July 2012

Safety and Efficacy of Drug-Eluting Balloons in the Treatment of Drug-Eluting In-Stent Restenosis: Experience of a Tertiary Care Hospital

Sajid H. Dhakam
Aga Khan University

Asif Jafferani

Hafeez Ahmed

Nasir Rahman

Ambreen Gowani

Safety and Efficacy of Drug-Eluting Balloons in the Treatment of Drug-Eluting In-Stent Restenosis: Experience of a Tertiary Care Hospital

Sajid Dhakam, MD[1], Asif Jafferani, MBBS[2], Hafeez Ahmed, MBBS[1], Nasir Rahman, MBBS[1], Ambreen Gowani, BScN[1]

ABSTRACT: Background. The advent of drug-eluting balloons (DEBs) is a promising development for coronary revascularization procedures, especially for in-stent restenosis (ISR). This study aims to highlight our experience with DEBs in the treatment of drug-eluting ISR at a tertiary care hospital in Pakistan. **Methods**. All patients presenting to our institution from August 2008 to February 2011 with significant drug-eluting in-stent restenosis (DES-ISR) who were eligible to receive treatment via DEB were included in the analysis. Patient baseline characteristics and angiographic data about the lesion characteristics were obtained. Postprocedural and follow-up endpoints, including cardiac death, myocardial infarction, and repeat revascularization, ie, major adverse cardiovascular events (MACE), were included in the analysis. **Results.** A total of 26 patients received treatment with DEB in the study period, with a significant number having major predisposing factors for the development of ischemic heart disease (IHD; 46% diabetics; 92% hypertensives). The culprit lesion was most commonly identified in the left anterior descending (31%), with presence of American College of Cardiology/American Heart Association lesion type C in 68% of patients. The SeQuent Please paclitaxel-eluting balloon (B. Braun) was used for revascularization. Patients were followed for a median of 16 months. Only 5 patients (19%) developed MACE during this period. **Conclusion.** Our experience demonstrates the effectiveness of DEBs in the treatment of drug-eluting ISR, especially in complex lesions with patients having significant risk factors for development of IHD. However, further studies are needed to define their indications in this role.

J INVASIVE CARDIOL 2012;24(7):335-338

Key words: drug-eluting balloon, SeQuent Please balloon

The drug-eluting balloon (DEB) was designed[1] to address the incumbent issues of neointimal proliferation and stent thrombosis, which are the banes of the established technology of the bare-metal stent (BMS) and drug-eluting stent (DES).[2,3] Theoretically, this device could deliver the drug evenly to the vessel wall, limiting neointimal proliferation and at the same time reducing dependency on long-term anti-platelet therapy for vessel patency.[4] This concept tested favorably in preclinical studies, with adequate delivery of drug from balloon (~90% in 1 minute of inflation),[1] and significant reduction in areas of neointimal proliferation,[1,5,6] diameter stenosis, and late luminal loss.[7] Clinical studies following them are limited; however, they clearly demonstrate a favorable reduction in late luminal loss, restenosis rates, and major adverse cardiovascular events (MACE) in *de novo*[8] and bifurcation lesions.[9] However, their efficacy in lesions with in-stent restenosis (ISR) is the most promising,[10,11] and as such, needs further research to define the adequate place of the DEB in the interventionalist's armament.[12] Hence, this registry aims to determine the safety and efficacy of the use of DEBs in patients with drug-eluting ISR at a tertiary care hospital in Pakistan.

The SeQuent Please DEB (B. Braun) was used primarily in this study. It is a coated balloon delivering paclitaxel directly to the lesion site. Paclitaxel 3 µg/mm^3 is embedded in a hydrophilic, bioabsorbable matrix which, after balloon deflation, adheres to the vessel wall to allow prolonged drug delivery to the lesion site.[4]

Methods

Registry setup. The Aga Khan University Hospital (AKUH) in Karachi is a major tertiary care hospital serving more than 10 million people of Karachi and the surrounding region.[13] The registry was approved by the Institution's Ethics Review Committee. The registry did not receive any external funding. All the patients gave written informed consent for the procedure.

Inclusion/exclusion criteria. All patients who presented to our Institute during the period from August 2008 to February 2011 with angiographic evidence of >50% luminal diameter stenosis ISR with clinical or imaging evidence of ischemia, or >70% luminal narrowing of ISR in the absence of evidence of ischemia in their prior implanted DES, who subsequently underwent treatment with DEB were included. Patients with narrowing in the prior balloon only treated segments were excluded.

