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Original Research Article

Clinical Outcomes of Successful Sirolimus-Eluting Stent Implantation in Patients with Chronic Total Occlusion in the Real Clinical Practice

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Abstract

Objectives: We aimed to evaluate the clinical outcomes in patients with chronic total occlusion treated with Indolimus, biodegradable polymer coated sirolimus-eluting stent, in real clinical practice.
Methods: We evaluated clinical outcomes in 170 patients, who underwent successful recanalization of chronic total occlusion with Indolimus between April-2012 and June-2014. During 9-month, primary endpoint was target lesion failure (TLF), a miscellany of cardiac death, myocardial infarction (MI), target lesion revascularization (TLR) and target vessel revascularisation. We considered stent thrombosis as a clinical outcome parameter.
Results: The mean age was 50.7years and 142(83.5%) patients were predominantly male. The average stent length and diameter were 30.8±8.4 mm and 3.1±0.4 mm, respectively. The cumulative TLF at 9-month was 2.9% which included one, one and three cases of cardiac death, TLR and MI, respectively.
Conclusion: In real clinical practice, treatment of chronic total occlusionwith Indolimus sirolimus-eluting stentshowed favourable clinical outcomes with high success rates.
Keywords: Coronary occlusion; drug-eluting stent; percutaneous coronary intervention; sirolimus; target lesion failure.

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1. Introduction

Coronary chronic total occlusion (CTO) is marked by profound atherosclerotic plaque burden in the artery, resulting in complete (or nearly complete) occlusion of the vessel [1, 2]. Percutaneous coronary intervention (PCI) of CTOs account for 10% to 15% of all angioplasties [2-4]. The CTO-PCI can provide angina relief, improve left ventricular function, reduce the need for coronary artery bypass graft surgery and mostly benefit patients who have angina refractory to optimal medical management and those with large ischemic burden [5-8].

However, even after successful recanalization, there was an augmented rate of subsequent restenosis and reocclusion after PCI compared to non-occlusive stenosis, prior to the introduction of drug-eluting stent (DES)[9, 10]. Since the advent of DES, there have been several reports

about the efficacy of DES for the reduction of restenosis after implantation, and the reports have described a remarkable reduction of restenosis as compared with the use of bare metal stents (BMSs) [11-13].

With recent advances in technology (special techniques and devices) and increased operator experience, the initial success rate of opening occlusions has reached quite high, so there are much higher rates of recanalization of CTO and much lower incidence of restenosis[14]. We therefore intended to evaluate the clinical outcomes of sirolimus-eluting stents implantation in patients with CTO in the real clinical practice.

2. Methods

2.1. Study Design and Patient Population

From April-2012 to June-2014 at four tertiary care centres in India, a total of 170 patients, exclusively treated with Indolimus SES in patients with CTO, were examined in the non-randomized, observational, retrospective, multi-centre study. The study was conducted in accordance with the Declaration of Helsinki and country-specific regulatory requirements. Signed informed consent forms were obtained from all the patients.

The inclusion criteria for the study were: 1) patients of age 18 years or above 2) patients who had stable or unstable angina or acute recent myocardial infarction and 3) patients with CTO who were undergoing coronary intervention. The patients were excluded if they refused to give written informed consent or if they had any allergy to aspirin, clopidogrel, ticlopidine, heparin, cobalt chromium, sirolimus or polymers used in a study stent.

2.2. Description of the Study Stent

The Indolimus biodegradable polymer coated sirolimus-eluting coronary stent involves L605 cobalt chromium (Co-Cr) alloy as its stent platform. The biodegradable polymer gives it a strut thickness of 60 µm anddrug load of 1.4µg/mm^2. About 70% of drug is released within 7 days and remaining drug is released over a period of 48 days **(Figure 1).**

The drug is released within 7 weeks after the stent implantation from the polymeric layers coated onto the surface of the stent. The biodegradable polymeric film is a blend of different biodegradable polymers- Poly L-Lactide, 50/50 Poly DL Lactide-co-Glycolide and Polyvinyl Pyrrolidone, which undergoes hydrolysis. This process takes approximately 9 to 12 months after which all the polymer degrades naturally and excretes from body in the form of their metabolites. The average coating thickness of Indolimus stent is between 5 to 6 µm. The Indolimus stent is available in lengths of 8, 12, 16, 20, 24, 28, 32, 36 and 40 mm and available diameters were 2.5, 2.75, 3.0 and 3.5 mm.

