Drug-Coated Balloons

Paclitaxel-coated balloons show promise as a treatment option for intravascular interventions.

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Although the technical success rate of most intravascular interventions has been significantly improved during the last decades by advanced medical devices and interventional methods, long-term success remains an area of concern in many applications. Unlike technical success, long-term outcome frequently depends on biological processes that are stimulated by acute effects of the intervention itself (eg, early restenosis), by implants (eg, thrombotic events), or occur in the natural history of the disease and aging.

EVIDENCE OF SAFETY AND EFFICACY

Principle

The main reasons for restenosis are elastic recoil, which usually occurs shortly after the balloon has been deflated, and neointimal hyperplasia resulting in lumen narrowing several months or, rarely, years after the intervention. Inhibition of neointimal hyperplasia was believed to be best achieved by continuous pharmacotherapy or sustained-release formulations of antiproliferative drugs. Systemic therapy proved to be ineffective for most drugs, or the doses required would be too high. The best outcome was achieved with local drug delivery from stents as a permanent platform for sustained release. Failure of drug-eluting stents to inhibit restenosis was blamed on too fast and uncontrolled release of the drug. It was therefore considered very unlikely that the same drug that required sustained release from a stent would also inhibit restenosis if coated on a balloon and released during the very short time of balloon inflation.

> " . . . studies in animals and clinical trials in coronary and peripheral arteries have consistently shown the efficacy and safety of paclitaxel-in-contrast-medium-matrix coated balloons."

As happens often, the first hint came from a study not primarily devoted to the subject. In a study investigating the potential impact of the choice of contrast media on restenosis in pigs, it was found that a taxane admixed to a contrast agent used to visualize coronary arteries during stent implantation inhibited neointimal proliferation. Because under free-flow conditions, as in this study, the contact time between the contrast medium/paclitaxel mixture and the arterial wall is very short, coating of paclitaxel on balloon catheters was tried next. Now that we know that paclitaxel coated on a balloon and immediately released upon inflating the balloon in a stenotic artery is able to prevent restenosis in a large proportion of patients for months and years, it may be possible in retrospect to explain why short-term exposure during balloon expansion works: neointimal proliferation is initiated by the vessel injury, an event of short duration. It therefore appears sufficient to prevent the initiation of the subsequent chain of events leading to neointimal proliferation instead of inhibiting the ongoing process for a prolonged period of time at a later stage.