Procedural details. All patients received 300 mg aspirin and 300 mg clopidogrel 6 hours preprocedure and had intravenous heparin administered to maintain activated clotting time at >250 seconds during the procedure. Administration of glycoprotein IIb/IIIa inhibitors was left to the physician's discretion.

Technique. A lesion deemed sutiable for treatment with DEB was first prepared with either a compliant or a non-

From the [1]Section of Cardiology, Department of Medicine and the [2]Department of Biological and Biomedical Sciences, Aga Khan University, Karachi, Pakistan.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

Manuscript submitted December 13, 2011, provisional acceptance given January 16, 2012, final version accepted March 27, 2012,

Address for correspondence: Asif Jafferani, MBBS, Department of Biological and Biomedical Sciences, the Aga Khan University, Karachi, B-4, Al-Qahir Apt., Violet Street, Garden East, Karachi 74550, Pakistan. Email: asifahsan_ali@yahoo.co.uk

Table 1. Patient characteristics with those having DES-ISR.

Characteristic	Patients (n = 26)
Age (years)	65.69 ± 12.74
Male	21 (80.8%)
Diabetic	12 (46.2%)
Hypertensive	24 (92.3%)
Dyslipidemic	7 (31.8%)
Chronic kidney disease	4 (18.2%)
Data given as mean ± standard deviation or mean (percentage).	

Table 2. Morphology and lesion characteristics of patients with ISR treated with DEB.

Characteristic	n = 26
Vessel diffusely diseased	12 (46.2%)
Ostial target lesion	4 (15.4%)
Bifurcation lesion	5 (19.2%)
Evidence of calcification	14 (53.8%)
Intracoronary thrombus	2 (7.7%)
Severe tortuosity	4 (15.4%)
Coronary artery disease	
Single-vessel disease	5 (20.8%)
2-vessel disease	8 (33.3%)
3-vessel disease	11 (45.8%)
Treated vessel	
Right coronary artery	6 (23.1%)
Left circumflex	7 (26.9%)
Left anterior descending	8 (30.8%)
Saphenous vein graft	2 (7.7%)
Left main	1 (3.8%)
Obtuse marginal	1 (3.8%)
Diagonal	1 (3.8%)
Stenosis (%)	91.92 ± 9.52
Mean lesion length (mm)	25.63 ± 11.97
Lesion type	
A	0 (0%)
B1	3 (12%)
B2	5 (20%)
C	17 (68%)
Vessel diameter (mm)	3 ± 0.24*
*Data given as numbers (percentages), mean ± standard deviation, or *median ± interquartile range.*	

compliant balloon as per requirement to fully expand the lesion in order to achieve its maximal luminal diameter, according to the reference vessel diameter. DEB was used as the last step for the lesion treatment with no further ballooning done after DEB to ensure maximum availability of the drug delivered to the vessel wall. The balloon-to-artery ratio for the study subjects was kept at 0.9:1. The DEB was inflated at the site of ISR for 60 seconds at its nominal pressure. If the lesion length was large and such a size was not available, then two short-length DEBs were used sequentially to completely cover the lesion. Angioplasty was considered adequate at <20% residual stenosis.

Follow-up and endpoints. All patients were followed in the clinic post discharge. MACE included all postprocedural cardiac deaths, myocardial infarctions (MIs), and need for repeat revascularization.

Statistical analysis. Statistical analysis was carried out using SPSS version 17.0 (SPSS Inc). Continuous variables were presented as mean ± standard deviation (SD) or median ± interquartile range (IQR) and categorical variables were presented as numbers (percentages). No confirmatory analysis was performed.

Results

A total of 26 patients with DES-ISR underwent revascularization using DEB during the study period. Baseline patient characteristics of those having ISR are given in Table 1. Hypertension and diabetes were identified as important risk factors.

Most patients had more than 1 diseased vessel and the target vessel most frequently revascularized was the left anterior descending (LAD) artery. Morphology and lesion characteristics are given in Table 2, while procedure-related details of the DEB used are given in Table 3. No patient required stenting at the lesion treated with DEB.

In-hospital results. No acute postprocedural complications were observed, including no-reflow and dissection. During the hospital stay, 1 patient developed cardiogenic shock and died. No other patients developed MACE; however, 4 patients still had angina symptoms and were managed medically.

Follow-up results. Patients were followed for a median of 16 months; during this time, 8 patients continued to remain symptomatic, of which 4 patients developed MACE, with 1 presumed cardiac death and 3 revascularizations. Therefore, the total MACE rate was 19%. There were also 2 deaths due to proven non-cardiac causes in the follow-up period; 1 with epidural tuberculous abscess and 1 secondary to cerebral hemorrhage almost 1.5 years after the procedure. The remaining patients considered symptomatic had complaints of chest discomfort, with no objective evidence for the presence of ischemia or MI. Details of the above, including MACE rates, are given in Table 4.