2.3. Interventional Procedure and Adjunctive Medication

All patients received a loading dose of 300 mg of aspirin and clopidogrel (300 mg) or prasugrel (60 mg) or ticagrelor (180 mg). The procedural anticoagulation was brought about either with heparin or bivalirudin. However, the intra-procedural administration of glycoprotein IIb/IIIa-inhibitor was at the investigator's volition. The procedure was performed according to the standard treatment guidelines of each participating centre. All the patients received dual antiplatelet therapy (aspirin 75-300 mg daily indefinitely and clopidogrel 75 mg daily or prasugrel 10 mg daily or ticagrelor 90 mg twice daily for at least 6 months) after the procedure.

2.4. Endpoints of the Study

The primary end-point of the study wastarget lesion failure (TLF), a miscellany of cardiac death, myocardial infarction (MI), target lesion revascularization (TLR) and target vessel revascularisation (TVR). Stent thrombosis (ST) was also considered as other clinical outcome parameter.These end-points were observed during in-hospital stay, at 30-day, 6-month and 9-month follow-up. TLF will be evaluated as secondary endpoints at 12 and 24 months.

2.5. Definition of Endpoints and Clinical Events

Procedural success was defined in terms of in-hospital TLF. TLF is composed of cardiac death, MI, TLR and TVR. Death can be cardiac or non-cardiac death. Any death due to undetermined cause was reported as cardiac death. The Q-wave MI was considered when there was development of new Q-wave of more than 0.04 seconds in two or more adjoining leads along with increase in cardiac markers like Troponin I or T, creatine kinase or MB isoform. Non Q-wave MI was considered when there was more than three times elevation in creatinine kinase levels along with elevation in MB isoform and Troponin markers T or I without development of new Q-waves.[15] The TLR was considered when there was stenosis in treated segment (5mm proximal and 5mm distal edges). The TVR was considered when there was stenosis in any segment of the treated vessel. The ST was considered acute when it occurred within 24 hours, sub-acute when it occurred between 1 and 30 days, and late when it occurred after 30 days[15].

A "Definite" ST was defined by symptoms suggestive of an acute coronary syndrome and angiographic or pathologic confirmation of stent thrombosis. A "Probable" ST was described as unexplained death within 30 days or target vessel myocardial infarction without angiographic confirmation of stent thrombosis. A "Possible" ST was defined as any unexplained death after 30 day[16].

2.6. Follow-up

All patients were subjected to in-hospital, 30-day, 6-month and 9-month follow-up. Clinical follow-up was scheduled by telephone communication or clinic visit at 30-day, 6-month and 9-month. Follow-up data were collected relating to the clinical status, any hospitalisation and occurrence of any adverse events. Further follow-up are scheduled to be taken at 12- month and at 24-month.

2.7. Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as counts and percentages. The event free survival curve was calculated according to the Kaplan-Meier method **(Figure 2)**. All data were analysed using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 15.

3. Results

3.1. Baseline Demographics and Lesion Characteristics

A total of 170 patients were enrolled in the study. The basic demographic details of the patients are outlined in **Table 1**. The mean age was 50.7±10.2 years and 142 (83.5%) patients were predominantly male. Patients with hypertension and diabetes were 29.4% and 25.9%, respectively. Of the 170 lesions treated, all were type C lesions. A total of 191 stents were implanted at index procedure with an average stent length and diameter of 30.8±8.4 mm and 3.1±0.4 mm, respectively. The mean number of stents implanted per patient was 1.1±0.4. The lesion and angiographic procedural details are outlined in **Table 2.**

3.2. Clinical Outcomes

The cumulative TLF at 9-month was 2.9% which included 1 (0.6%) cardiac death, 1 (0.6%) TLR and 3 (1.8%) MI. There was no case of ST up to 9-month follow-up.The detailed clinical outcomes of the study are outlined in **Table 3.** Long term follow-up of the study would further confirm safety and efficacy.

