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Basic Science Review

Optimization of Drug-Eluting Balloon Use for Safety and Efficacy: Evaluation of the 2nd Generation Paclitaxel-Eluting DIOR-Balloon in Porcine Coronary Arteries

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Objectives: The aim of this preclinical study was to optimize the use of drug-eluting balloon (DEB) DIOR$^{2nd\ generation}$ by measurements of tissue and plasma paclitaxel concentrations in porcine coronary artery overstretch and prove efficacy in inhibition of neointimal growth without complementary use of stent. Background: The usually recommended DEB 60 sec inflation time causes prolonged ischemia and arterial injury. Methods: Tissue, plasma, and balloon surface concentrations of paclitaxel were measured in pigs 45 min and 12 hr after balloon inflation times of 15, 20, 30, 45, and 60 sec. Extent of neointimal hyperplasia was compared using DIOR$^{2nd\ generation}$ or noncoated balloon at two-week follow-up. Paclitaxel was replaced by fluorescent paclitaxel derivative in DEB and DES to demonstrate the distribution of the drug in arterial wall. Results: DIOR$^{2nd\ generation}$ DEB provided 29 ± 3 μM/L, 52 ± 6 μM/L, 196 ± 44 μM/L, 202 ± 36 μM/L, and 184 ± 59 μM/L paclitaxel to the vessel wall after 15, 20, 30, 45, and 60 sec of dilation, reaching plateau at 30 sec inflation time. Paclitaxel penetrated up to 2 mm tissue deepness. Measurable plasma paclitaxel level (45 ± 28 ng/mL) was found only after 60 sec balloon inflation time. At follow-up, the dilated arterial segment neointimal area and maximal neointimal thickness were significantly smaller with DIOR vs. uncoated balloon use. Fluorescence images of DIOR showed a homogenous distribution of the drug on the vessel, in contrast with DES. Conclusion: Using the DIOR$^{2nd\ generation}$ DEB, a maximal balloon inflation time of 30–45 sec is optimal, reducing effectively the neointimal hyperplasia. © 2010 Wiley-Liss, Inc.

Key words: angioplasty; follow-up studies; revascularization; catheterization; coronary disease

INTRODUCTION

Local antiproliferative therapy with drug-eluting stents (DES) is an effective approach in the treatment of different type of atherosclerotic coronary lesions. However, concerns have been raised that the biostable or bioreabsorbable polymeric matrix of the stent, in which the drug is embedded, might induce sustained inflammation with increased neointimal proliferation. Additionally, the tissue drug concentration in the stent area is not homogenous: it is highest near to the stent struts, and lowest between the struts, which causes non-uniform inhibition of smooth muscle cell proliferation and may induce delayed and in-homogenous re-endothelization in different stent segments. Both mechanisms have been suggested to contribute significantly to late thrombosis and in-stent restenosis.

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Drug-eluting balloon (DEB) may become an attractive treatment modality for coronary artery disease avoiding most of the limitations of DES [1–5]: local drug delivery without polymeric matrix and high antiproliferative activity of the drug reached very early when platelet activation and acute inflammatory infiltration trigger the restenosis cascade. We have previously shown [6] that there are measurable paclitaxel concentrations in the coronary arterial tissue after 1st generation DIOR (**DI**lation **O**f **R**estenosis) (Eurocor GmbH, Bonn, Germany) paclitaxel-coated balloon dilation of a porcine coronary artery. However, the disadvantage of the 1st generation DIOR balloon (similar to other DEBs) was the relatively long inflation time (60 sec) needed to achieve a measurable paclitaxel penetration into the arterial wall [7].

The aim of this study was to investigate the safety in terms of time-dependent release of paclitaxel from the balloon into systemic circulation and accumulation of paclitaxel within the vessel wall, together with the efficacy of the 2nd generation of paclitaxel-eluting DIOR balloon in porcine coronary artery overstretch injury model.

TABLE I. Differences Between the 1st and 2nd Generation DIOR Drug-Eluting Balloon

	DIOR 1st generation	DIOR 2nd generation
Drug load	3 μg/mm^2	3 μg/mm^2
Physical coating	Paclitaxel	Paclitaxel
Technical coating	DMSO	Shellac
Coating color	White	Transparent
Coating appearance	Crystaline	Resinous
Folding type	3-fold	3-fold
Release of drug from balloon surface at		
30 sec inflation time	20%	75%
60 sec inflation time	25%	85%

MATERIALS AND METHODS

Animal Preparation

After overnight fasting, 33 domestic pigs (weight 18–30 kg) were premedicated with intramuscular injection of 12 mg/kg ketamine hydrochloride, 1 mg/kg xylazine, and 0.04 mg/kg atropine. The anesthesia was deepened with isofluran and O_2 via a mask, followed by intratracheal intubation. The anesthesia was maintained with 1.5–2.5 vol% isofluran, 1.6–1.8 vol% O_2, and 0.5 vol% N_2O O_2 saturation. Blood pressure and electrocardiogram were monitored continuously. Arteriotomies of the right femoral arteries were performed under sterile conditions, and a 6F introduction sheath was inserted.

