Journal of Indian College of Cardiology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Indian College of Cardiology

journal homepage: www.elsevier.com/locate/jicc

Drug-eluting balloons (DEB) for the treatment of femoropopliteal occlusive diseases

M. Henry[a,b,*], I. Henry[c]

[a] Cardiology, Luxembourg
[b] Asia Pacific Vascular Society, India
[c] Polyclinique Bois-Bernard, 62 320 Bois-Bernard, France

ARTICLE INFO

Article history:
Received 26 May 2017
Accepted 10 June 2017
Available online xxx

Keywords:
Femoro popliteal diseases
Angioplasty
Drug eluting balloons

1. Introduction

Femoropopliteal occlusive diseases are the most common cause of claudication. The lesions are often diffuse even when only focal disease is angiographically apparent and typically bilateral. These lesions are often progressive. At 3-year follow–up, 1 out of 7 occlude. Indications for treatment are stage 2 of Fontaine Classification after failure or predictive failure of walking program and medical therapy in claudicants, and stage 3 or 4.

The following 2 treatments can be proposed: surgery or endovascular procedures. Endovascular treatment is now the first treatment to be proposed and numerous techniques are currently available on the market (balloon angioplasty, scoring/cutting balloons, atherectomy, laser, stents, etc.). Balloon angioplasty was the first used. But despite the effectiveness of PTA in establishing immediate revascularization, the vascular injury generated can lead to elastic recoil and plaque dissection, which can lead to abrupt vessel closure. To solve these issues, stents have been proposed by providing a metal scaffold. However, exaggerated neointimal hyperplasia can lead to a high rate of in-stent restenosis. Rates of restenosis for both PTA and stenting can approach up to 50–70%, depending on the arterial bed, lesion length, lesion characteristics, etc. Rocha-Singh et al.[1] reported a combined 12-month primary patency of 33% with PTA alone, pointing out the decreasing role of PTA alone and in particular for lesions longer than 5 cm.

Neointimal hyperplasia is caused by vascular smooth muscle migration and proliferation following vascular injury. This problem occurs frequently whether arterial intervention included PTA alone or PTA and stenting. To overcome this problem, a chemotherapeutic agent, paclitaxel, delivered locally has been proposed to reduce neointimal hyperplasia, thereby restenosis rate and late lumen loss.[2,3]

Local drug delivery for paclitaxel and other chemotherapeutic agents can be accomplished by utilizing drug-eluting stent (DES). These DESs are the preferred therapeutic option in coronary vasculature, and are also used for infrainguinal lesions with success and good long-term results.

Drug-eluting balloons (DEB) have also been proposed and may provide a viable treatment option for patients with infrainguinal diseases. Advantages of these DEBs should include decreased rates of restenosis compared with PTA alone due to local delivery of antirestonotic agents without the use of a permanent scaffold such as a stent. DEBs can be used where stent placement is not ideal, such as tortuous arteries flexion points or bifurcations lesions. DEBs have also been proposed to treat in-stent restonosis.

We will analyze the main published data for native Fem. Pop. Arterial Diseases and for Fem. Pop. In-Stent Restenosis.

2. Drug coating process

This process is well described by Sethi.[4] Local drug delivery using a stent-based platform typically occurs over a period of months. In contrast, DEBs provide a localized bolus of drug without

* Corresponding author at: 4 A Romescht, Residence Les Marronniers 1, L 7465 Bofferdange, Luxembourg.
E-mail addresses: michel.henry62@gmail.com (M. Henry), isabelle.henry27@wanadoo.fr (I. Henry).

http://dx.doi.org/10.1016/j.jicc.2017.06.005

a permanent indwelling implant.[5] To accomplish this task, the DEB platform included three key components, the angioplasty balloon, the antirestenotic agent, and a carrier molecule or excipient that facilitates binding and transfer of the drug to the tissue during balloon inflation. The challenge is to deliver a therapeutic dose of the drug for an adequate period of time in order to achieve meaningful inhibition of neointimal hyperplasia.

Paclitaxel is an antineoplastic drug that inhibits smooth muscle proliferation as well as extracellular matrix secretion and migration. Certain drug properties of paclitaxel allow it to be used in DEB strategy. Given its lipophilicity, crystalline paclitaxel can be combined with contrast media, the excipient, to coat the angioplasty balloon. Furthermore, paclitaxel remains bound to the excipient and balloon during arterial transit to the target vessel. Lastly, short inflations of the balloon allow local delivery of therapeutic doses of paclitaxel, which can last for months. Only 10–20% of the drug is finally taken up by the vessel wall. Given the experience with DESs, if therapeutic doses can be sustained for months, neointimal hyperplasia should be adequately inhibited. Furthermore, toxicity can be limited due to small dosages and local application.

Several DEBs are currently available on the market with the same drug but different coating, and different doses of paclitaxel (Fig. 1).

3. Technical aspects of a procedure with DEB

When using a DEB, some technical points and guidelines must be respected if we want optimal drug delivery and DEB outcomes:

- Aggressive lesion predilatation.
- DEB will be used only after optimal angiographic result.
- It is critical to obtain at least a 1:1 ratio of the DEB to the reference vessel diameter.
- Balloon transit time < 30 s.
- Balloon inflation pressure > 7 atm.
- Balloon inflation time > 2 min.
- Final % diameter stenosis < 20%.

