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Original Article

A prospective study evaluating efficacy of polymer free Pronova XR stent in treatment of denovo coronary artery stenosis

N.V. Deshpande [a], Parag Admane [b], Mohan Deshpande [b], H.M. Mardikar [c,*]

[a] Director-Cardiac Cath Lab, Spandan Heart Institute and Research Center, Nagpur, India
[b] Clinical Associate, Spandan Heart Institute and Research Center, Nagpur, India
[c] Director, Spandan Heart Institute and Research Center, 31, Off Chitale Marg, Dhantoli, Nagpur 440010, India

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ABSTRACT

Background: Drug eluting stents have remarkably improved results of percutaneous coronary angioplasty. Most of the currently available drug eluting stents uses a durable polymer as drug carrier which has been implicated in local inflammatory response and continued incidence of late and very late stent thrombosis. The Pronova XR stent is one from those new generation polymer free sirolimus eluting stents in which pharmaceutical excipient is used for the timed release of sirolimus from the XR stent platform instead of a polymeric coating.

Methodology: We consecutively recruited 121 patients undergoing elective or urgent PCI at our center. All the patients were followed up clinically and mandatory follow up angiogram at 6 months was done for one third of the total patients. An independent core lab analyzed paired angiograms.

Results: The primary efficacy endpoint was death, MI, TVR at 6 months which occurred in 6.66% patients. The QCA analysis showed reference vessel diameter of 2.5 + 0.44 mm at baseline and the minimal luminal diameter was 0.88 + 0.43 mm giving baseline diameter stenosis of 65.26 + 15.89%. The immediate post procedure in-segment diameter stenosis assessed was 23.68 + 8.96% which increased to 36.02 + 24.48% at follow up with a late lumen loss of 0.25 + 0.76 mm at mean of 191 days.

Conclusion: Coronary angioplasty with polymer free Pronova XR stents results in acceptable late lumen loss and very low target lesion revascularisation at short and intermediate term in unselected patients.

Drug eluting stents (DES) have remarkably improved results of percutaneous coronary angioplasty.[1] Most of the currently available DES use a durable polymer as drug carrier which has been implicated in local inflammatory response and continued incidence of late and very late stent thrombosis.[2–4] A recent study has shown significant reduction in incidence of late stent thrombosis with the newer stent with biodegradable polymer. Consequently, these observations have stimulated

* *Corresponding author*. Tel.: +91 (0) 712 2443333, +91 9823082609 (mobile); fax: +91 (0) 712 2443426.
E-mail addresses: drmardikar@spandanheart.com, drmardikar@cadindia.co.in (H.M. Mardikar).
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development of novel stent systems employing biodegradable polymers as drug carriers or being completely polymer free (PF) DES.[5]

The Pronova XR stent is one from those new generation PF sirolimus eluting stents (SES), in which a pharmaceutical excipient is used for the timed release of sirolimus from the XR stent platform instead of a polymeric coating. Release of drug is maintained uniformly up to 30 days. After this time less than 25% of the drug remains on the surface of the stent. The aim of the present study was to evaluate safety and efficacy of the novel stent system in consecutive patients with denovo coronary lesions in a single center, prospective real world study.

1. Methods

The study was conducted between December 2008 and September 2009 at Spandan Heart Institute and Research Center, Nagpur. Patients undergoing elective or urgent PTCA were enrolled consecutively after obtaining informed consent. The study was conducted in accordance with declaration of Helsinki and the study protocol was approved by Local Ethical Committee of Spandan Heart Institute.

We planned to include 120 patients for the study. Angiographic follow up was planned for 1/3rd of the patients and was defined by a random table at the time of initial PTCA. All patients were followed up for 6 months for clinical outcomes. The study included all patients older than 18 years undergoing elective or urgent PTCA with following exclusions – patients with acute ST elevation MI, Chronic total occlusion, other medical illnesses with life expectancy less than 1 year, known allergy to aspirin or clopidogrel, Pregnancy or lactation and participation in another study. All other patients willing to undergo Pronova XR stent implantation were included after obtaining informed consent.

2. Study procedures and medications

Coronary angioplasty was performed using femoral approach and standard practice. Lesions were predilated using undersized balloons and study stent was deployed at 12 atm pressure. Post dilatation of the stents was performed using non compliant balloon for suboptimal deployment assessed visually. Procedural success was defined as successful delivery of stent at the intended lesion with visual residual stenosis less than 50%.