After administration of 200 IU/kg of heparin sodium, selective angiography of the left and right coronary arteries were performed and a guide-wire was introduced into the distal part of the left anterior descending (LAD) and left circumflex (LCx) coronary arteries. The balloon catheters (2.75–3.0 mm in diameter, 15 mm in length) were inserted into the LAD past the origin of the first major diagonal branch, and into LCx beyond the origin of the first marginal branch, and balloon dilation was performed. Coronary angiography confirmed the full contact of the balloon with the vessel wall during each balloon inflation. The inflation time was chosen in accordance with the protocol, e.g. either the safety or the efficacy phase of the study. The animals were then euthanized for the safety study or allowed to recover for the efficacy study.

The experiments were conducted in the Institute of Diagnostics and Oncoradiology, University of Kaposvar, Hungary. The animal investigations conform to the "Position of the American Heart Association on Research Animal Use," adopted by the AHA on November 11, 1984, and the relevant specific Hungarian laws were followed.

Local Drug Delivery Device

The 2nd generation DIOR balloon is a coronary dilation balloon for human use with a 3.0 μg/mm^2 balloon-surface paclitaxel-coating, using a new CE-marked coating technique (Table I). The drug is dissolved in shellac, which is composed of a network of hydroxy fatty acid esters and sesquiterpene acid esters with a molecular weight of about 1000; aleuritic acid and jalaric acid and/shelloic acid are the major constituents of shellac (Fig. 1). Shellac is graded as food and is listed as "generally recognized as safe" and approved by the Food and Drug Administration. Shellac is also used as surface coating of polymer-free DES in ISAR trials [8]. The 1:1 mixture of paclitaxel and shellac is coated onto the microporous DIOR-balloon-surface structure (Fig. 1). During the insertion of the DIOR balloon catheter and tracking to the coronary lesion, the three-folded DIOR balloon protects the loaded drug from an early wash-off effect.

Safety Study

For measurements of tissue paclitaxel concentration after balloon inflation, the DIOR balloon was inserted into the LAD and LCx. To assess the increase in tissue paclitaxel concentrations as a function of balloon inflation times, the DIOR balloons were inflated for 15 sec in 10 coronary segments, for 20 sec in six coronary

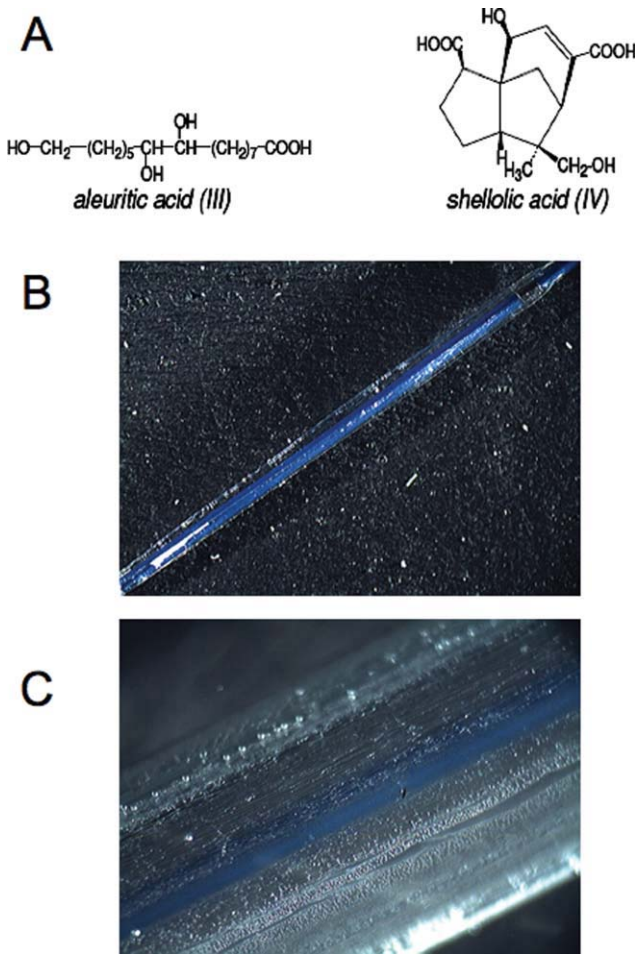

Fig. 1. DIOR balloon. A: Chemical structure of the aleuric acid and shelloic acid, the main components of the shellac coating technology. B: Dior balloon coated with shellac and paclitaxel. C: The optical refraction of Shellac gives balloon a shiny appearance.

segments, for 30 sec in six coronary segments, for 45 sec in seven coronary segments and 2 × 30 sec in six coronary segments and at 6–14 atm (1.3:1 balloon/artery ratio). Blood samples were taken 5, 10, and 30 min after balloon inflation. Euthanasia was performed with saturated potassium chloride at 45 min or 12 hr after DIOR balloon inflation. The balloons were then stored for measurements of remnant surface paclitaxel amount. The LAD and LCx dilated coronary arterial segments were prepared with additional proximal and distal reference segments (max. 10 mm proximal or distal from the dilated segment), and fresh-frozen for determination of tissue paclitaxel concentrations. Tissue samples (connective tissue, fat and myocardium), 1, 2, and 3 mm beneath the artery were prepared for determination of the depth of vertical paclitaxel penetration into the tissue.

