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Original Article

Drug-eluting balloon: Initial experience in patients with in-stent restenosis (ISR)

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ABSTRACT

Background: In-stent restenosis is the most important limitation of modern coronary angioplasty. Drug-eluting stents solve this problem but at the cost of late stent thrombosis and longer duration of dual-antiplatelet therapy. Drug-eluting balloon (DEB) technology is now available and offers an attractive option for treatment of restenosis.

Methods: A cohort of 20 patients with in-stent restenosis after stenting were treated with a drug-eluting balloon and were followed up clinically and angiographically for 6 months.

Results and conclusion: Procedural success was achieved in all patients. 6 month clinical follow-up was available for all and 6 month angiographic follow up for 17 patients. On 6 month follow-up, 5 of the 20 patients had recurrence of angina and 4 patients had angiographic restenosis (2 focal, 2 diffuse). The mean Canadian Cardiovascular Society angina score improved significantly from 3.1 to 1.1. DEB offers a novel method of treatment for patients with in-stent restenosis with a good safety and efficacy profile.

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Introduction

Restenosis is the “Achilles heel” of modern coronary intervention in the era of almost universal stenting. In-stent restenosis (ISR) is due to aggressive neointimal proliferation leading to a narrowing in the luminal diameter.^{1,2} Drug-eluting stents (DES) have established themselves as the best treatment for restenosis. Drug-eluting stents decrease neointimal proliferation and the need for repeat revascularization; however, late stent thrombosis, dependency on prolonged dual-antiplatelet therapy, and continued restenosis

remain limitations.^{3–5} Drug-eluting balloon (DEB) technology offers an attractive option for treatment of restenosis, without the risk of thrombosis. Paclitaxel was identified as the primary drug for DEB because of its rapid uptake and prolonged retention.⁶ In small clinical randomized trials, paclitaxel-coated balloons have been shown to be safe and effective in reducing restenosis among patients with coronary ISR and de novo femoropopliteal lesions.^{7,8} There is no systematic data on this technique in Indian patients. This study was carried out to document the short term efficacy of drug-eluting balloon in treatment of restenosis following PCI for obstructive CAD in Indian patients.

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Material and methods

Study population and revascularisation procedures: The study population was drawn from the follow-up cohort who had undergone angioplasty and stenting for significant coronary artery disease after 01 Oct 2010. Patients presenting with chronic stable angina (CCS class $\geq$ III) more than six months after initial angioplasty were screened. Patients with left main disease, ostial LAD, ostial LCx disease, and any bifurcation disease were excluded. Conventional coronary angiography was performed in all. Twenty consecutive patients identified as in-stent restenosis were included in the study.

The segment showing in-stent restenosis was first dilated by conventional angioplasty balloon with a balloon:artery ratio of 1:1. All patients then underwent balloon angioplasty with drug-eluting balloon (Aachen Resonance Elutax) with inflation times of at least 1 min. This balloon is coated with 2.0 μ g paclitaxel/mm². The paclitaxel is released by contact with the vessel wall intima during balloon inflation. A balloon performed for at least 30 s ensures a sufficient drug release (95%).

Patients were maintained on dual anti-platelets for 30 days and on aspirin thereafter. All patients were to undergo check angiography six months after the DEB procedure. The institutional review board at the hospital approved the protocol.

Outcome variable and definitions: The primary end point was improvement of Canadian Cardiovascular Society (CCS) angina score (9) at 6 months after the procedure. The secondary end point was occurrence of restenosis on check angiogram at 6 months. Quantitative coronary analysis (QCA) software provided along with the Philips Xcelera catheterization laboratory was used for all angiographic measurements. Stenosis of $\geq$ 50% within the stented segment was defined as in-stent restenosis. Pattern of restenosis was further characterised as focal ($<$ 10 mm) or diffuse ($>$ 10 mm), in-stent (stenosis not extending beyond stent edge) or in-segment (stenosis extending at least 5 mm beyond stent edge). Cardiovascular death, myocardial infarction, and stroke were defined as major adverse events.

Data collection and follow up: Clinical data was recorded in a separate proforma and angiographic data recorded in a dedicated database. All patients were called for clinical follow up at 30 days, 90 days and for follow-up angiogram after 180 days. All those who could not come for clinical follow up were contacted on telephone and symptoms elicited.

