Drug-Eluting Balloons in Below-the-Knee Applications

A new technique for treating below-the-knee occlusive disease.

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During the last few years, new techniques and technologies have been developed for the endovascular treatment of arterial occlusive disease affecting the infrapopliteal arteries. This development allowed the treatment of complex and very extensive lesions, with a high technical success rate and a low complication rate. As in other vascular territories, restenosis (and in particular, in-stent restenosis) remains a problem that significantly affects mid- and long-term outcomes.[1] In fact, the rate of recurrent stenosis after percutaneous transluminal angioplasty (PTA) and stenting is higher in the below-the-knee territory than in femoropopliteal procedures.[2]

To overcome this problem, drug-eluting stents have been used. In a single-center, prospective registry, it was found that in patients with critical limb ischemia who underwent infrapopliteal revascularization with angioplasty and "bailout" use of a drug-eluting stent or bare-metal stent, lesions treated with drug-eluting stents were associated with significantly better primary patency, reduced binary restenosis, and fewer repeat interventions at 3-year follow-up.

No significant differences were seen with regard to overall 3-year patient mortality and limb salvage. However, the use of drug-eluting stents is limited by the unavailability of stents of sufficient length to treat the frequently encountered long or multifocal lesions, the problem of stent thrombosis (with the need for prolonged dual-antiplatelet therapy), and the occurrence of stent fractures.[3] Finally, indications in the animal model show that extensive and long-term exposure to paclitaxel at a low-dose (as commonly used in drug-eluting stents) might be associated with negative long-term effects with regard to inflammation and late in-stent restenosis.[4]

TECHNICAL AND PRACTICAL CONSIDERATIONS

The concept of drug-eluting balloons is based on the local delivery of drugs on site, with an exact control of the drug dosage, thus achieving an effective and sufficient local concentration and avoiding systemic exposure to the drug. Advantages of this technology are the possibility of a homogeneous drug transfer as compared to stent-mediated drug release, in which the drug is only delivered at the contact site of the stent struts with the vessel wall. Approximately 85% of the stented vessel wall area is not covered by the stent struts, resulting in low tissue concentrations of the antiproliferative agent in these areas.[5] Furthermore, drug-eluting balloons allow for a drug concentration that is highest at the time of the vessel wall injury that occurs during balloon angioplasty and therefore can prevent the initiation of the chain of events that will eventually lead to neointimal proliferation.

The absence of metal struts makes the technique suitable for treating long lesions, especially in small-diameter vessels and areas in which flexion and compression of stents may occur (the occurrence of stent fractures in the below-knee area is not uncommon, as demonstrated by Siablis and colleagues).[3]

The absence of a stent allows the artery's original anatomy to remain intact, which is especially important in lesions at the level of a bifurcation. The absence of the polymer that is included in most drug-eluting stents could decrease chronic inflammation and, with the absence of complete endothelialization (due to slow, long-lasting dual-antiplatelet therapy), is considered a trigger for late thrombosis, thus obviating the need for long-term dual-antiplatelet therapy.[3,6] By not using stents, follow-up

TABLE 1. CHARACTERISTICS OF DRUG-ELUTING STENTS VERSUS DRUG-ELUTING BALLOONS[a]	
Drug-Eluting Stents	**Drug-Eluting Balloons**
• Slow release	• Immediate release
• Persistent drug exposure	• Short-lasting exposure
• Approximately 100–200 µg per dose	• Approximately 300–600 µg per dose
• Polymer	• No polymers
• Stent mandatory	• Premounted stent optional
	• Matrix optional
[a]*Adapted from Scheller B et al. Heart (2007;93:539-541).*[7]	

treatment options (re-PTA, anastomosis site for surgical bypass) are preserved, and treating in-stent restenosis becomes possible with or without debulking (Table 1).[7]

Most of the currently available drug-eluting balloons use dry-state paclitaxel, the active ingredient of Taxol (Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, New York, NY), which has been approved by the US Food and Drug Administration and is widely used in oncological therapy. In oncology applications, paclitaxel is typically infused intravenously up to a dose of 175 mg/m^2 body surface equivalent to approximately 300 mg per patient. Usually, the treatment is repeated several times, with a treatment-free interval of 1 month.