Measurement of Tissue, Balloon Surface, and Plasma Paclitaxel Concentrations

The paclitaxel concentration in the artery walls, the underlying tissue at 1, 2, and 3 mm deep layers, balloon surface, and plasma was measured by high-performance liquid chromatography (HPLC) (AnaKat Institut für Biotechnologie GmbH, Berlin, Germany). Briefly, after thawing, the tissues were weighed at ambient temperature and, depending on weight different volumes of ethanol were added to the samples (sufficient ethanol to cover the tissue completely). The samples were then treated with ultrasound for 40 min, and 200-μL aliquots were then centrifuged and stored for subsequent measurements.

A calibration line was produced in the range between 50 and 5,000 ng/mL. The samples for the calibration line were prepared by dilution of a stock solution with a concentration of 1,000 μg/mL. Aliquots of all samples (samples from tissue and calibration line) were transferred into auto-sampler vials and the same volume of 0.1% formic acid was added. The flow rate of the HPLC system was 0.2 mL/min through a column of ODS Hypersil (ThermoElectron Corporation), particle size 5 μm, pore size 120 Å. The isocratic mobile phase consisted of 70% methanol and 30% 0.1% formic acid. Paclitaxel was detected by mass spectrometry in multiple reaction monitoring mode with a transition of paclitaxel from 854 to 105 AMU. The tissue paclitaxel concentration was expressed in μM/L, which measure is independent from the sample weight. The plasma paclitaxel amount was given in ng/mL.

Efficacy Study

The neointimal proliferation caused by balloon overstretch injury (1.3:1 balloon/artery ratio) was compared using conventional ($n = 6$) or DIOR balloons ($n = 6$) in the LAD and LCx. Loading dose of clopidogrel (300 mg per os) and acetylsalicylic acid (250 mg per os) were administered 24 hr prior to the procedure. The medication was continued with a daily dose of 75 mg clopidogrel and 100 mg acetylsalicylic acid during the two-week follow-up (FUP). Each pig was treated with both conventional and DIOR balloons in a randomized fashion (DIOR in either LAD or LCx). The balloons (2.75–3 mm of diameter, 15 mm of length) were inflated with 10–18 atm for 30 sec in order to achieve the 1.3:1 balloon:artery ratio. Control angiography was performed at two-week FUP, followed by euthanasia. For histopathological and histomorphometric analyses, the coronary arteries were flushed with 100 mL saline followed by pressure fixation in 4% buffered formaldehyde for 30 min at 100–110 mmHg. The arteries were then cut from the

epicardial surface and the location of the previous dilation was carefully identified based on the anatomical landmarks (side branches). The dilated segment (divided into three sections, such as proximal, mid and distal dilated segments), the proximal and distal reference segments (max. 10 mm proximal or distal from the dilated segment) were then fixed in 2% buffered formalin. Following this preparation, the arterial sections were embedded in paraffin and cut into 4- to 6-μm-thick slices and routinely stained with hematoxylin-eosin and Verhoeff-van Gieson-elastin.

Histopathology and Histomorphometry of the Arteries Two Weeks After Overstretch Injury

The histological analysis was performed by experienced investigators blinded to the treatments [9,10] and focused on the arterial injury, and measurements of the neointimal hyperplasia.

The following histopathological parameters were measured: injury score, fibrin and inflammation scores, and endothelialization. Vessel injury was determined by the anatomic vessel structures similar to the injury score after stenting [11], and adapted for balloon injury only [12]. A numeric value was assigned according to the severity of injury: Grade 0: (no injury): internal (IEL) and external elastic lamina (IEL) and media intact; Grade 0.05: IEL minimal disruption, media and EEL intact; Grade 1: IEL lacerated, media and EEL intact; Grade 1.5 IEL lacerated, media <half thickness lacerated, EEL intact; Grade 2: IEL lacerated, media >half thickness lacerated, EEL intact; Grade 2.5: IEL and media (full thickness) lacerated, IEL minimal disruption; Grade 3: IEL, media (full thickness) and EEL lacerated. Inflammation score was graded as 0 for no inflammation to minimal amount of interspersed inflammatory cells in media or adventitia; 1 for mild inflammatory infiltration or focally moderated in <25% of the vessel area in media or adventitia; 2 for moderate inflammatory infiltration or focally marked in 25–50% of the vessel area in media or adventitia; 3 for heavy inflammatory infiltration or focally marked in >50% of the vessel area in media or adventitia, and 4 for granulomatous inflammatory reaction in any layer of the artery. Fibrin score was graded from 0 to 3 as no fibrin deposition or mild, moderate, or heavy fibrin deposition, involving <10%, 10–25%, or >25% of the circumference of the vessel, respectively. Endothelialization was evaluated with a score system comprising absent, partial, or complete.