Baseline demographic characteristics, risk factor profile, and outcome were noted and results were tabulated and analysed. The CCS score for angina was calculated before procedure and at 6 months after the procedure and the 2 scores were compared by the Wilcoxon signed rank test. *p* value was calculated from the Wilcoxon table for a two tailed test.

Results

A total of 20 consecutive patients were included in the study. Their baseline characteristics are shown in [Table 1](#).

Table 1 – Baseline characteristics.

Age (years)	60.12 years	
Males	75%	15/20
Diabetes	60%	12/20
Hypertension	90%	18/20
Smoking/tobacco use	10%	2/20
Dyslipidemia	60%	12
Family history of premature CAD	20%	4

All patients underwent angioplasty with a DEB catheter. Procedural success was achieved in all patients. Clinical follow-up was available for all and angiographic follow up for 17 patients. The three patients for whom angiographic follow-up was not available had moved out of locality but telephonic follow up was available.

There was significant improvement in the mean CCS score for angina from 3.1 to 1.1 (*p* = 0.024). Recurrence of angina $\geq$ CCS 2 was seen in 5 patients. 4 of these patients underwent the 6 month follow-up angiogram and were found to have restenosis.

17 patients underwent angiographic follow-up; 4 of these 17 patients had angiographic restenosis. Thus the secondary end point of angiographic restenosis was reached in 23.52%. All these 4 patients had recurrence of angina as well. Of these, 2 had focal restenosis and 2 had diffuse restenosis. Both the patients with diffuse ISR had both in-stent and in-segment restenosis. Of the 2 patients with focal restenosis, one patient had edge restenosis and one had in-stent restenosis. All were treated with PCI with a DES successfully. There were no deaths, myocardial infarctions or stroke recorded during the course of the study.

Angiographic analysis revealed that the mean vessel diameter in the intervened segments was 2.86 mm. Lesion length ranged from 8 mm to 60 mm. The balloon size used in these patients ranged from 2.25 to 4.5 mm 19 balloons were used in 17 lesions in 17 patients. 2 patients underwent ballooning with 2 balloons each as the lesion length exceeded the available balloon length. Angiographic characteristics analysed are shown in [Table 2](#).

Discussion

In this study of drug-eluting balloon for the treatment of in-stent restenosis, it was found that short term safety and efficacy were good and that 75% of patients remained free from angina at 6 months after the intervention. There were no major complications reported with the balloon catheter and no major adverse cardiovascular outcomes during the study.

The majority of our patients were male as this study was conducted in an armed forces hospital. The proportion with diabetes is slightly higher as is expected in a subset with restenosis. Hypertension and smoking were similar in proportion to other sub-groups with CAD. The patient subgroup had very high angina load ($\geq$ CCS 3). However, all complex, tortuous lesions and lesions with bifurcation issues were excluded thus the lesion subset represents essentially

Table 2 – Angiographic characteristics.

	Number	Percentage
CAD		
SVD	11	55%
DVD	3	15%
TVD	6	30%
Vessel treated		
LAD	11	55%
LCX	4	20%
RCA	6	30%
Combination of vessels in any	Nil	
Segment of vessel intervened		
Ostial	Nil	
Proximal	4	20%
Middle	16	80%
Distal	Nil	
Lesion morphology		
Average lesion length	26 mm	
Average lesion diameter	2.86 mm	
Complications		
Dissection	Nil	
No reflow	Nil	
Acute closure	Nil	
Groin haematoma	Nil	

restenosis in a straight segment of a small to medium sized vessel in a highly symptomatic group of well followed up patients.

The improvement in the angina score in this study is highly significant and closely matches the angiographic restenosis seen. The follow up period results reveal that angina relief is sustained for a duration of 6 months. The pattern of restenosis seen was diffuse in two patients. This subset probably represents a cohort with propensity for aggressive restenosis as both these patients entered the study with diffuse restenosis. One patient had edge restenosis after DEB suggesting inadequate drug delivery at the edges of the balloon. This issue will need to be explored further in larger studies.