Patients who were on chronic oral aspirin and clopidogrel therapy did not receive loading of the drugs. Antiplatelet treatment naïve patients received 300 mg of clopidogrel and 325 mg of aspirin at least 2 h before the procedure. Unfractionated heparin was used as anticoagulant, initial dose being 70 IU/kg and subsequent doses administered to keep ACT above 250. Use of Gp IIb/IIIa inhibitors was left to the discretion of the operator. Sheaths were pulled out between 4 and 6 h as soon as ACT declined below 150. Patients were advised to continue aspirin (150 mg) indefinitely and clopidogrel (75 mg BID) for at least 6 months.

Follow up angiogram were performed in 1/3rd of the patients who were scheduled at the time of the index procedure. All other patients were followed up clinically and catheterized if clinically indicated. The paired angiograms were sent to the QCA core lab where further analysis was done. QCA parameters included reference vessel diameter, percent diameter stenosis, minimal luminal diameter, and late lumen loss. Binary re-stenosis was defined as stenosis of >50% or greater of the minimal luminal diameter in the target lesion.

3. Data collection and core laboratory analysis

All the data were submitted to the independent core laboratory which was blinded to the clinical data and procedural information. Digitally recorded coronary angiograms at baseline, immediate post procedure and 6 months were analyzed by the core laboratory using automated edge detection technique. The contrast filled nontapered catheter tip was used for calibration. All angiographic measurements of the target lesion were obtained in the “in-stent” zone, within 5 mm proximal and distal margins to each stent edge, and over the entire segment (“in-segment” zone). The predefined QCA parameters were calculated using Sanders Data System QCA plus software (Palo Alto, CA, USA).

4. Study endpoints

The primary endpoint of the study was clinical outcome (MACE) at the end of 6 months which included Myocardial Infarction (Q or NonQ wave), Death, clinically indicated target vessel revascularization and stent thrombosis (definite, possible or probable). Angiographic in-stent and in segment restenosis along with late lumen loss constituted secondary endpoints.

5. Statistical analysis

Continuous variables were presented as mean and standard deviation. A probability <0.05 was considered to be statistically significant. For angiographic parameters one-sided paired *t*-test or Wilcoxon signed-rank test (depending on normality) was used, because measurements were dependent and direction of difference was known; only the significance of observed differences was investigated.

The primary endpoint and all study endpoints were analyzed on the per-treatment evaluable population. Patients lost in follow up were not included in the denominator for calculations of binary endpoints.

6. Results

One hundred and twenty one patients undergoing elective or urgent PTCA at our center were included in the study. The patient population was predominantly male (103 males and 18 Females). And the mean age of the enrolled patients was

53.8 + 9 years. Eighty percent patients had hypertension and 36% were known diabetics. Additionally 15% patients were detected to be diabetic during the hospitalization. Of the total population 13% were smokers and 8.25% patients had family history of premature coronary artery disease. The details of angina status and LV ejection fraction are summarized in Table 1.

Of the total population, 57% (69 patients) had single vessel disease while double and triple vessel disease was present in 38% (46 patients) and 4.9% (06 patients). Of these 96 patients underwent PTCA to single vessel only while double vessel PTCA was performed on 24 patients (32.6%). One patient underwent triple vessel stenting. A total of 147 lesions were treated with 147 stent implantations (1.22 + 0.4 stents per patients). The average stent diameter was 2.75 + 0.36 mm and average stent length was 22.9 + 8 mm. Sixty stents of the 147 stents implanted were >28 mm. The device success rate was 100%. Details of the vessels stented are shown in Fig. 1.

Six months clinical follow up was available in 119 of 121 patients. One patient died due to sudden cardiac death 2 weeks after PTCA and one was lost to follow up. Follow up angiography was planned for 40 patients of whom 39 underwent angiography at a mean of 191 days after the index procedure. One asymptomatic patient declined follow up angiogram. The core lab provided analysis of 42 lesions in 36 patients. Three angiograms could not be included in the final analysis due to technical difficulties. The QCA analysis showed reference vessel diameter of 2.5 ± 0.44 mm at baseline and the minimal luminal diameter was 0.88 ± 0.43 mm giving baseline diameter stenosis of 65.26 ± 15.89%. The immediate post procedure in-segment diameter stenosis assessed was 23.68 ± 8.96 which increased to 36.02 ± 24.48 at follow up with a late lumen loss of 0.25 + 0.76 mm at mean of 191 days. Other details of QCA are provided in Table 2. The binary restenosis rate according to QCA was 9.52% (4 lesions 42 analyzed).