The following quantitative histomorphometric parameters of the dilated segment, and proximal and distal reference segments were measured: (1) lumen area, (2) IEL area, (3) EEL area, and (4) maximal neointimal thickness.

The calculated histomorphometric parameters were as follows: (1) neointima area (difference between IEL and lumen area), (2) media area (difference between EEL and IEL area), (3) % area stenosis ((neointimal area/IEL area)*100[UW1]), (4) remodeling index (EEL area of the dilated arterial segment/EEL area of the proximal reference segment).

Tissue Distribution of Paclitaxel Using Paclitaxel-Eluting Stent and DIOR Balloon

Tissue distribution of paclitaxel after coronary intervention with fluorescent-paclitaxel (Oregon Green 488 Fluorecent paclitaxel conjugate, Molecular Probes, Invitrogen, Paisley PA4 9RF, UK) conjugate-coated stent or DIOR balloon (both 3.0 mm in size and 15 mm in length, balloon inflation time 30 sec with 10 atm) was compared.

The arteries were prepared from the epicardial surface. The stent was removed carefully, and the arteries were cut longitudinally and unfolded. The intimal surface was displayed with fluorescent microscopy.

Statistics

Continuous parameters were expressed as mean ± standard deviation. Continuous variables were compared with the two-sided Student *t* test. A *P* value of <0.05 was considered to be significant. The statistical analyses were performed with SPSS for Macintosh version 17.

RESULTS

There was no procedural or postprocedural complication after the use of the DIOR balloon for dilation of the coronary arteries.

Safety Study

Paclitaxel concentrations in arterial tissue 45 min and 12 hr postdilation increased with increasing duration of balloon inflation times (15, 20, 30, and 45 sec) reaching a plateau with 30 sec (Fig. 2), with no further increase even after 60 sec inflation time.

The measured arterial tissue paclitaxel concentrations were 29 ± 3 μM/L, 52 ± 6 μM/L, 196 ± 44 μM/L, 202 ± 36 μM/L, and 184 ± 59 μM/L after 15, 20, 30, 45, and 60 sec of inflation, respectively, 45 min after exposure of the artery with the drug. Paclitaxel concentrations were also detected in proximal and distal reference segments (Fig. 2). There were gradually decreasing remnant amount of paclitaxel on the balloon surfaces after balloon inflation times of 15 (182 ± 12 μg), 20 (144 ± 10 μg), 30 (131 ± 12 μg),

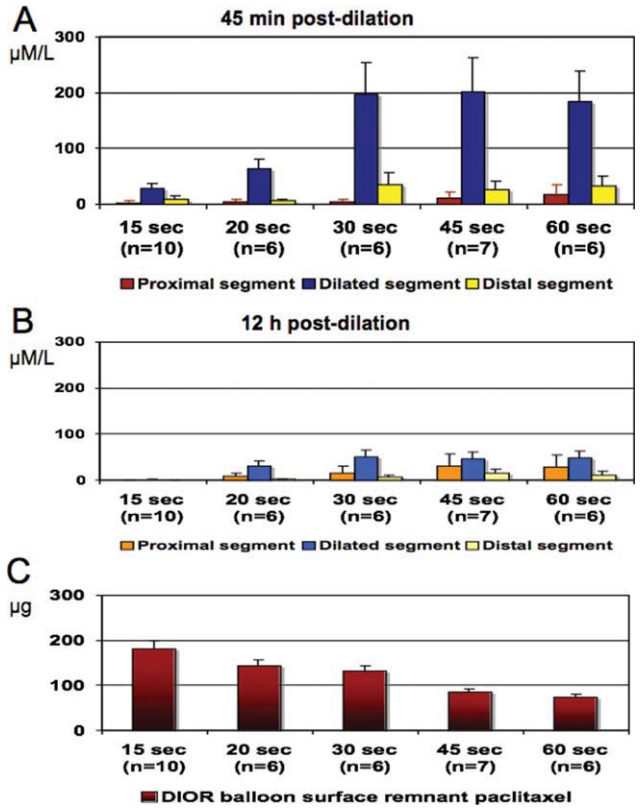

Fig. 2. Inflation time-dependent tissue and balloon surface paclitaxel concentrations. A: Coronary artery tissue paclitaxel concentrations of dilated segments, and proximal as well as distal reference segments 45 min after 15, 20, 30, 45, and 60 sec balloon inflations. B: Coronary artery tissue paclitaxel concentrations of dilated segments, and proximal as well as distal reference segments 12 hr after 15, 20, 30, 45, and 60 sec balloon inflations. C: Remnant paclitaxel amount of the balloon surface, after 15, 20, 30, 45, and 60 sec balloon inflations.