Brachytherapy is also a one-time treatment of short

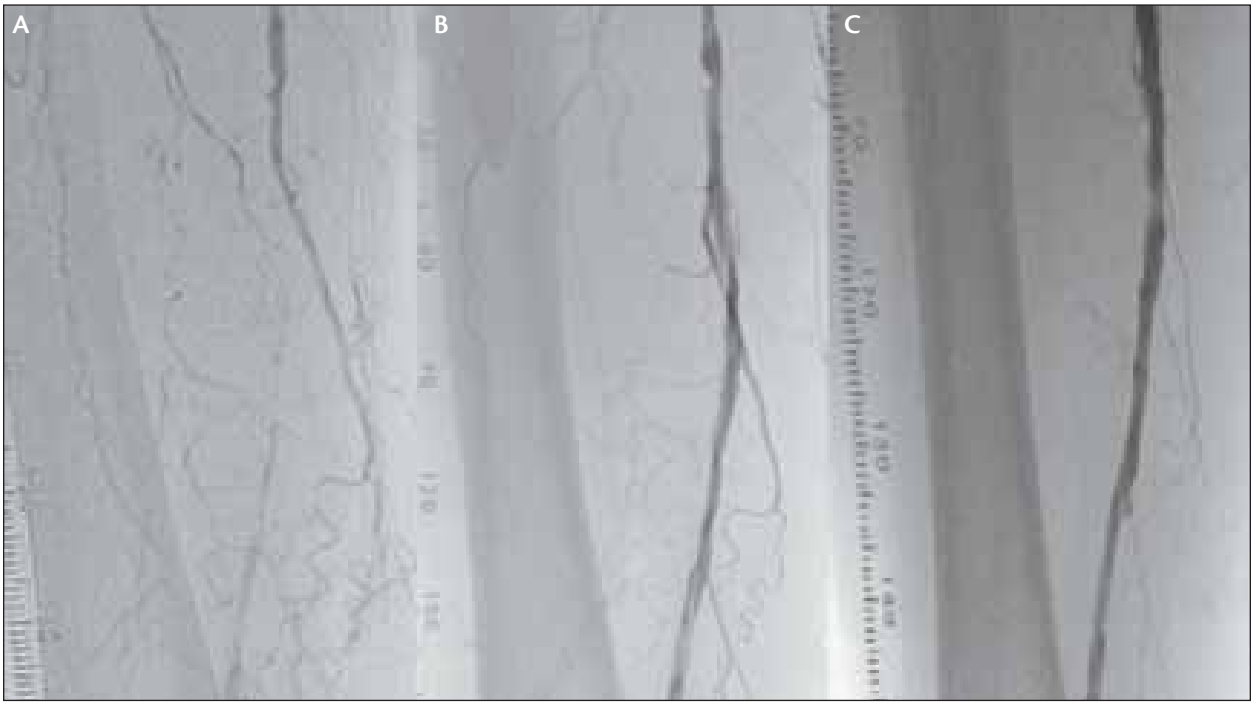

Figure 1. Angiograms of a patient who presented with Rutherford class 3 peripheral arterial occlusive disease. The patient was treated with a paclitaxel-coated balloon within the THUNDER study. Initial angiogram (A); postprocedure angiogram (B); 6-month follow-up angiography, showing no restenosis (C).

duration. However, the mechanism of action is quite different from pharmacotherapy as also indicated by the late fibrotic transformation of irradiated tissue. Furthermore, cell culture experiments indicated that exposure time may be shortened by increasing the drug concentration, although neither the in vivo drug exposure time nor the achievable drug concentration were predictable. Early studies in animals indicated efficacy of drugs despite short exposure times, but these results were not reproducible.

Animal Trials

As soon as technical problems (such as deposition of a sufficient drug dose on the balloon, uniformity of coating, and adequate adherence during handling, chemical stability, and ethylene oxide sterilization) were solved, drug-coated balloon catheters were tested in animals under conditions as close as possible to the clinical setting.[1-3] The porcine arterial overstretch model was preferred. In this model, stents are implanted so that the resulting vessel injury causes pronounced and reproducible neointimal proliferation. In most studies, stents were premounted on balloons to achieve a perfect fit between the vessel injury and drug transfer to the vessel wall, and all but one study was performed in coronary arteries to allow comparison with the majority of published data. Information on drug release during balloon expansion, inhibition of neointimal proliferation, and tolerance was obtained using chemical analytical methods, quantitative angiography, histomorphometry, and histology. The results can be summarized as follows (Table 1).

Even if no specific measures are taken for handling the catheters, a large proportion of the coating resists the transfer through the hemostatic valve, introductory, or guiding catheter. Premounted stents further protect the coating. The release of the drug from a matrix consisting of a nonionic contrast medium during balloon inflation is almost complete. Forty to 60 minutes after balloon inflation, approximately 10% to 20% of the dose was detected in the vessel wall, and values in the upper range were achieved in combination with stents, either implanted before balloon dilatation or premounted on the balloon. A dose of 3 µg/mm^2 balloon surface was sufficient to obtain almost the maximum achievable inhibition of angiographic stenosis, and neointimal proliferation was measured 4 to 5 weeks after treatment. A dose of up to 10 µg/mm^2 was equally well tolerated. Efficacy of the balloon with 3 µg paclitaxel/mm^2 compared favorably to the Cypher stent (Cordis Corporation, Warren, NJ). The usual balloon inflation pressure was between 8 and 14 atm; the inflation time

TABLE 1. STUDIES IN ANIMALS

Purpose	Animal Model	Main Result	Reference
Drug-adherence, release, transfer to the vessel wall	Swine, coronary arteries	About 10% of dose lost on the way to the treated vessel segment, 80% release during inflation, 40 to 60 minutes later 10%–20% of dose in the vessel wall	Scheller (2004)[3]
Inhibition of neointimal proliferation	Swine, coronary arteries	Dose-dependent inhibition with a mixture of paclitaxel and an iodinated contrast medium	Scheller (2004)[3]
Efficacy in peripheral arteries	Swine, arteries of the limbs	Less late lumen loss if treated with the drug-coated balloon compared to uncoated balloon	Albrecht (2007)[1]
High dose, short inflation time	Swine, coronary arteries	Highest dose tested (>3 times standard dose) neither more efficacious nor toxic; 10-second inflation time sufficient	Cremers*
Comparison to drug-eluting stent	Swine, coronary arteries	Drug-coated balloon at least equally efficacious as drug-eluting stent	Speck (2006)[2]

**These findings have been submitted to* Thrombosis and Haemostasis *(Cremers B, Speck U, Kaufels N, et al. Drug-eluting balloon: very short-term exposure and overlapping. August 2008.).*

was 60 seconds. Shortening the inflation time to 10 seconds did not significantly affect efficacy.