The dose of paclitaxel that is used by almost all manufacturers is 3 µg/mm^2 of the balloon surface. With this dosage regimen, the total dose of paclitaxel administered to the patient remains well below the dosage schemes used in cancer treatment (eg, 3 µg of paclitaxel per mm^2 of balloon surface results for the largest balloon [6 X 120 mm] in about 8 mg total). Paclitaxel is a potent inhibitor of smooth muscle cell proliferation, smooth muscle cell migration, and extracellular matrix formation in vitro, with all three phases of the restenosis process effectively inhibited.[8]

The effective transfer of drug to the arterial wall is controlled by how the drug is loaded onto the balloon (coating engineering) and the relative solubility of the drug between the cell wall and the coating. Several techniques are available to make the drug adhere to the balloon and to optimize drug release. Paclitaxel can be made to adhere to the balloon surface by using ethyl acetate or acetone as a solvent.[9] More recent developments in balloon coating technology use the contrast agent iopromide as a hydrophilic spacer (Paccocath, Bayer AG, Leverhausen, Germany). In this way, the solubility of paclitaxel is increased, and the transfer of paclitaxel to the vessel wall is enhanced.[9]

The second method (FreePac coating, Medtronic Invatec, Frauenfeld, Switzerland) uses urea as a matrix to improve adherence of the drug to the balloon and facilitates drug elution by separating paclitaxel molecules and balancing hydrophilic and lipophilic properties. Urea is a natural degradation product of protein and is one of the most common substances in human serum (100–500 mg/L). It is synthesized in the liver in an amount of approximately 18 to 35 g/d, and its main role is to detoxify and excrete nitrogen derived from proteins. Urea has very low toxicity and causes no hypersensitivity reactions. The dose of urea on the balloon is approximately 0.5 µg/mm^2 of the balloon surface, which for a large balloon (6 X 120 mm) results in a total dose of 1.1 mg. This is the amount of urea contained in 10 mL of serum or < 0.01% of the urea synthesized during one day, and this can be considered totally harmless.

The third type of balloon uses a coating matrix that consists of a natural resin (composed of shellolic and aleuritic acid or a shellac coating [Freeway peripheral balloon, Eurocor GmbH, Bonn, Germany]). Once it comes in contact with blood, the hydrophilic network of the composite swells and opens the structure to allow a pressure-induced release of paclitaxel.

Although technically similar to the use of noncoated angioplasty balloons, there are several issues that must be considered when using drug-eluting balloons. The presence of the coating on the balloon will only slightly increase its crossing profile, and therefore the drug-eluting balloon will not require a larger introduction sheath size. However, it is generally recommended to upsize one French size to avoid scraping off the coating while crossing the sheath.

The inflation time recommended for optimal release of the drug (up to 80% of the total amount) is between 30 and 60 seconds (shorter inflations should be avoided in all cases, longer inflation times will not lead to a significant additional release of drug).[1]

Balloon length should always exceed lesion length, and predilation is recommended not only to avoid loss of drug from the balloon when crossing the lesion to be treated (especially in total occlusions and heavily cal-

cified lesions), but also to ensure an equal distribution of the drug across the vessel surface. When treating lesions with a length that exceeds the total balloon length, an additional balloon or balloons should be used to cover the whole lesion length (as mentioned previously, 80% of the drug is released after one inflation, which renders the balloon inept for a second drug release).

In an animal study, it was demonstrated that an increase of a local dose due to overlapping balloons does not lead to an increase in adverse reactions and does not influence the reduction of neointimal proliferation. No adverse reactions were seen as the dose was increased to more than three times the clinically tested dose.[10]

It is of utmost importance to avoid a so-called geographic miss, that is, a segment of the lesion not being treated with the drug-eluting balloon. Bony landmarks or a ruler can be used to ensure proper overlapping of the drug-eluting balloons. As a reliable alternative, the road map feature of the angiography system can be used. With the first balloon inflated, the road map is activated. After balloon deflation and exchange for the second balloon, fluoroscopy is used, and the image of the first balloon and its markers will be visible as a "negative image." The markers of the second balloon will be projected onto this image as "positive," and the most distal marker of the first balloon and the most proximal marker of the second balloon can be superimposed easily (Figure 1).

In a case of early and in-stent restenosis, debulking is probably key and can be achieved by using orbital atherectomy, Silverhawk atherectomy (ev3 Inc., Plymouth, MN), and laser-assisted atherectomy (Turbo Elite [Spectranetics Corporation, Colorado Springs, CO]) (only the last tool mentioned can be used safely in cases of in-stent restenosis) (Figure 2).

RESULTS

Preclinical trials have shown the efficacy of balloons coated with a paclitaxel-iopromide mixture for inhibiting neointimal proliferation in the coronary arteries in the porcine model.[9] These results have been confirmed by a study in patients with coronary in-stent restenosis and who underwent treatment of stenotic or occlusive disease in the superficial femoral artery. Two-year follow-up data of a randomized trial comparing uncoated balloons with paclitaxel-coated balloons in patients with coronary in-stent restenosis demonstrated a statistically significant reduction of target lesion revascularization.[11]