7. Major adverse events

Total 08 (6.66%) patients suffered major adverse events at the end of 6 months. One patient who underwent bypass surgery 8 years ago with severe LV dysfunction suffered sudden cardiac death 2 weeks after PTCA. Six patients underwent repeat revascularization- one CABG and 5 repeat PTCA for focal restenosis. Of these six patients who underwent repeat revascularization, 3 were from planned angio follow up and 3 patients required symptom driven re angio and revascularization. In addition one patient developed subacute stent thrombosis after he stopped all medications 6 weeks after index PTCA. Overall 93.4% patients were free of any events at 6 month follow up.

We continued to follow these patients and extended follow up was available for 115 patients for 2 years (mean 21 ± 4 months). Four additional events were recorded between 6 months to the last follow up. One additional patient underwent PTCA after 9 months, one patient required CABG after 13 months, one patient succumbed after 10 months (cause could not be ascertained) and one patient developed myocardial infarction in untreated vessel after 14 months. Three additional patients haveing exertional angina, are being managed medically. Thus the 2 year MACE rate in this study was 10.08%.

Table 1 – Angina status.

Recent MI	36.9% ($n = 44$)
Thrombolyzed	30.6% ($n = 37$)
Non-thrombolyzed	05.8% ($n = 07$)
Acute coronary syndrome	28.1% ($n = 45$)
H/o MI	09.1% ($n = 11$)
H/o CABG	01.6% ($n = 02$)
Chronic stable angina	26.4% ($n = 32$)
LV ejection fraction	51.4 + 6.8%
Patients with LVEF <45%	33.1% ($n = 40$)

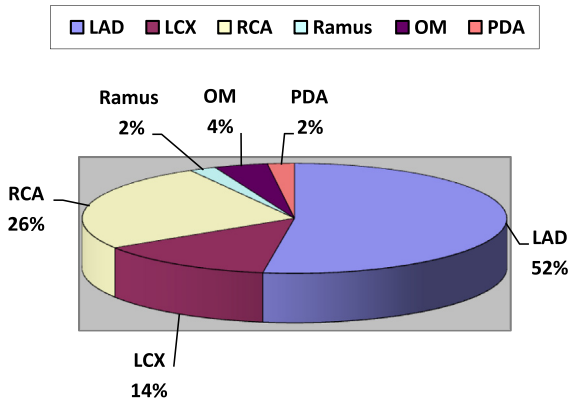

Fig. 1 – Vessels treated.

8. Discussion

This study aimed at establishing a preliminary safety and efficacy of Pronova XR, a novel polymer free sirolimus eluting stent. This was a prospective single center study of patients with denovo lesions with mandatory angiographic follow up in 1/3rd of the enrolled patients at 6 months. The primary endpoint was MACE at 6 months which occurred in 6.66% patients treated with Pronova XR stent. The angiographic restenosis rate in mandatory follow up angiography group was 9.52% and the in-segment late lumen loss noted in these patients was 0.0.25 ± 0.76 mm. Considering the fact that there were very high number of diabetics and the average stent length was of 22.9 + 8 mm these results are in tune with the published results of other contemporary DES.[6] It is also noteworthy that 60 stents out of total 147 stents were longer than 28 mm and the average reference vessel diameter was 2.5 ± 0.44 at baseline. The primary efficacy endpoint was freedom from Death, MI and TVR at the end of 6 months which occurred in 6.66% patients included in the study. The observed MACE rate at 6 months in our study is comparable to LEADERS trial which reported the primary endpoint of death, MI and TVR in 9% patients treated with Biolimus eluting stent

Table 2 – QCA parameters.