There have been several studies comparing DEB in different subsets. The first report of DEB use in humans was published in 2006.⁷ They have been studied for ISR, compared with plain balloon angioplasty,⁷ DEB followed by bare metal stent and DES.^{8–10} Varied results were found in these studies. DEB was found to be superior to plain balloon angioplasty and DEB followed by bare metal stent. When compared with DES for ISR, superiority of DES was shown in this subset w.r.t angiographic markers (e.g. late lumen loss); however, clinical end-points were comparable.⁹ DEB has also been used for de novo lesions and for the treatment of the side branch in a bifurcation strategy, with acceptable results.¹⁰ **Table 3**

compares various initial studies with DEB along with patient subset.

In the current study, the study population consists of patients with small vessel disease (mean vessel size 2.86 mm sq.), similar to the lesions size in the PEPCAD and PICCOLETTTO studies. Of these, only the PEPCAD II group looked at ISR as the patient subset. Although late luminal loss was not systematically studied in the current study, the 6 month restenosis rate of 23.2% seen is higher than that seen in the PACCOATH trial (binary restenosis: 5%) and the PEPCAD trial (binary restenosis: 20%). However, the mean vessel size in our study was smaller than that in both these studies. One study with the DEB catheter in small vessels (<2.75 mm) in de novo lesions (PICCOLETTTO trial) was noted to have a restenosis rate of 46.2%.

DEB represents an important addition to the treatment options in the treatment of coronary artery disease especially in different subset like ISR, small vessel disease, and patients where stenting is contraindicated. DEB in a de novo lesion is an option but the risks of plain balloon angioplasty (abrupt closure and dissection) limit its use and thus it is often followed by stenting, usually with a bare metal stent. However, segments with restenosis are likely to be stable and less prone to abrupt closure and dissection and thus represent an attractive subset for a trial of a DEB catheter. The exact cause and pattern of restenosis also probably differ between patients undergoing plain balloon angioplasty versus those undergoing stenting.^{5,11}

Current treatment options for in-stent restenosis are plain balloon angioplasty, cutting balloon angioplasty, drug-eluting stents (possibly with a different drug) and drug-eluting balloon catheter. Paclitaxel exerts its potent antiproliferative effect by binding to the beta subunit of tubulin, resulting in arrest of microtubule function. The highly lipophilic character of paclitaxel promotes rapid cellular uptake by enabling it to easily pass through the hydrophobic barrier of cell membranes. Thus, even after a brief, single-dose application at low concentrations results in a long-lasting antiproliferative action.⁶

Conclusion

The study is small and suggests short-term safety and efficacy of the DEB catheter in the treatment of patients with ISR in a patient subset with a relatively straight vessel. Long-term safety and results are not addressed. The balloon is, however, bulky and difficult to deliver in tortuous segments specially when the length of the intended balloon catheter is longer than 20 mm. Performance of the DEB catheter in more complex lesions and the real world remains to be tested. Ideally,

Table 3 – Studies with DEB catheter.^{8,11–13}

Study name	Patient subset	Treatment subsets	End-point	Results
Paccocath	ISR	DEB vs POBA	Late luminal loss (LLL)	DEB better
PEPCAD	De novo lesions	DEB with BMS vs DEB alone	In-segment LLL	DEB better
PEPCAD II	ISR (3 mm dia.)	DEB vs DES	In-segment LLL	DEB better (TLR 6% vs 15%)
PEPCAD III	De novo lesions (2.5–3.5 mm)	DEB vs DES	In stent LLL	DES better
PICCOLETTTO	De novo lesions (<2.75 mm)	DEB vs DES	In stent LLL TLR	DES better

the DEB catheter must be tested against a DES strategy to document equivalence or superiority in ISR subset. The pattern of baseline angioplasty, type of stent used, the deployment pressure of stent placement have not been analysed, however it is unlikely that they would influence the response to treatment of restenosis.

In this small study, the safety and feasibility of DEB for treatment of ISR for Type A and Type B lesions was established. The short-term results are acceptable and definitely superior to the results of plain balloon angioplasty in this subset, that are reported in literature (8). Current strategy for ISR treatment is to use a DES; however, our study has shown efficacy of a DEB in this subset. Ideally, the next step is to perform a randomised, double blinded controlled trial of DEB against DES in patients with ISR in patients in our setup.

Conflicts of interest

All authors have none to declare.

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