



The current status of drug-coated balloons in in-stent restenosis treatment

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Abstract Restenosis after angioplasty has always been a significant problem in interventional cardiology and is associated with significant morbidity and costs, with a wide spectrum of clinical presentation. The population treated with bare metal stents and drug eluting stents is very large and because of the complex subset of patients and lesions the overall rate of in-stent restenosis remains significant. For interventional cardiologist several treatment options are available nowadays such as repeat stenting, balloon angioplasty, drug-coated balloons but due to lack of precise guidelines the management remains challenging. In this paper authors provide comprehensive review of novel technique in in stent restenosis treatment: drug eluting balloons.

Key words in-stent restenosis, drug eluting balloons, drug coated balloons.

Introduction

Percutaneous coronary interventions (PCI) has evolved to the mainstream revascularization method far outnumbering coronary artery bypass grafting (CABG). However, the major drawback of PCI is a higher rate of target lesion revascularization (TLR) in comparison to CABG due to in-stent restenosis. Restenosis after angioplasty has always been a significant problem in interventional cardiology and is associated with significant morbidity and costs, with a wide spectrum of clinical presentation. The disadvantages of balloon angioplasty has been removed when bare metal stents (BMS) were invented. The introduction of these devices significantly reduced restenosis after angioplasty. Development of drug eluting stents (DES) another milestone in treatment of patients with coronary artery disease. The high efficacy of these devices in prevention of restenosis compared with bare metal stents has allowed percutaneous coronary intervention to be used in complex lesions. Introduction of DES reduced the number of target lesion revascularizations but did not eliminate the in-stent restenosis (ISR). The population treated with BMS and DES is very large¹ and because of the complex subset of patients and lesions the overall rate of ISR remains significant. Although several treatment options are available nowadays such as repeat stenting, balloon angioplasty (BA), drug-coated balloons (DCB) there it is always a dilemma for interventional cardiologist which devices to use, so management remains challenging. We provide comprehensive review of novel technique in ISR treatment: drug eluting balloons (DEBs).

Definition

Restenosis is defined as reduction of $\geq 50\%$ of lumen diameter after PCI at follow-up angiography. Although this definition was used as end point in large number of clinical trials it has to be emphasized that apart from angiographic findings clinical manifestation of ischemia plays significant role in decision of treatment.

Pathophysiology

After stent implantation, which damages the endothelium and leads to regional and systemic inflammatory reaction, process of neointima proliferation begins and in months leads to neointimal hyperplasia². Stent underexpansion or not optimal atherosclerotic plaque coverage with stent favors ISR. But according to the latest findings it seems that one more factor is responsible for ISR, especially in late stage - neoatherosclerosis³. What is interesting novel atherosclerotic plaques are formed faster in drug eluting stent (after one year) than in bare metal stent (after four years). Detailed description of pathophysiology of ISR will not be the subjects of this paper. Type of ISR and cause of its occurrence determines its treatment.

Treatment

When treating ISR we should take several possibilities into consideration and these are: optimal medical therapy (OMT), balloon angioplasty, stenting (BMS, the same DES, different DES), DEB and cardiac surgery. In first human trial on DEB - a PACCOATH ISR I/II patients with BMS-ISR were randomized to Paccocath DEB versus standard balloon angioplasty. After 6 months major cardiac