Discussion

DEB development has been one of the most promising approaches for the treatment of ISR lesions. In the first clinical study for DEB, the PACCOCATH ISR I trial, the paclitaxel-eluting balloon was compared with an uncoated balloon for the treatment of coronary ISR. Six-month post-

Table 3. Procedural details of DEB use in ISR.

Procedure	n = 26
Balloon size x length (mm)	
2.5 x 17	2
2.5 x 26	2
2.75 x 20	1
3.0 x 17	1
3.0 x 20	3
3.0 x 26	5
3.0 x 30	5
3.25 x 26	1
3.25 x 30	1
3.5 x 26	2
3.5 x 30	3
Residual stenosis (%)	11.54 ± 9.25
Data given as numbers or mean ± standard deviation.	

Table 4. Complications in patients undergoing revascularization with DEB.

Complication	In-Hospital Rates (n = 26)	At Follow-up (n = 25)
Bleeding	1 (3.8%)	—
Angina symptoms	4 (15.4%)	8 (32%)
Postprocedural mortality Cardiac Non-cardiac	 1 (3.8%) —	 1 (4%) 2 (8%)
CABG required	—	3 (12%)
RePTCA required	—	
CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.		

angiography follow-up showed a significantly decreased late lumen loss in the coated balloon groups.[10] Results of the PACCOCATH ISR I and II trials, both of which had identical protocols, were pooled to get a larger sample size and longer follow-up period. These results further confirmed the previous, with lower rates for binary restenosis and MACE in the coated-balloon group until 2 years.[11]

However, the real question remained about the relative efficacy and safety of the DEB as compared to the DES, which is the standard of care in lesions with ISR. This was answered in the PEPCAD II trial, comparing the SeQuent Please paclitaxel-eluting balloon with a paclitaxel-eluting stent (Taxus Liberté) in lesions with ISR. At 6-month follow-up, the trial showed a lower late lumen loss in the DEB group, with lower binary restenosis rates.[14] Thus, the DEB was at least as safe and efficacious as the DES in patients with ISR.

It must be remembered that while the PEPCAD II trial enrolled patients with ISR in BMS,[14] data are still accumulating on the role of DEB in DES-ISR. It is well known that ISR occurring in DES is more difficult to treat, with further DES in this situation also having higher MACE and revascularization rates.[15-17] A recent report by Raja et al demonstrates their experience in the use of SeQuent Please DEB in the treatment of DES-ISR for bifurcating lesions.[18] Further experience comes for another DEB technology with the Dior (Eurocor), which was evaluated by a Spanish multicenter registry evaluating 1-year outcomes for ISR in both BMS as well as DES.[19] Results were favorable in both groups, with a MACE rate of 16.7%; however, the DES group had a non-significant trend toward higher MACE at 1 year. In the same vein, a larger multicenter registry published their data on the use of the Dior in ISR lesions in BMS as well as DES.[20] Their results also demonstrated a favorable cumulative MACE rate of 11.5% at 7.5 months follow-up. Recent studies on the SeQuent Please include the PEPCAD-DES, and data from this trial reported at the Transcatheter Cardiovascular Therapeutics (TCT) 2011 conference showed the SeQuent Please to be superior to plain old balloon angioplasty in preventing late lumen loss (0.43 ± 0.61 mm vs 1.03 ± 0.77 mm, respectively; *P*<.001) and binary restenosis (17.2% vs 58.1%, respectively; *P*<.001) in DES-ISR lesions at 6-month angiographic follow-up.[21]

As this is a relatively new technology, DEBs have not been adequately evaluated in different patient populations with different risks and baseline characteristics. Of note is the fact that in this registry, there was a significantly larger number of patients with diabetes as compared to the patient populations enrolled in the previously discussed trials. Diabetes is known to be a risk factor for developing ISR,[19,22,23] and results from this study support the fact that the DEB prevents development of binary restenosis in patients with diabetes, among other cardiovascular risk factors. Furthermore, patients had fairly complex lesions and this may have resulted in the slightly higher rate for MACE as compared to those reported in other registries.

Study limitations. This study has several limitations that must be taken into account. The registry size was relatively small; thus, it may not reflect all the ramifications of treatment with DEB for such patients. However, since research into the role of DEBs in treating DES-ISR lesions is still in its infancy, it remains for designed well-powered trials to truly establish its role for this indication. Also, our patients did not undergo follow-up angiography to determine if the procedure had remained successful and thus, those who presented with mortality may not actually have the DEB-treated lesion as the culprit for MACE. This follow-up was, however, beyond the resources of this study.