Table 1: Baseline demographic characteristics

Characteristics	Indolimus SES 170 patients
Age (mean ± SD, yrs)	50.7 ± 10.2
Male, n (%)	142 (83.5%)
Cardiovascular risk	
Diabetes mellitus, n (%)	44 (25.9%)
Hypertension, n (%)	50 (29.4%)
Serum creatinine (mean ± SD, mg/dl)	1.20 ± 0.21
Smoker, n (%)	35 (20.6%)
Family history of CAD, n (%)	6 (3.5%)
Previous stroke, n (%)	2 (1.2%)
Previous MI, n (%)	16 (9.4%)
Previous PCI, n (%)	35 (20.6%)
Previous CABG, n (%)	2 (1.2%)
Clinical presentation	
Stable angina	15 (8.8%)
Unstable angina	39 (22.9%)

SES - Sirolimus-Eluting Stent, CAD- Coronary Artery Disease, MI - Myocardial Infarction, PCI - Percutaneous Coronary Intervention, CABG - Coronary Artery Bypass Grafting

Table 2: Lesion and procedural characteristics

Characteristics	Patients = 170 / Lesions = 170
Lesion location	
Left anterior descending, n (%)	76 (44.7%)
Right coronary artery, n (%)	70 (41.2%)
Left circumflex, n (%)	23 (13.5%)
Left main, n (%)	1 (0.6%)
ACC/AHA lesion classification	
A, n (%)	0 (0%)
B1, n (%)	0 (0%)
B2, n (%)	0 (0%)
C, n (%)	170 (100%)
No. of diseased vessels	
Single vessel disease, n (%)	117 (68.8%)
Double vessel disease, n (%)	42 (24.7%)
Triple vessel disease, n (%)	10 (5.9%)
Total occlusion, n (%)	170 (100%)
Total no. of stent	**N = 191**
No. of stents per patient, (mean ± SD, mm)	1.1 ± 0.4
No. of stents per lesion, (mean ± SD, mm)	1.1 ± 0.4
Average stent length, (mean ± SD, mm)	30.8 ± 8.4
Average stent diameter, (mean ± SD, mm)	3.1 ± 0.4

ACC/AHA - American College of Cardiology/ American Heart Association

Table 3: Cumulative clinical outcomes up to 9-month (n= 170)

	In Hospital	30-day follow-up	6-month follow-up	9-month follow-up
Death, n (%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
Cardiac death, n (%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)
Non-cardiac death, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Myocardial infarction, n (%)	0 (0%)	0 (0%)	2 (1.2%)	3 (1.8%)
Q-wave, n (%)	0 (0%)	0 (0%)	2 (1.2%)	2 (1.2%)
Non Q-wave, n (%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)
TLR, n (%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.6%)
TVR, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
ST, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	**1 (0.6%)**	**1 (0.6%)**	**4 (2.4 %)**	**5 (2.9%)**

TVR - Target Vessel Revascularization; TLR - Target Lesion Revascularization, ST - Stent Thrombosis