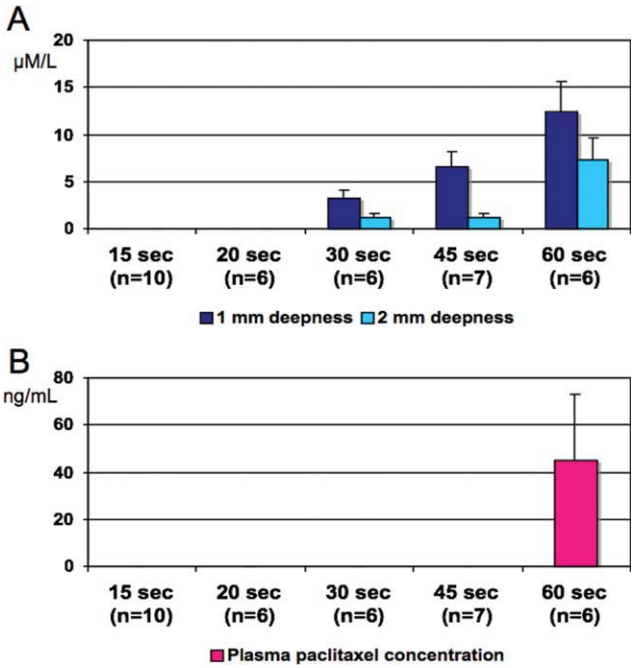

Fig. 3. Inflation time-dependent tissue and plasma paclitaxel concentrations. A: Vertical penetration of the paclitaxel at 1 and 2 mm deepness depending on balloon inflation time. B: Plasma paclitaxel concentration 5 min post-balloon inflation. Pacliataxel could be measured only 60 s balloon inflation time. No paclitaxel was detected 10 min post-dilation.

45 (85 ± 4 µg), and 60 (73 ± 6 µg) sec with an 75 ± 7 and 81 ± 6% drug release from the balloon surface after a balloon inflation duration of 30 or 45 sec, respectively. The arterial tissue paclitaxel concentration decreased up to 1 ± 0.1 µM/L, 31 ± 3 µM/L, 50 ± 8 µM/L, 47 ± 9 µM/L, and 48 ± 7 µM/L 12 hr post-dilation, according to increasing balloon inflation time (Fig. 2). The tissues beneath the arteries contained paclitaxel in increasing amount up to 60-sec inflation time at 1 and 2 mm vertical deepness 45 min post-dilation (Fig. 3), with maximal paclitaxel concentrations of 12.4 ± 3.2 and 7.3 ± 1.9 µM/L respectively, while no paclitaxel was detected at 3 mm deepness.

Paclitaxel concentrations in plasma (up to 85.8 ng/mL; mean 45 ± 28 ng/mL) were only detectable after a balloon inflation time of 60 sec, 5 min post exposure. Ten min after DIOR use, no paclitacel could be measured in plasma, even not after 60 sec balloon inflation time.

Efficacy Study

Two weeks post-overstretch injury, histopathological analyses revealed similar fibrin score and injury score in the groups. The inflammation score was somewhat higher in the conventional balloon group, without significant difference between the groups (Table II). No giant cells or granulomatous reaction was found in either group. The endothelialization was complete in both groups.

Histomorphometry showed significant smaller neointimal hyperplasia and neointimal thickness in the DIOR DEB group compared with the conventional balloon group (Fig. 4). Consequently, lumen area in the coronary arteries increased and was larger in the DIOR DEB compared with the conventional balloon (Table I). No relevant vessel remodeling was found in any of the groups (Table II).

Tissue Distribution of Paclitaxel

Fluorescence paclitaxel derivative-coating of DIOR balloon showed a homogenous distribution of the drug onto the vessel, in contrast with the uneven distribution caused by the fluorescence paclitaxel derivative-coated stent (Fig. 5).

