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Sajid H. Dhakam
Aga Khan University

Asif Jafferani

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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, Asif Jafferani, MBBS, Hafeez Ahmed, MBBS, Nasir Rahman, MBBS, Ambreen Gowani, BScN

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. 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 primarily in this study. It is a coated balloon delivering paclitaxel directly to the lesion site. Paclitaxel 3 µg/mm³ 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. 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.

Key words: drug-eluting balloon, SeQuent Please balloon

The drug-eluting balloon (DEB) was designed to address the incumbent issues of neointimal proliferation and stent thrombosis, which are the bane of the established technology of the bare-metal stent (BMS) and drug-eluting stent (DES). 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. This concept tested favorably in preclinical studies, with adequate delivery of drug from balloon (~90% in 1 minute of inflation), and significant reduction in areas of neointimal proliferation, diameter stenosis, and late luminal loss. 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 and bifurcation lesions. However, their efficacy in lesions with in-stent restenosis (ISR) is the most promising, and as such, needs further research to define the adequate place of the DEB in the interventionist’s armament. 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/mm³ 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.
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-
Thus, the DEB was at least as safe as the DES, which was evaluated by a Spanish multicenter registry evaluating 1-year outcomes for ISR in both BMS as well as DES. 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. 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.

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, and 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

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**Table 3. Procedural details of DEB use in ISR.**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n = 26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon size x length (mm)</td>
<td></td>
</tr>
<tr>
<td>2.5 x 17</td>
<td>2</td>
</tr>
<tr>
<td>2.5 x 26</td>
<td>2</td>
</tr>
<tr>
<td>2.75 x 20</td>
<td>1</td>
</tr>
<tr>
<td>3.0 x 17</td>
<td>1</td>
</tr>
<tr>
<td>3.0 x 20</td>
<td>3</td>
</tr>
<tr>
<td>3.0 x 26</td>
<td>5</td>
</tr>
<tr>
<td>3.0 x 30</td>
<td>5</td>
</tr>
<tr>
<td>3.25 x 26</td>
<td>1</td>
</tr>
<tr>
<td>3.25 x 30</td>
<td>1</td>
</tr>
<tr>
<td>3.5 x 26</td>
<td>2</td>
</tr>
<tr>
<td>3.5 x 30</td>
<td>3</td>
</tr>
<tr>
<td>Residual stenosis (%)</td>
<td>11.54 ± 9.25</td>
</tr>
</tbody>
</table>

Data given as numbers or mean ± standard deviation.

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**Table 4. Complications in patients undergoing revascularization with DEB.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>In-Hospital Rates (n = 26)</th>
<th>At Follow-up (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>1 (3.8%)</td>
<td>—</td>
</tr>
<tr>
<td>Angina symptoms</td>
<td>4 (15.4%)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Postprocedural mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>1 (3.8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Non-cardiac</td>
<td>—</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>CABG required</td>
<td>—</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>RePTCA required</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.
its indications can be better identified to serve the patient population at large.

References