

Treatment of Coronary In-stent Restenosis with Drug-eluting Balloon Catheter: Real-world Outcome and Literature Review

Dear Editor,

Currently, coronary stent implantation is employed in approximately 90% of percutaneous coronary intervention (PCI) cases. Despite the use of drug-eluting stents (DES), coronary in-stent restenosis (ISR) remains an Achilles' heel of PCI and can occur in about 10% of patients in the real-world population.^{1,2} We explored the efficacy of a novel approach using drug-eluting balloon (DEB) in the treatment of our patients with ISR.

Materials and Methods

A total of 53 patients who presented to the National University Heart Centre, Singapore, with coronary ISR between March 2008 and March 2010, and underwent repeat PCI, were studied. All patients presented with symptoms and evidence of coronary ischaemia. In-stent restenosis was defined as a diameter stenosis of >50% within the stented segment based on quantitative coronary angiography. All patients received adequate antiplatelet therapy prior to the procedure, which included a loading dose of 300 mg clopidogrel on the day before the index procedure or a 600 mg dose immediately before the PCI and aspirin 100 mg a day. The PCI procedure entailed initial lesion dilation with conventional balloon catheter or cutting balloon. This was followed by the use of a DEB; second generation DIOR™ DEB (Eurocor GmbH, Germany) or SeQuent™ Please DEB (B Braun Melsungen, Germany). The DIOR™ balloon contained 3 µg of paclitaxel/mm² within a nanoporous balloon surface with paclitaxel microcrystals embedded in a shellac coating. The SeQuent Please™ DEB was coated with the same concentration of paclitaxel using iopromide as a hydrophilic spacer. The size of the DEB was selected so as to achieve a balloon-to-vessel ratio of 1:1 and a longer length than the lesion to cover any area that had been treated by the initial balloon dilatation in order to avoid geographical miss. Prolonged inflation of the DEB for the duration of 40 to 60 seconds was carried out to ensure adequate drug delivery. Patients received dual antiplatelet therapy of aspirin 100 mg and clopidogrel 75 mg for 1 month after the procedure. No patients received additional stent implantation after DEB dilatation.

Procedural success was defined as residual stenosis of <30% of the luminal diameter with TIMI grade III antegrade flow. Clinical follow-up was achieved by means of telephonic interviews, outpatient follow-ups or hospital records. The study endpoints were major adverse cardiac events (MACE) of death, myocardial infarction (MI), repeat target vessel revascularisation (TVR) and stent thrombosis at 1- and 6-month follow-ups.

Results

A total of 53 patients were enrolled in this study. The mean age of the patients was (59.7 ± 10.7) years, and males constituted 83.0% of the cohort. Diabetes mellitus was present in 26 (49.1%) patients.

Among these patients, 19 (35.2%) received prior DES. The majority (n = 40, 75.5%) of the ISR patterns were of the diffusely proliferative type. A total of 44 (83.0%) patients were treated with DIOR™ DEB, while the rest were treated with Sequent Please™ DEB. The diameter of the pre-procedural reference vessel was (2.5 ± 0.6) mm, and the minimal luminal diameter was (0.4 ± 0.3) mm. The mean lesion length was (23.5 ± 11.5) mm. The mean DEB size used was (3.1 ± 0.4) mm in diameter and the mean pressure and time of inflation were (15.6 ± 1.7) atmospheres and (45.7 ± 8.5) seconds, respectively. Except for one patient with significant residual stenosis of 46% and TIMI grade II flow, primary procedural success was achieved in all patients. The post-procedural mean minimal luminal diameter was (2.7 ± 0.5) mm, and the mean residual stenosis was (7.5 ± 7.1)% in the remaining 52 patients (98.1%). No major procedural or in-hospital complications occurred in the cohort.

At follow-up of all the patients, the rates of MACE at 1-month and 6-month follow-up were 1.9% and 9.4%, respectively (Table 1). The MACE was driven by recurrent MIs. There was no angiographically-documented stent thrombosis. The TVR was 7.5% at 6 months for the whole cohort. Among the 4 patients who underwent TVR, 3 had bare-metal stents (BMS) previously implanted. Two out of the 4 patients were diabetics.

Table 1. Results of Clinical Follow-up (n = 53)

Variable	No. (%)
Target vascular revascularisation	
At 1 month	1 (1.9%)
At 6 months (2 CABG)	4 (7.5%)
Myocardial infarction	
At 1 month	0 (0.0%)
At 6 months	4 (7.5%)
Death	
At 1 month	0 (0.0%)
At 6 months	0 (0.0%)
Stent thrombosis	
At 1 month	0 (0.0%)
At 6 months	0 (0.0%)
MACE no. (%)	
At 1 month	1 (1.9%)
At 6 months	5 (9.4%)

CABG: coronary artery bypass graft; MACE: major adverse cardiac events

Discussion

We presented the clinical results of real-world patients treated with DEB for their ISR, which showed a low rate of MACE at 6 months of 9.4% and TVR of 7.5%. While there was no routine angiographic follow-up for this cohort of patients, the low event rate reflected the true clinical outcomes and avoided any potential oculo-stenotic reflex, which could spuriously drive TVR.