TABLE II. Histomorphometric Parameter of Dilated Arteries Two Weeks Post-Balloon Dilatation With Conventional or DIOR Paclitaxel-Eluting Balloon

	DIOR balloon ($n = 6$)	Conventional balloon ($n = 6$)	P Value
Histopathologic parameter			
Injury score	1.00 ± 0.89	0.83 ± 0.75	0.734
Fibrin score	0.50 ± 0.55	0.33 ± 0.52	0.599
Inflammation score	0.17 ± 0.41	0.50 ± 0.84	0.401
Endothalialization complete	6/6 (100%)	6/6 (100%)	1.0
Histomorphometric parameter			
Lumen area (mm^2)	1.20 ± 0.27	0.59 ± 0.22	<0.001
Neointimal area (mm^2)	0.19 ± 0.04	0.70 ± 0.66	0.045
Internal elastic lamina area (mm^2)	1.39 ± 0.26	1.28 ± 0.72	0.366
Media area (mm^2)	1.14 ± 0.35	1.10 ± 0.59	0.443
External elastic lamina area (mm^2)	2.50 ± 0.55	2.38 ± 1.24	0.417
% Area stenosis (%)	14.44 ± 3.80	44.81 ± 22.93	0.005
Maximal neointimal thickness (mm)	0.13 ± 0.06	0.29 ± 0.19	0.039
Vessel remodeling index	0.86 ± 0.14	0.86 ± 0.16	0.977

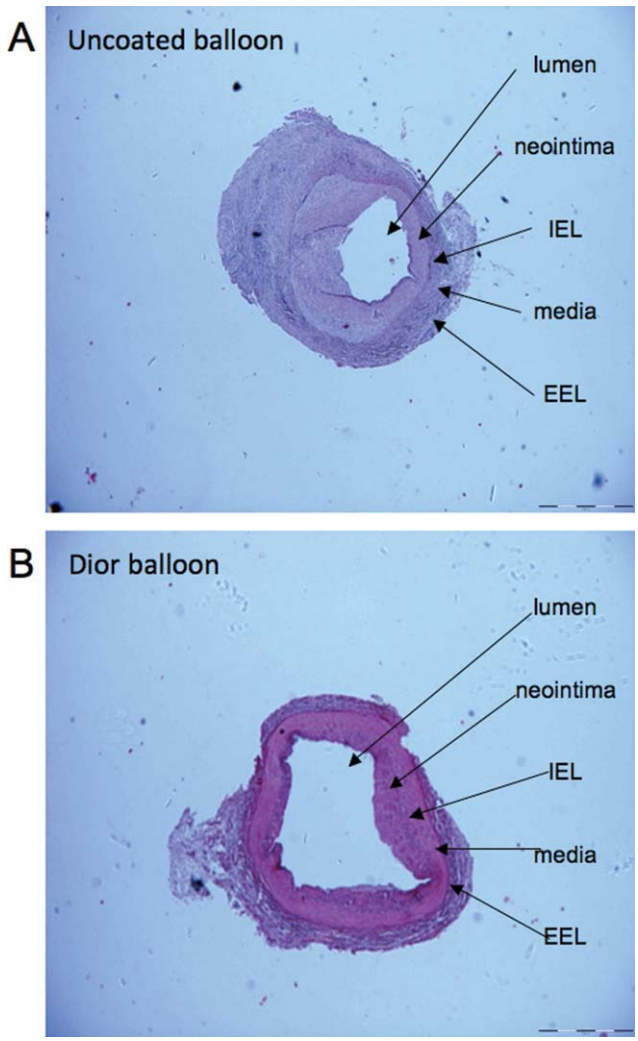

Fig. 4. Histology of overstretch injury after DIOR or non-coated balloon use. Representative histologic slides two weeks after balloon overstretch injury with conventional (A) or DIOR (2nd generation) (B) balloon.