Whereas acute reactions, such as pronounced spasm of the coronary arteries immediately after overdilatation with the risk of arrhythmia, are common in this animal model, no late reactions that may indicate thrombotic occlusion due to delayed healing were observed. In some experiments, histology revealed slightly increased inflammation in vessel segments treated with the paclitaxel-coated balloons compared to those treated with uncoated balloons and bare-metal stents; in other studies, no difference was found. Follow-up for up to 6 months revealed no increased inflammation or other signs of toxicity. Because the drug is administered by the balloon only during the short time of its inflation, and premounted bare-metal stents carry no polymeric coating, delayed adverse effects are not expected.

Coronary Trials

At the end of 2003, the first multicenter clinical trial was started to compare the efficacy and tolerance of the paclitaxel-coated balloon catheters with conventional uncoated catheters in 52 patients suffering from coronary in-stent restenosis after previous bare-metal stent implantation.[4] Late lumen loss measured by angiography 6 months after treatment was selected as the primary endpoint. Although the number of patients enrolled was small, the study fulfilled quality requirements in respect of randomization, blinding, evaluation of angiograms by a central independent core lab, and clinical follow-up for 2 years. Shortly after all patients were enrolled, a second group of 56 separately randomized and evaluated patients was added to increase the probability of observing potential adverse events and to check the reproducibility of the results of the first trial.

The main results of both trials were almost identical (Table 2). Compared to the patients treated with the uncoated balloon, a statistically significant and much lower late lumen loss, fewer reinterventions, and an overall reduced rate of adverse cardiac events were

TABLE 2. RESULTS OF STUDIES IN PATIENTS WITH IN-STENT RESTENOSIS*

	ISR I	ISR II	*P* Value
n	52	56	
Age	63.6±10.8 y	68±8.9 y	.021
Male gender	37 (71 %)	36 (64 %)	.289
Diabetes mellitus	10 (19 %)	18 (32 %)	.095
Angiographic Findings			
Lesion length	18±7 mm	18.8±10.5 mm	.669
Late lumen loss in-segment Uncoated/drug-coated balloon	0.74±0.86 mm/0.03±0.48 mm	0.83±0.73 mm/0.16±0.4 mm	ISR I .002 ISR II .001
Difference between groups	0.71 mm	0.67 mm	
24-Month Clinical Follow-Up (Total Event Rate)			
Target lesion revascularization Uncoated/drug-coated balloon	6 (23%)/0	14 (50%)/3 (11%)	ISR I .011 ISR II .001
MACE Uncoated/drug-coated balloon	9 (35%)/1 (4%)	16 (57%)/5 (18%)	ISR I .005 ISR II .003

**Multicenter, randomized, blinded study. Primary endpoint: late lumen loss after 6 months by independent central core lab. MACE indicates target lesion revascularization, myocardial infarction, acute and subacute closure, stroke, and death; ISR, in-stent restenosis.*

observed in the patients treated with the coated balloon. The benefit in respect of target lesion revascularizations and major adverse cardiac events persisted until the end of the observation period 2 years after the initial treatment.[5] A differently coated balloon was tested with good acute results in bifurcation lesions;[6] efficacy data are expected to be reported soon.

THUNDER and Femoral Paclitaxel Trials

Shortly after initiating the coronary in-stent restenosis study, the first patients were also enrolled in two additional trials addressing de novo stenosis and occlusion as well as restenosis in the superficial femoral or popliteal arteries.[7,8] Both trials randomly compared paclitaxel-coated and uncoated balloon catheters using late lumen loss 6 months after treatment as the primary endpoint, which was determined by blinded independent core labs, and both trials included a 2-year follow-up. The THUNDER trial contained a third treatment arm with paclitaxel in the contrast medium used to visualize the treated artery. Selected data and results of the THUNDER trial are presented in Table 3. Six months after the intervention patients treated with the paclitaxel-coated balloons displayed far less late lumen loss than patients of the control group (no local drug delivery) or patients treated with paclitaxel dissolved in the contrast medium ($P<.001$); fewer patients of the coated-balloon group required target lesion revascularization. An angiographic example of a patient treated with a paclitaxel-coated balloon within the THUNDER study

