES were deployed into the right coronary artery (46.2%), followed by the left anterior descending artery (43.6%) and the left circumflex artery (10.3%). The percentages of long stents deployed of lengths 38 mm, 43 mm and 48 mm were 10.3%, 53.8%, and35.9%, respectively. The percentages of stent diameters deployed with 4.0 mm, 3.5 mm, 3.0 mm, 2.75 mm and 2.5 mm diameters were 2.6%, 17.9%, 41.0%, 33.3% and 5.1%, respectively. The angiographic and procedural characteristics are described in **Table 2.**

Clinical endpoints

Patients were followed up over a period of one year (mean: 15.8±5.0 months) with a range from 11.1 months to 30.5 months. Angiographic success rate was 100% and procedural and clinical success was 97%.

One patient developed acute ST after PCI with a long stent within 24 hours and was managed with thrombosis aspiration, balloon dilation and GP IIb/IIIa inhibitor. No untoward effect occurred after that. After one year, coronary angiogram showed patent stent with no clinical symptoms and good effort tolerance.

There was one patient with clinical ISR i.e. complaints of angina on exertion. It was later found that he had abandoned his antiplatelet regime. A follow-up coronary angiogram after one year showed type IV pattern restenosis of the stented vessel i.e. complete occlusion. The patient was advised imaging to demonstrate viability and when territory was viable the patient was advised revascularization.

A total of four (11.8%) patients had angiographic ISR (>50% restenosis in stent) observed in five stented vessels.

There were no incidents of death or MI. TVR was performed in two (5.9%) patients, one who presented with acute ST and one with type IV pattern ISR and had clinical symptoms. The clinical outcomes are detailed in **Table 3**. Follow-up echo revealed left ventricular ejection fraction (LVEF) range from 25% to 69% with an average of 53.4±9.0%.

DISCUSSION

This study has reported favourable outcomes post implantation of long SES in patients with CAD. Smoking, diabetes, hypertension and dyslipidaemia have been identified as traditional risk factors [11]. Our study too identified a high number of smokers (76.5%) and hypertensive (41.2%).

Numerous studies have indicated longer stent length as an independent predictor of restenosis [12, 13]. Chang SH et al. [14] compared lesion length impact on angiographic and clinical outcomes between BMS and DES. Restenosis rates for BMS stent lengths <14 mm, 14–21 mm and >21 mm were 14%, 18% and 29%, respectively. Similarly, restenosis rates for DES of stent length <16 mm, 16–24 mm and >24mm were 4.7%, 3.3% and 7.8%, respectively after 6 months follow-up. It was found that stents of greater length had higher rates of restenosis.

Previously, the LONG-DES-III study [15] compared clinical outcomes of everolimus eluting stents (EES; n=224) with sirolimus-eluting stents (SES; n=226) for long coronary lesions. The average length of EES and SES implemented were 46.5±16.9 mm and 46.4±17.4 mm, respectively. The study demonstrated clinical outcomes, death in 0.4% vs. 0% patients, MI in 9.8% vs. 8.0% patients, ST in 0.4% vs. 0% patients, TLR in 3.1% vs. 2.2% patients and TVR in 4.0% vs. 2.7% patients who were implanted with EES and SES, respectively. The study demonstrated favourable outcomes for both DES. The present study, reported two cases (5.9%) of TVR as compared to six cases (2.7%) of TVR when long SES were used in the LONG-DES-III. The LONG-DES-III study however, was a much larger study.

A recent 'real world' study [16] examined the safety and efficacy of the 40 mm Indolimus SES (Sahajanand Medical Technologies Pvt. Ltd, India) in Indian patients (n= 258) with long coronary lesions. After the 6 months follow-up the study findings were two (0.8%) deaths, three (1.2%) MI, and no events of TLR, TVR or ST. This study is comparable to our study in terms of the percentage of hypertensive (38.4% vs. 41.1%), single vessel disease patients (64.0% vs. 58.8%) and average stent length (40.0±0.0 mm vs. 44.3±3.2 mm). In the present study, higher rates of acute ST (2.9%), angiographic ISR (11.8%) and TVR (5.1%) were recorded despite no reported incidences of death and STEMI.