Conclusion

The DEB appears to be a promising technology for ISR, especially of the DES. Our experience, however, illustrates the need for further evidence in terms of randomized trials in different patient populations with results stratified to take into account established risk factors for ISR, and further elucidation of patient characteristics of those developing MACEs and mortality after the DEB procedure, before

its indications can be better identified to serve the patient population at large.

References

1. Scheller B, Speck U, Abramjuk C, et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. *Circulation.* 2004;110(7):810-814.
2. Hoffmann R, Mintz GS, Dussaillant GR, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation.* 1996;94(6):1247-1254.
3. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med.* 2007;356(10):998-1008.
4. De Labriolle A, Pakala R, Bonello L, et al. Paclitaxel-eluting balloon: from bench to bed. *Catheter Cardiovasc Interv.* 2009;73(5):643-652.
5. Cremers B, Biedermann M, Mahnkopf D, et al. Comparison of two different paclitaxel-coated balloon catheters in the porcine coronary restenosis model. *Clin Res Cardiol.* 2009;98(5):325-330.
6. Cremers B, Speck U, Kaufels N, et al. Drug-eluting balloon: very short-term exposure and overlapping. *Thromb Haemost.* 2009;101(1):201-206.
7. Albrecht T, Speck U, Baier C, et al. Reduction of stenosis due to intimal hyperplasia after stent supported angioplasty of peripheral arteries by local administration of paclitaxel in swine. *Invest Radiol. 2007*;42(8):579-585.
8. Cortese B, Micheli A, Picchi A, et al. Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO study. *Heart.* 2010;96(16):1291-1296.
9. Fanggiday JC, Stella PR, Guyomi SH, Doevendans PA. Safety and efficacy of drug-eluting balloons in percutaneous treatment of bifurcation lesions: the DEBIUT (drug-eluting balloon in bifurcation Utrecht) registry. *Catheter Cardiovasc Interv. 2008*;71(5):629-635.
10. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med. 2006*;355(20):2113-2124.
11. Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *Clin Res Cardiol.* 2008;97(10):773-781.
12. Banning AP, Lim CC. Drug-eluting balloons: what is their place on the interventionalist's shelf? *Heart.* 2010;96(16):1257-1258.
13. Tariq M, Jafri W, Ansari T, et al. Medical mortality in Pakistan: experience at a tertiary care hospital. *Postgrad Med J.* 2009;85(1007):470-474.
14. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation.* 2009;119(23):2986-2994.
15. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J Am Coll Cardiol.* 2010;55(24):2710-2716.
16. Steinberg DH, Gaglia MA Jr, Pinto Slottow TL, et al. Outcome differences with the use of drug-eluting stents for the treatment of in-stent restenosis of bare-metal stents versus drug-eluting stents. *Am J Cardiol.* 2009;103(4):491-495.
17. Levisay JP, Price MJ, Shaba W, et al. Longer-term outcomes of paclitaxel stent implantation as an initial treatment strategy for sirolimus-eluting stent restenosis. *J Invasive Cardiol.* 2010;22(5):216-219.
18. Raja Y, Doshi SN, Townend JN. Kissing drug eluting balloons for in-stent restenosis complicating bifurcations treated with drug-eluting stents. *Catheter Cardiovasc Interv.* 2012;79(3):392-396.
19. Vaquerizo B, Serra A, Miranda-Guardiola F, et al. One-year outcomes with angiographic follow-up of paclitaxel-eluting balloon for the treatment of in-stent restenosis: insights from Spanish multicenter registry. *J Interv Cardiol.* 2011;24(6):518-528.
20. Stella PR, Belkacemi A, Waksman R, et al. The Valentines trial: results of the first one week worldwide multicentre enrollment trial, evaluating the real world usage of the second generation DIOR paclitaxel drug-eluting balloon for in-stent restenosis treatment. *EuroIntervention.* 2011;7(6):705-710.
21. Rittger H. A prospective, randomized trial of a paclitaxel coated balloon vs. uncoated balloon angioplasty in patients with drug-eluting stent restenosis: PEPCAD-DES study. Presented at *Transcatheter Cardiovascular Therapeutics* 2011: San Francisco, CA.
22. Abizaid A, Kornowski R, Mintz GS, et al. The influence of diabetes mellitus on acute and late clinical outcomes following coronary stent implantation. *J Am Coll Cardiol.* 1998;32(3):584-589.
23. Kastrati A, Schomig A, Elezi S, et al. Predictive factors of restenosis after coronary stent placement. *J Am Coll Cardiol.* 1997;30(6):1428-1436.