TABLE 3. RESULTS OF THE THUNDER STUDY*

	Control (No Paclitaxel)	Paclitaxel on Coated Balloon	Paclitaxel in Contrast Medium	*P* Value A/B
Total no. of patients	54	48	52	
Age (y)	68±9	69±8	68±8	.35
Male gender (%)	63	65	69	1
Smoking (%)	22	23	27	1
Diabetes mellitus (%)	46	50	52	.84
Mean Rutherford class, baseline (mean±SD)	3.1±0.8	3.4±0.8	3.4±1.0	.03
Ankle-brachial index, baseline (mean±SD)	0.5±0.3	0.5±0.3	0.5±0.3	.71
Length of target lesion/investigators (cm, mean±SD)	7.4±6.7	7.5±6.2	7.4±6.5	.93
Patients with restenotic lesions				
After PTA without stenting (%)	19	21	27	.81
After PTA with stenting (%)	11	17	15	.57
Late lumen loss, 6 mo (mm)	1.7±1.8	0.4±1.2	2.2±1.6	<.001
Binary restenosis (%)	44	17	54	.01
Target lesion revascularization, 6 mo (%)	37	4	29	<.001
Target lesion revascularization, 12 mo (%)	48	10	35	<.001
Target lesion revascularization, 24 mo (%)	52	15	40	<.001

**Multicenter, randomized study. Primary endpoint: late lumen loss after 6 months by independent central core lab.*

is given in Figure 1. The latter difference was maintained over the full observation period. The second study (Femoral Paclitaxel) confirmed the results of the THUNDER trial; however, late lumen loss in the control group was less, and therefore, the difference to the group treated with the coated balloon was smaller. Nevertheless, the advantage of the coated-balloon group in respect of fewer target lesion revascularizations was also maintained until the end of the observation period.

Handling of the paclitaxel-coated balloons did not differ from handling of conventional percutaneous transluminal angioplasty balloon catheters in that the same inflation pressures and 1-minute standard inflation time were used. In the patients treated with the paclitaxel-coated balloon catheters, no adverse events were observed that were not common to the interventional procedure, and no increase in such events occurred.

POSSIBLE FUTURE INDICATIONS

The extent to which drug-coated balloons are used in daily practice will be influenced by the limitations of other available endovascular techniques. Currently, the technical success rate of endovascular therapy in patients with Rutherford stage 1 through 3 peripheral

vascular disease is very high, although long-term patency is poor, especially in longer lesions. In short focal lesions, plain balloon angioplasty has acceptable results, and therefore, it will not be replaced by other techniques, such as stent implantation in which foreign material is left behind. In addition, larger studies have to show superiority of primary stent implantation compared to the standard techniques. Specific devices for the prevention of late lumen loss will be used in lesions with a higher probability of restenosis, such as lesions requiring treatment of longer vessel segments, total occlusions, and lesions in patients with diabetes mellitus. To date, none of the devices on the market has been shown to reduce restenosis rates to an extent justifying their broad application. Cryoplasty and cutting balloons, despite the complexity of use and the additional costs, have not been tested in prospective randomized controlled trials. Therefore, there is lack of evidence for any efficacy.

In contrast, several trials with nitinol stents have shown that, depending on the stent design and lesion characteristics, long-term patency of self-expanding stents is higher compared to plain balloon percutaneous transluminal angioplasty. These studies led to the wider use of stents in peripheral vascular disease patients. The wider use of stents not only for treatment of dissection or residual stenosis after balloon angioplasty but also as a primary treatment strategy for prevention of restenosis, is under discussion. On the other hand, there is also a controversy regarding the best primary stenting strategy because there are also drawbacks, such as stent fractures, the problem of in-stent restenosis, and the fact that foreign material is left behind. If a new method for prevention of restenosis can be shown to be comparable to stenting in terms of long-term outcome, such a method would replace bare nitinol stents for the prevention of restenosis while the technical indications for stent placement, namely to ensure the primary technical success, will remain untouched. If the initial results obtained with paclitaxel-coated balloons are confirmed in larger studies and in clinical practice, it is likely that, in the future, a large proportion of patients will be treated with drug-coated balloons. In addition, the extension of endovascular therapy to longer and more demanding lesions might also increase the demand for a method that reduces the risk of restenosis without irreversibly affecting the structure of the vessel. An interesting approach would be the combination of local drug delivery with atherectomy devices. In theory, plaque removal might work well together with local inhibition of excessive neointimal formation. The combination of atherectomy and drug-coated balloons might be especially suitable for treating lesions of the popliteal artery, a highly mobile vessel not very amenable to stent placement.

Until now, no data are available on the use of drug-coated balloons in patients with critical limb ischemia. Sirolimus-coated stents (Cypher) have been shown to reduce restenosis in small arteries below the knee. It is doubtful that this observation is of any clinical relevance. It is still unknown how long a below-knee artery has to be patent after endovascular treatment in order to allow an ulceration to heal.

In summary, studies in animals and clinical trials in coronary and peripheral arteries have consistently shown the efficacy and safety of paclitaxel-in-contrast-medium-matrix coated balloons. Drug-coated balloons and other local drug delivery methods will change endovascular therapy in the foreseeable future. ■

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