events (MACE) appeared in 4% in DEB arm and 31% in BA group⁴. After 24 months observation MACE rated 11% vs 46% and target lesion revascularization (TLR) 6% and 37% respectively in DEB and BA arm⁵. In other trial on drug-coated balloons use of DEB resulted in smaller late lumen loss (LLL) in BMS restenosis to compare with DES restenosis (-0,05 vs 0,19 mm respectively) what reflected in fewer revascularizations at one year (2.4 vs 17.1% respectively)⁶. Similarly, both the Spanish DIOR and the SeQuent Please registries^{7, 8} highlighted better clinical outcomes with BMS ISR compared to DES ISR. However, outcomes of paclitaxel versus non-paclitaxel DES ISR treated with Sequent Please did not differ (TLR: 8.3% versus 10.8%; P=0.46). Perhaps the efficacy of drug coated balloons in treating BMS ISR reflects the fact that a drug is introduced for the first time, whereas DCB is less efficacious in a 'drug-resistant' vessel manifesting DES ISR. Another reason could be that drug eluting stents are implanted in complex lesions which predisposes to restenosis. Comparison of drug-coated balloons with drug eluting stents (SeQuent Please, B. Braun versus TAXUS stent by Boston Scientific) in management of in-BMS restenosis was analyzed in PEPCAD II trial which demonstrated non-inferiority. After 6 months of follow up late lumen loss was estimated as 0,38±0,61 mm in DES and 0,17±0,42 mm in DEB (P=0,03) and binary restenosis respectively 20% i 7% (P=0,03). After 12 months of observation MACE appeared in 22% in DES and 9% in DEB group (P=0,08)⁹. In recently published German consensus on drug-coated balloon [10] authors suggest to treat BMS in-stent restenosis with drug-coated balloons leaving DES as a bailout therapy when dissection after predilatation appears with TIMI flow < III or when residual stenosis exceeds 30%. The used DEB should extend 2-3 mm beyond the pre-dilated area, balloon/vessel ratio should equal 0.8-1.0 and pressure 8-10 atm, whereas time of inflation must not be shorter than 30 second. The authors suggest predilatation with conventional balloon not longer than stent if ISR is restricted to stent, with diameter approximately 0.5 mm smaller than vessel diameter and with nominal pressure. Second conventional balloon should be shorter than stent with balloon to vessel diameter ratio 0.8-1.0 and inflated with pressure 12-16 atm. The European guidelines give DEB class IIa and level of evidence B in bare metal stent restenosis treatment¹¹.

In DES ISR situation is more complicated and there is now clear evidence what kind of management gives the best results. There is evidence that implantation of another DES is better than BA¹². ISAR DESIRE 2 study was designed to answer the question whether we should use stent eluting the same or alternative drug. There was no difference between sirolimus eluting stent (SES) or paclitaxel eluting stent (PES) in LLL, TLR or binary restenosis¹³. In other trial, PEPCAD-DES¹⁴, where DEB and BA in treatment DES ISR were compared the TLR and MACE rated significantly lower in group of drug-coated balloon (16.7% vs 50% and 15.3% vs 36,8% respectively). The treatment with DEB resulted with significantly lower LLL (0.43 versus 1.03 mm) and restenosis (17.2% versus 58.1%). Finally in recent ISAR DESIRE 3 study¹⁵ the comparison of all three methods (BA, DEB, DES) in

treatment of DES in-stent restenosis was made. There was no difference between diameter stenosis between DEB and DES (38% and 37.4% respectively) and both methods were superior to BA (54.1%). In terms of binary stenosis DEB and DES were comparable (26.5% and 24.0%) and superior to BA (56.7%). As for TLR in DEB 22.1%, in DES 13.5% (P=0.09), in BA 43.5%. That led authors to conclusion that in patients presenting with 'limus'-DES restenosis, DEB therapy is non-inferior to repeat stenting with PES. Both DEB and PES therapy are superior to balloon angioplasty alone.

It may seem counterintuitive that short balloon inflation with DEB can be superior to DES which have a longer duration of drug but delivery there are several theoretical advantages of DEB:

- avoiding the problem of permanent implant causing inflammation and hypersensitivity reaction
- delivery of antiproliferative medication when needed, for instance immediately after the barotraumas induced by balloon angioplasty
- avoiding multiple layers of stent
- avoiding the potential risk of corrosion of the stent: the mechanical friction between overlapping stents and chemical reactions between dissimilar alloys if mixing different stent types could lead to corrosion. Stent alloys form a protective oxide film, insulating the stent struts from the corrosive body fluids. There is a risk of mechanical damage of the oxide film caused micromotion at point of stent overlap. If this protective film is getting scratched off by overlapping stent struts the underlying stent struts get exposed and may undergo corrosion.
- overlapping stents of different alloys could theoretically lead to galvanic corrosion. This can be avoided by DEB. However, these concerns are rather theoretical, there is no clinical evidence which indicates a problem of using different types of overlapping stents¹⁶.

Conclusion

By obviating the need for additional stent implantation treatment with a drug-eluting balloon may be the treatment of choice in patients presenting with 'limus'-DES restenosis. In bare metal stent restenosis the drug-coated balloon should be the golden standard therapy leaving DES implantation only as bailout therapy. Balloon angioplasty can be successfully used when stent under-expansion diagnosed with IVUS is cause of ISR and when dealing with focal restenosis.

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