	Proximal edge	In-stent	Distal edge	In-segment
Reference vessel diameter (mm)				
Baseline	2.5 ± 0.44			
After procedure	2.81 ± 0.38	2.57 ± 0.35	2.44 ± 0.38	
At FU	2.83 ± 0.57	2.65 ± 0.52	2.55 ± 0.51	
Minimal lumen diameter (mm)				
Baseline	0.88 + 0.43			
After procedure	2.43 ± 0.50	2.2 ± 0.35	1.99 ± 0.41	1.93 ± 0.37
At FU	2.44 ± 0.70	1.84 ± 0.76	2.07 ± 0.64	1.72 ± 0.75
Acute Gain		1.29 ± 0.48		
Late lumen loss (mm)				
At FU	−0.01 ± 0.53	0.36 ± 0.73	−0.1 ± 0.58	0.25 ± 0.76
Diameter stenosis (%DS)				
Baseline	65.26 ± 15.89			
After procedure	13.75 ± 10.53	14.09 ± 9.27	18.36 ± 11.39	23.68 ± 8.96
At FU	14.23 ± 15.79	31.76 ± 24.02	19.26 ± 19.76	36.02 ± 24.48

and 11% in SES at 9 months. Extended follow up of 21 + 4 months in ours study showed MACE rate of 10.08%. These observations are comparable to long term follow up in Resolute All comers study[7] which showed MACE rate of 11.1% and 14.2% in EES and SES at the end of 1 year. Three year follow up of ISAR-TEST 4 study which compared stents with biodegradable polymer to that with durable polymers was reported by Byrne et al.[8] This long term follow up study showed event rate of 20.1% and 20.9% respectively in patients treated with biodegradable polymer DES and durable polymer DES. Our follow up period was shorter (2 years), but shows comparable results to that of ISAR-TEST 4 study. Real world patients have been reported to have higher MACE as compared to the patients included in randomized trials. Cosgrave et al[9] reported real world experience using paclitaxel eluting stents (PES) and sirolimus eluting stents (SES) in patients with denovo lesions. One year follow up showed MACE rate of 21.3% in PES and 21.1% in SES groups. This study included patients with multi-vessel disease, left main disease, bifurcations and diffuse disease. Our population was similar to this with exception of left main disease. Raber et al[10] compared long term outcomes using EES and SES and reported MACE rate of 11.1% and 14.2% in EES and SES groups at the end of 1 year. MACE rate of 10.08% in our study is comparable to these results.

Late lumen loss is identified as a more robust outcome measure than binary restenosis, especially for the smaller stent studies as shown by Mauri et al.[11] Late loss from 0.1 to 0.7 mm predicted incremental binary restenosis according to the observations made by them using 22 clinical trials of DES. The in-stent late lumen loss observed in the current study (0.36 + 0.73 mm) was numerically higher than the late lumen loss observed with the durable polymer-based sirolimus eluting stents like Cypher, or for newer everolimus eluting stents (Xience/Promus) in randomized trials; however it did not translate in increased TLR or clinical events. ISAR-TEST 1 study[12] of ChoiceDES reported LLL of 0.48 + 61 mm, while the subsequent ISAR-TEST 2[13] reported a lower LLL. Another study using hydroxyapatite-based release of sirolimus from the VESTAsync system[14] demonstrated LLL of 0.36 + 23 which is similar to the LLL observed by us in the current study. Late lumen loss observed in real world patients for PES and SES was 0.52 + 0.7 mm and 0.27 + 0.75 mm in the study by Cosgrave et al.[9] Late lumen loss observed by us in the current study is superior to that observed for PES by Cosgrave et al and similar to the late lumen loss for SES.

Binary restenosis observed in our study was 9.52% which is numerically higher than the randomized trials of drug eluting stents. However symptom driven TLR at 6 months was very low occurring in only 4.16% patients (total 5 patients – 2 from mandatory angio follow up and 3 others). TVR at the end of extended follow up in our study occurred in 6.66% patients (8 of the 120 patients). Raber et al[10] reported a TVR of 7.0% and 9.6% at median interval of 1.5 years of the index procedure in EES and SES groups. TVR observed in our study is comparable to EES group and superior to SES group of this study.

9. Conclusions

Coronary angioplasty with the polymer free Pronova XR stent results in acceptable LLL and very low TLR at short and intermediate term in unselected patients.

10. Study limitations

This study was a single center experience using Pronova XR stent with relatively small number of patients. Mandatory follow up angio was performed for 1/3rd patients only. However these patients were scheduled for follow up angio at the time of index angioplasty removing the selection bias for the check angiogram. A multi center trial with larger number of patients will be important to evaluate the stent further.

Conflicts of interest

All authors have none to declare.

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