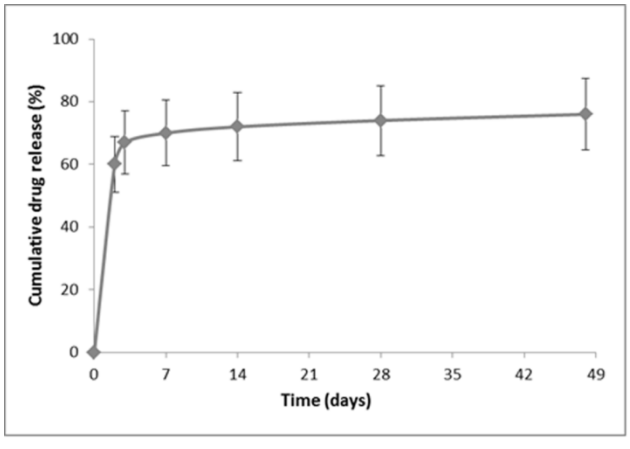

Figure 1: *In-vitro* drug release from Indolimus stent

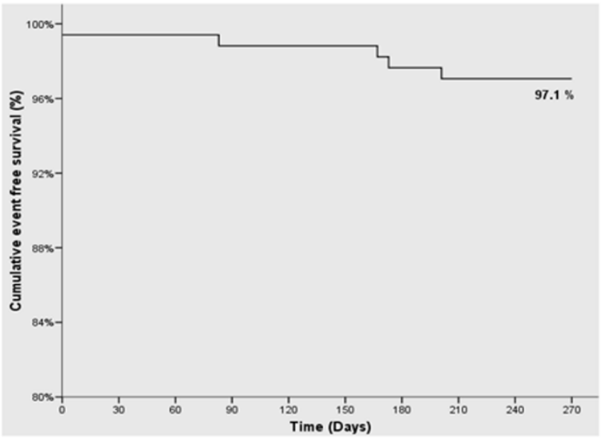

Figure 2: Cumulative event-free survival curve at 9-month follow-up

4. Discussion

PCI of coronary CTOs has historically been limited by technical success rates of 50% to 70%, despite being performed in highly selected cases [17-19]. The major limitation for successful outcome in the intervention of a CTO is the inability to cross the lesion with a wire [7, 20]. In recent years, there have been significant improvements in wire technology, with the development of several specialized wires dedicated to CTO treatment along with advances in CTO-PCI specific experience, which have led to achievement of technical success rates of >80% in more unselected and complex population of CTO patients[5, 21].

There has been escalating interest in percutaneous treatment of CTO in coronary arteries due to evidence that successful treatment of coronary CTO is associated with significant changes in cardiac function and outcome[22]. DES have proved to be superior over BMS even in treating CTOs, which has been stated in many studies that demonstrate significantly fewer adverse events with DES, with drastically less restenosis and need for TLR[13, 23-26].

In the treatment of non-occluded lesions, Indolimus SES markedly reduce the restenosis rate and adverse events, with continued benefit documented up to long term follow-up [27-32]. Similar results can be extrapolated to more complex lesions such as CTOs which has been demonstrated in the present study. Patients with hypertension and diabetes were 29.4% and 25.9%, respectivelyand unstable angina was present in 22.9% patients. The combinations of these factors make the study population peculiarly complex. Regardless of such complications, cumulative TLF at 9-month follow up was found to be only 2.9% which consisted of 1 case of cardiac death, 3 cases of MI and 1 case of TLR.

In the Sirolimus Eluting Stent in Chronic Total Occlusion (SICTO) study, patients with chronic total occlusions >3 months old were treated with SES and showed a TLR rate of 4% and TVR rate of 12% at 12-month follow-up[33]. Suttorp *et al*[24] depicted that the first-choice treatment for total coronary artery occlusions is PCI with the use of a sirolimus-eluting stent, which showed results as 2% MI, 3% TLR, 5% TVR and 2% ST. Another study evaluated the safety and efficacy of various DES with different anti-proliferative agents, on the outcome of patients with CTO. The results represented TLR to be 4.5% for Everolimus-eluting stent, 5.5% for SES, 5.9% for Biolimus-A9, 7.0% for Zotarolimus-eluting stent, 8.3% for Paclitaxel-eluting stent and 17.9% for endothelial progenitor cell (EPC) capture stent at 12-month follow-up[34].

With the advances in perspective, it was often stated that successful recanalization of CTOs of coronary arteries represents the “last frontier” of PCI. This statement was made in regard to the fact that CTOs represent the most technically challenging lesion subset that interventional cardiologists face[35]. However, with magnificent advances in current era, DES implantation has transpired as the preferable technique to treat CTO [24]. We therefore evaluated the clinical outcomes of Indolimus SES implantation in patients with CTO in the real clinical practice.

5. Conclusion

In real clinical practice, treatment of chronic total occlusion with Indolimus sirolimus-eluting stent showed favourable clinical outcomes with high success rates.

Authors’ contribution:

VP, RSP, AS, KT, JP - Literature review and drafting of the manuscript.

All authors had performed interventional procedure, final approval of the version to be published.

All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

Conflict of interest:

The authors declare no conflict of interest

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