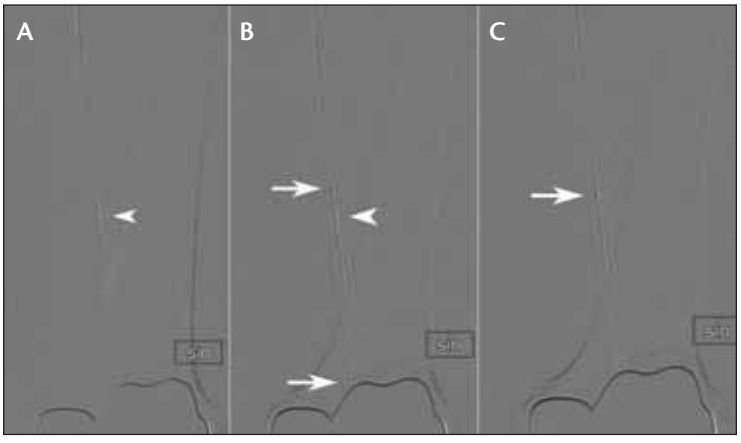

Figure 1. A patient with in-stent occlusion of the distal superficial femoral artery. After laser debulking and predilatation, drug-eluting balloons are used. A road map image obtained with the first drug-eluting balloon in place (A), the distal marker (arrowhead) can be clearly seen as a white dot. Using this road map image during advancement of the second drug-eluting balloon (B), the markers of this balloon can be identified as black dots (arrows), the "ghost image" of the first balloon still being visible (arrowhead). Overlap of the distal marker of the first balloon (white dot) and the proximal marker of the second balloon (black dot, arrow) (C).

Figure 2. A patient with in-stent restenosis (stent placement 3 months prior; before stent placement, several PTA procedures were performed at this level in within a 6-month time frame). Angiogram showing high-grade stenosis at the level of the stent in the distal popliteal artery and proximal anterior tibial artery (arrow) (A). Laser debulking was performed, and a drug-eluting balloon was positioned at the level of the area of maximum stenosis (B). Control angiogram (C) shows restoration of flow without any residual stenosis; the subsequent clinical course was uneventful for 1 year.

Similar results were obtained in a randomized comparison of paclitaxel-coated balloon angioplasty versus a paclitaxel-coated stent for the treatment of coronary in-stent restenosis.[5]

The FemPac pilot trial randomized 87 patients with femoropopliteal peripheral artery disease to treatment with either uncoated or paclitaxel-coated catheters. In patients treated with the drug-eluting balloon, angiographic late lumen loss at 6 months was significantly reduced, and a significant reduction in target lesion revascularization at 6 months was also seen, which was maintained up to 24 months.[12]

In the THUNDER trial, 154 patients with femoropopliteal stenotic or occlusive disease were randomly assigned to treatment with paclitaxel-coated catheters, uncoated catheters with paclitaxel dissolved in the contrast medium, or uncoated catheters (the last tool mentioned being the control group). The use of paclitaxel-coated balloon catheters significantly lowered the incidence of restenosis at 6 months and the rate of target lesion revascularization at 6, 12, and 24 months. Adding paclitaxel to the angiographic contrast medium did not have a significant effect.[13]

The only currently available clinical data on the use of drug-eluting technology in the below-the-knee arteries is a prospective registry of 107 patients treated with In.Pact Deep (Medtronic Invatec), which was presented by Andrej Schmidt, MD, during EuroPCR 2010. Mean lesion length was 174 ± 89 mm, 60.5% of patients had an occlusion, and the remaining 39.5% had stenotic disease. The follow-up comprised angiography after 3 months and clinical follow-up at 3, 6, and 12 months.

Three-month follow-up was available for 100 patients (seven patients died, one due to major amputation and six due to cardiovascular deaths), and thus 93 patients were alive within the 3-month follow-up window. Of these 93 patients, 71 (81 lesions) had a control diagnostic angiogram available. Clinical improvement was seen in 76.3% of cases, whereas 22.4% remained unchanged and 1.3% worsened clinically. After 3 months, an angiographic restenosis rate of more than 50% was seen in 27% of all lesions treated, with restenosis of the entire treated segment of 11% (in the other cases of restenosis of more than 50%, only focal, short restenotic lesions were seen).

These data compare favorably to the data from the same investigators in a similar group of 58 patients who were treated with noncoated balloons: at 3-month angiographic follow-up, restenosis of more than 50% was seen in 69% of cases, with restenosis of the whole treated segment in 56% of cases. Long-term data are not yet available in regard to cost effectiveness and the outcomes of stenting after the use of drug-eluting balloons.

Two currently enrolling randomized trials (the IN.PACT DEEP and the EURO Canal studies) will evaluate the clinical utility and angiographic outcomes of angioplasty using drug-eluting balloons in the infrageniculate arteries in comparison with plain balloon angioplasty. Hopefully, they will provide definitive evidence of the clinical benefit of drug-eluting balloon application in the arteries below the knee.

CONCLUSION

Drug-eluting balloons provide a safe technology, and even short-term exposure to paclitaxel-coated balloon catheters is sufficient to inhibit restenosis. The results in animal studies and coronary arteries, as well as in the superficial femoral artery, have demonstrated feasibility, and the first results in below-the-knee applications are very promising. ■

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