4. DEB for de novo Fem. Pop. Arterial Diseases

4.1. DEB vs PTA balloon in short lesions literature data

- As recently reported by Zeller[5] 7 trials/6 DEB. Technologies showed that DEB gives better results than PTA alone (Fig. 2) as demonstrated by the primary endpoint, the late lumen loss (LLL) at 6 months. If these results are promising, we have to point out that they concern short lesions at short-term follow-up.
- The first randomized control trial in the Fem. Pop. system was the THUNDER Trial.[6] 154 symptomatic patients were randomized with at least 70% stenosis of at least 2 cm in length in the femoral or popliteal arterial segment into 3 groups (paclitaxel coating balloon, PCB), uncoated balloon with paclitaxel in contrast media, and uncoated balloons. The primary outcome was late lumen loss at 6 months. Angiographic follow-up was completed in 83% of patients.

Manufacturer	DEB	Drug	Dose (µgr/mm²)	Excipient
MEDRAD	Paccocath	Paclitaxel	3	Ultravist
MEDTRONIC	In.Pact	Paclitaxel	3,5	Urea
BARD	Lutonix	Paclitaxel	2	Polysorbate & Sorbitol
EUROCOR	Freeway	Paclitaxel	3	Shellac
BIOTRONIK	Passeo 18 Lux	Paclitaxel	3	BTHC
COOK	Advance PTX	Paclitaxel	3	none
Spectranetics	Stellarex	Paclitaxel	2	PEG
ACHEN RESONANCE	Elutax	Paclitaxel	3	none
BOSTON Scientific	Ranger	Paclitaxel	3	Transpax
BBraun	Sequent Please	Paclitaxel	3	Resveratrol

Fig. 1. DEBs available on the market.

The PCB group had less LLL (0.4 mm vs 1.7 mm, $P < 0.001$) compared with the control group (uncoated balloons) as well as less TLR at 6 months (4% vs 37%; $P < 0.001$).

Fig. 3 shows the results of the THUNDER Trial at 6, 12, and 24 months concerning the LLL, in favor of PCB, PACCOCATH.

The 5-year follow-up data were available for only a minority of the initially enrolled patients since only the PCB and control arm group were followed.[7] TLR occurred in 30 of 54 patients (56%) in the control group compared with 10 of 48 patients (21%) in the PCB groups ($P < 0.001$). The primary outcome of LLL also maintained the initial statistical difference seen (0.7 ± 1.5 mm for PCB vs 1.9 ± 1.9 mm for control $P = 0.01$).

- The Fem. Pac. Trial randomized 87 patients with significant Fem. Pop. stenosis to PTA alone.[8] At 6-month follow–up, the PCB group had significantly less LLL (0.5 mm vs 1.0 mm, $P = 0.03$) compared with PTA alone. TLR decreased in the PCB group (6.7% vs 33.3%; $P = 0.01$). At 2-year follow-up, the results remained in favor of DEB.

Fig. 4 shows the long-term freedom from TLR in FEMPAC and THUNDER trials with a significant and sustained TLR reduction up to 5 years.[5] So DEBs maintain their effectiveness in primary lesions for long periods, but these 2 trials concern patients with short lesions (mean lesion length 5 cm for the FEMPAC Trial and 7.5 cm for the THUNDER Trial).

- 2 other randomized studies of DEB vs PTA balloon were recently reported, the IN-PACT trial and LEVANT II trial.[5]
  The IN-PACT trial randomized 331 patients with a mean lesion length of 8.9 cm. The primary patency at 12 months was higher in the DEB group (82.2% vs 52.4%; $P < 0.001$); TLR was lower in the DEB group (2.4% vs 20.6%; $P < 0.001$) (Fig. 5). The LEVANT II trial randomized 316 patients with a mean lesion length of 8.1 cm. The primary patency at 12 months was higher in the DEB group (71.5% vs 56.8%; $P < 0.001$) (Fig. 5).

If DEB was superior to PTA balloon at 1 year in the 2 studies, at 2 years there was only a marginal benefit seen in LEVANT II indicating a late catch up. The 2-year primary patency was 78.9% for DEB and 50.1% for PTA balloon (difference 28.8%) in the IN-PACT trial and respectively 58.6% vs 53.0% in the LEVANT II trial (difference: 5.6%). Patency favors the IN-PACT Admiral Technology (Fig. 6).

- The Illumenate First-In-Human Study[9] showed encouraging results with a novel DEB, the Stellarex DEB. 58 Fem. Pop. lesions (mean lesion length 72.1 ± 46.7 mm) in 50 patients were first predilated with an uncoated balloon and then treated with DEB and compared with 30 patients who did not undergo predilatation. Similar outcomes were reported between these 2 groups with a high rate of 24-month primary patency, but rates of post-dilatation and stent placement are higher in the direct cohort so predilatation is recommended (Fig. 7).
-

Please cite this article in press as: M. Henry, I. Henry, Drug-eluting balloons (DEB) for the treatment of femoropopliteal occlusive diseases, J Indian Coll Cardiol. (2017), http://dx.doi.org/10.1016/j.jicc.2017.06.005