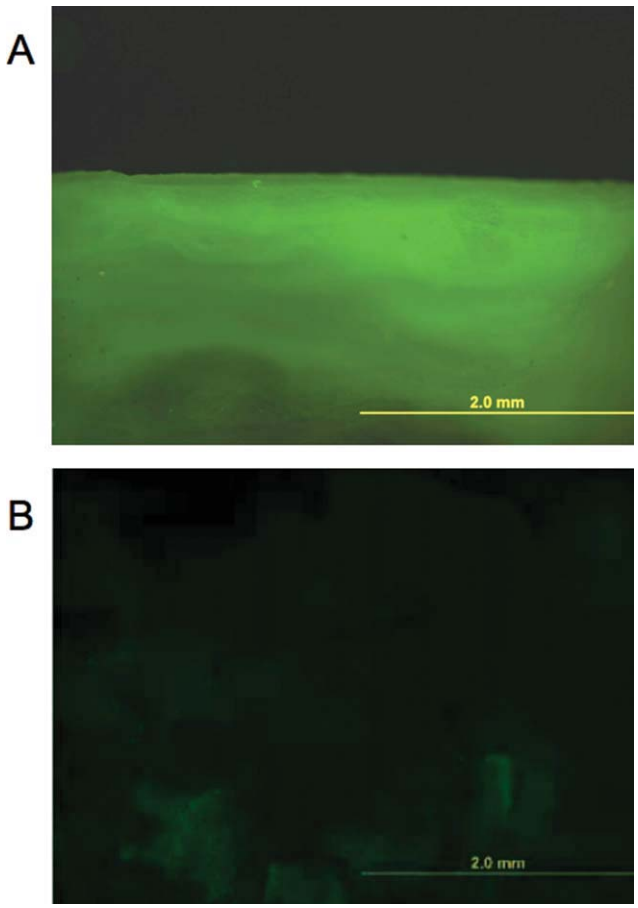

Fig. 5. Tissue distribution of paclitaxel. En face image of fluorescein distribution of endothelial surface of the artery after usig of fluorescent-paclitaxel derivative (Oregon Green) coating DIOR balloon (45 s balloon inflation time) (A) or coated stent (B), 45 min post intervention. Homogenous distribution of high amount of paclitaxel after DIOR DEB inflation, in contrast with the spatial heterogeneity of very low fluorescent concentration of paclitaxel when DES used.

DISCUSSION

Our study evaluated the safety and efficacy of the immediate bioavailability of locally applied paclitaxel in the arterial tissue, using the 2nd generation DIOR DEB in a preclinical model of percutaneous coronary intervention (PCI). We demonstrated horizontal/longitudinal (adjacent reference segments) distribution of paclitaxel as well as vertical drug penetration into the tissue up to deepness of 2 mm; this suggests the effective drug concentrations may be achieved in the presence of a thick plaque of an atherosclerotic coronary artery. The 2nd generation DIOR DEB with its novel coating technology resulted in an up to 20-fold higher tissue concentration as compared with the 1st generation of this balloon type [6], reaching an optimal tissue concentration for inhibition of smooth muscle cell proliferation. The balloon-inflation time-dependency study showed maximum tissue paclitaxel concentration after balloon inflation times of 30 sec, with minimal further increase in tissue drug concentration after 45 sec, and release of the drug into the circulation after a 1-min inflation time. The balloon inflation time of 30 sec causes less arterial injury and is better tolerated by patients in a clinical scenario. Our study also demonstrates the efficacy of short paclitaxel exposure onto the vessel wall as shown by significant smaller neointimal hyperplasia in the overstretch injury model as compared with the conventional balloon.

Clinical Advantages of the DEB

In 2002, Scheller et al. introduced the concept of using a balloon catheter to deliver an antirestenotic drug, such as paclitaxel, at the site of arterial disease [1,3,7]. The basic experiments proved that already a short exposure time of the artery to antiproliferative drugs was sufficient to penetrate into the vessel wall and to inhibit neointimal growth efficiently [3,13,14]. Therefore, DEB may be the logic response to prevent the "side effects" of DES.

Preclinical studies demonstrated effective inhibition of restenosis after percutaneous transluminal coronary angioplasty (PTCA) combined with stent implantation [5]. Subsequent clinical trials validated the efficacy of the paclitaxel-coated DEB to treat coronary in-stent restenosis [15–17] after a two-year follow-up. Compared with standard PTCA and stent technologies, DEB has a number of advantages: (1) lower restenosis rates than standard PTCA treatment; (2) less need for a permanent implant i.e. stent placement; (3) stand-alone use or combination with a bare metal stent (BMS) of choice; (4) no increase in device or procedural complexity to use of a standard PTCA balloon catheter; (5) immediate drug release without use of a polymer that may cause inflammatory reactions (as seen with certain DES); (6) potentially shorter duration of anti-platelet therapy; (7) potential for homogenous drug delivery to the vessel wall (unlike DES); (8) potential use for lesions unsuitable for stenting, i.e. small vessels, bifurcation lesions, and stent-in-stent restenosis. If a stent is indicated, any type of stent can be employed [16]. In addition, previously stented patients treated with DEB remain accessible to reintervention if needed without restricting the chance of a successful repeat treatment. As obvious from publications favoring the use of DEB for prevention of in-stent restenosis [15–17], increasing number of companies are developing DEB as an alternative to PTCA and stenting. Companies developing DEB catheters include B. Braun Melsungen AG (SeQuent Please), EuroCor (DIOR), Biotronik AG, Lutonix, Bayer AG, Cook Group Inc, Possis Medical, Aachen Resonance GmbH, Genesis Technologies, Invatec s.r.l., and DSM Biomedical in partnership with Caliber Therapeutics. Most of them are in the construction and preclinical testing phase; preclinical [3,4,6] and clinical data [16–20] have already been published for Sequent Please and DIOR.