Untimely withdrawal from antiplatelet therapy has been indicated as a prime predictor of ST [17, 18]. In line with these findings, a one year follow-up angiogram revealed type IV pattern restenosis of the stented vessel in the one patient of the trial who had discontinued his antiplatelet therapy.

Increased number of stents implanted increases the duration of the PCI procedure, and consequentially increases the exposure of radiation to both the patient and operator [19]. Majewska N. et al. [20] have demonstrated in their study, a 50% higher dose area product (DAP) for the concurrent implantation of three stents, as compared to the implantation of either one or two stents. The present study has greatly reduced radiation exposure by implementing single, long stents. At our centre, we recommend implantation of single long stent over multiple stenting in patients with long coronary lesions as it offers advantages of greater affordability, and less contrast and radiation exposure.

Study Limitations

The most evident limitation of this study was the small sample size. Direct comparison with multiple stenting strategies could have provided better insights into the outcomes of the long stents. For more reliable long term data, a follow-up period greater than one year would have been appreciated.

CONCLUSION

From the current study, implantation of SES of lengths ≥38 mm has been inferred as an apt approach for the treatment of long lesions. Implantation of single long stents could confer advantages such as greater affordability, especially in developing countries such as India, and less contrast and radiation exposure to both patients and clinicians. Future studies, however are needed with comparative analysis and a more adequate sample size.

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Table 1: Baseline demographic characteristics of patients

Characteristics	N= 34 patients
Age (mean ± SD, years)	53.4 ± 12.3
Male, n (%)	33 (97.0%)
Cardiovascular risk factors	
Diabetes mellitus, n (%)	5 (14.7%)
Hypertension, n (%)	14 (41.2%)
Smoker, n (%)	26 (76.5%)

Clinical presentation	
Myocardial Infarction, n (%)	19 (55.9%)
Inferior wall MI, n (%)	12 (35.3%)
Anterior wall MI, n (%)	7 (20.6%)
Chronic stable angina, n (%)	6 (17.7%)
Unstable angina, n (%)	5 (14.7%)
Non ST-Segment Elevation MI, n (%)	4 (11.8%)

SD: Standard deviation; MI: Myocardial infarction

Table 2: Angiographic and procedural characteristics of patients

Characteristics	Patients = 34
No. of diseased vessels	
Single vessel disease, n (%)	20 (58.8%)
Double vessel disease, n (%)	9 (26.5%)
Triple vessel disease, n (%)	5 (14.7%)
Location of treated lesion	
Left anterior descending, n (%)	17 (43.6%)
Right coronary artery, n (%)	18 (46.2%)
Left circumflex, n (%)	4 (10.3%)
Total no. of stents	**N = 39**
No. of stents per lesion	1.2
Average lesion length (mean, mm)	31.2±6.7
Average stent length (mean ± SD, mm)	44.3±3.2
38 mm, n (%)	4 (10.3%)
43 mm, n (%)	21 (53.8%)
48 mm, n (%)	14 (35.9%)
Average stent diameter (mean ± SD, mm)	3.00±0.32
2.5 mm, n (%)	2 (5.1%)
2.75 mm, n (%)	13 (33.3%)
3.0 mm, n (%)	16 (41.0%)
3.5 mm, n (%)	7 (17.9%)
4.0 mm, n (%)	1 (2.6%)

Table 3: Clinical outcomes over one year (N= 34)

Outcomes	Over one year follow-up
Acute stent thrombosis, n (%)	1 (2.9%)
Clinical ISR, n (%)	1 (2.9%)
Angiographic ISR, n (%)	4 (11.8%)
TVR, n (%)	2 (5.9%)
Myocardial Infarction, n (%)	0 (0%)
Death, n (%)	0 (0%)

TVR: Target vessel revascularization, ISR: In-stent restenosis

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