Coronary ISR is largely due to neointimal hyperplasia, although stent under-expansion may account for some of the cases. The optimal treatment for coronary ISR remains undefined, with a variety of treatment options evaluated earlier. These include the use of conventional balloon or cutting balloon angioplasty, excimer laser, high-speed rotational atherectomy, directional coronary atherectomy, intracoronary brachytherapy, repeat stent implantation, all of which had been previously employed with limited efficacy. The use of DEB angioplasty offers a simpler alternative with a shorter procedural time and dual antiplatelet duration. The DEB used in our study was coated with paclitaxel, a highly lipophilic drug, which has high absorption and retention rates and is able to exert a sustained effect despite a short contact time with the vessel wall. Paclitaxel, unlike sirolimus, has a cytotoxic effect, which acts by binding specifically to the beta-tubulin subunit of microtubules, preventing their depolymerisation. It appears to be the drug of choice for current DEBs, given its unique and favourable properties. The good results with the use

of DEB in our study is encouraging, given the high-risk nature of this group of patients for recurrent restenosis, and that dual antiplatelet therapy was administered for only 1 month. A total of 4 (7.5%) patients had NSTEMI events at the 6-month follow-up, with 2 (3.8%) patients undergoing repeat revascularisation in the form of coronary artery bypass surgery.

DEB may be applied in patients who develop ISR following both bare metal stent (BMS) and DES implantation, although the therapy is more efficacious in the former group. In the Valentines trial, which used the second generation DIOR™ DEB in treating 276 patients with ISR, the rate of target lesion revascularisation (TLR) in patients treated with DEB for ISR after prior BMS implantation was 5.1% while the rate was 10.8% for the DES group.³ In our study, there were more patients who had prior BMS implanted that required TVR after DEB therapy, compared with DES (3 vs 1). Published reports of comparison of DEB with DES for treatment of patients with ISR showed that DEB is as efficacious as DES.⁴ Importantly, it demonstrated that the inhibition of restenosis does not require a second stent implantation. Based on current evidence, the ESC has given a Class IIa recommendation for the use of DEB in patients with ISR after receiving BMS.⁵

Limitation

The limitations of our study included its small sample population and short duration of clinical follow-up. Selection bias for patients treated with DEB cannot be excluded as it is based on operators' decision.

Conclusion

Our study has shown that the use of DEB is feasible and effective in reducing the need for repeat intervention in patients with ISR. Drug-eluting balloon has the added advantage of simplifying the treatment of ISR while at the same time avoiding the addition of a second layer of metal and reducing costs. As of now, DEB may be employed as the first choice approach for the treatment of most cases of coronary ISR.

REFERENCES

1. Zahn R, Hamm CW, Schneider S, Zeymer U, Nienaber CA, Richardt G, et al. Incidence and predictors of target vessel revascularisation and clinical event rates of the sirolimus-eluting coronary stent (results from the prospective multicenter German Cypher Stent Registry). *Am J Cardiol* 2005;95:1302-8.
2. Mauri L, Silbaugh TS, Wolf RE, Zelevinsky K, Lovett A, Zhou Z, et al. Long-term clinical outcomes after drug-eluting and bare-metal stenting in Massachusetts. *Circulation* 2008;118:1817-27.
3. Stella PR, Belkacemi A, Waksman R, Stahnke S, Torguson R, von Strandmann P, et al. The Valentines Trial: results of the first one week worldwide multicentre enrolment trial, evaluating the real world usage of the second generation DIOR paclitaxel drug-eluting balloon for in-stent restenosis treatment. *EuroIntervention* 2011;7:705-10.
4. Unverdorben M, Vallbracht C, Cremers B, Heuer H, Hengstenberg C, Maikowski C, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* 2009;119:2986-94.
5. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on Myocardial Revascularization. *Eur Heart J* 2010;31:2501-55.

Hong Yuan Xia, ¹*MD* Adrian FH Low, ²*MBBS* Chi Hang Lee,
²*MD, FRCP* Swee Guan Teo, ²*MBBS, MRCP* Mark Chan, ²*MBBS, MHS*
 Koo Hui Chan, ²*BM, MRCP, MD* Huay Cheem Tan, ²*MBBS, MMed,*
FRCP

¹Cardiac Department, The 4th Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China

²National University Heart Centre, National University Health System, Singapore

Address for Correspondence: Dr Tan Huay Cheem, Cardiac Department, National University Heart Centre, Singapore, 1E Kent Ridge Road, NUHS Tower Block, Level 9, Singapore 119228.
 Email: Huay_Cheem_Tan@nuhs.edu.sg