Comparison of DIOR and Other DEBs

Changing the balloon-coating technology, the 2nd generation DIOR DEB achieves 2 to 20-fold higher tissue drug concentration in the arterial wall, as compared with the 1st generation DIOR DEB. These data are similar to those published by Scheller et al. [2,3] using paclitaxel mixed in contrast media or the SeQuent Please DEB. A potential disadvantage of the SeQuent Please is its contrast-medium-containing balloon surface, which might induce local allergic reaction in patients with known allergies to iodine and iodine-containing substances, as contrast media. In contrast, the DIOR surface coating consists of shellac, an FDA-approved substance. Another advantage with DIOR is that its balloon inflation time of 30 sec is as effective as the inflation time of 60 sec or 2×30 sec, which is usually recommended for DEBs. The measurements of the remnant paclitaxel amount on the DIOR balloon surface and the plasma allows the optimization of the DEB use. In summary, our time-dependency study pointed out that the tissue paclitaxel concentration reaches its maximum after 30 sec, with further rather vertical penetration into the tissue up to 60 sec DEB inflation time. The remnant amount of paclitaxel decreased with increasing inflation time (from 45 to 60 sec), and paclitaxel was detected in the blood only after 60-sec inflation. It appears that after 30 sec the tissue longitudinal/horizontal saturation limit is reached

with further, minor increase in tissue drug concentration only in the vertical direction, and undesirable release of the drug into the systemic circulation.

Homogenous Drug Distribution After Use of DIOR DEB

Compared with DES, in which about 85% of the stented plaque surface is not covered by struts, DEB allows a homogenous distribution of an antiproliferative compound, which goes beyond the area directly covered by the stent struts [21,22]. In addition, this uniformity of deliverance could enhance the efficacy of the drug to the vessel wall. The drug concentration within the vessel wall is highest at the time of injury when the inflammatory and proliferative processes are most vigorous. Using fluorescent paclitaxel-conjugate coating of a balloon with the same design of DIOR and a stent with polymer carrier coating, we have demonstrated that only a small amount of paclitaxel penetrated unevenly into the vessel wall after use of a DES; this contrasts with the uniform distribution of high amounts of paclitaxel when a DEB is used. These findings are similar to those of Hwang et al. who implanted Palmaz-Schatz Crown stents spray-coated with fluorescein sodium/ethylene vinyl acetate copolymer (Elvax 40P, Dupont Chemical Co) dissolved in dichloromethane and imaged the fluorescein release [21].

Efficacy of DEB in the Prevention of Stent Restenosis

Scheller et al. were the first to demonstrate that a combined treatment with a paclitaxel-coated balloon and bare metal stent led to a marked drug dose-dependent reduction in stent neointimal area [1]. In addition, the authors observed a dose-dependent inhibitory effect only when paclitaxel was dissolved in acetone, but failed to show any effect when it was dissolved in ethyl acetate; this suggests that it is important to use an appropriate solubilizing agent to increase optimal drug delivery. In an animal study, Albrecht et al. compared local administration of paclitaxel using drug-coated balloons or/and a mixture of paclitaxel to contrast medium during PTCA of peripheral arteries compared to balloon-only angioplasty [23]. They concluded that both methods of paclitaxel delivery reduced restenosis when compared with balloon-only angioplasty; in particular, DEB led to a 68% decrease in diameter stenosis and 56% decrease in late lumen loss [23]. Recently, Cremers et al. evaluated the influence of inflation time and increased dose due to overlapping balloons before BMS implantation in domestic pigs [24]. The results showed efficacy of paclitaxel-DEB in combination with BMS independent from inflation time. Treatment with DEB (5 μg paclitaxel/mm^2 balloon surface) for 10 sec reduced the neointimal area (by 57% compared with control) to the same extent as contact with the vessel wall for 120 sec (by 56%). Furthermore, neointimal proliferation and all other parameters characterizing in-stent restenosis could not be further decreased by inflating two DEB in the same vessel segment for 60 sec of each. These results suggest that the DEB releases most of the drug rapidly during the first seconds of inflation [24]. Using the overstretch injury model of the coronary arteries, we also demonstrated that the DEB results in less neointimal hyperplasia as compared with conventional balloon use, even without complementary stent implantation. The injury score was relatively low, with complete endothelialization in both groups, in spite of the 1.3:1 balloon:artery ratio, indicating a rapid healing process after balloon overstretch injury. Furthermore, the fibrin and inflammation scores were also relatively low, and no foreign body reaction or granulomatous reaction was found. These findings highlight the advantages of the exclusive use of balloon (even DEB), especially when compared with the histopathological consequences of coronary stent implantations [25,26].

CONCLUSIONS

Our study demonstrates the safety and efficacy of the DEB in the preclinical model of PCI. Using the enhanced version of DIOR with new coating technology, effective tissue paclitaxel concentration were achieved after balloon inflation times of 30 sec, which causes less arterial injury and is better tolerated by the patients in clinical scenario. Longer inflation of the balloon might lead to undesirable release of the drug into the systemic circulation. Short exposure of paclitaxel to the arterial wall results in penetration of the drug in both longitudinal and vertical directions. In contrast with DES, the drug delivery is rapid and homogenous using DEB, reaching the maximal tissue drug concentration at the time of the highest level of procedure-induced local tissue injury, which in turn triggers the restenotic and thrombotic cascade.

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