

An Experimental Study of Paclitaxel Embolisation During Drug Coated Balloon Angioplasty

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WHAT THIS STUDY ADDS

This experimental study is one of the first to compare five different drug coated balloons. It demonstrates that differences in drug coated balloon designs translate into differences in terms of embolisation and vessel wall penetration profiles. Although clinical implications remain to be demonstrated, the present results may have implications when choosing a drug coated balloon, especially in a critical limb ischaemia setting.

Objective: Drug coated balloons (DCB) improve the patency of femoropopliteal angioplasty but their use in infrapopliteal lesions is debateable as paclitaxel (PTX) particle embolisation has been suspected in some trials. The aim of this study was to compare experimentally five DCBs in terms of distal embolism of PTX.

Methods: Twenty-five New Zealand rabbits were divided into five groups according to the DCB used: Lutonix (Bard), In.Pact (Medtronic), Passeo-18 Lux (Biotronik), Ranger (Boston Scientific), and Stellarex (Spectranetics) ($n = 5$ in each group). After ligation of the right common iliac artery, a 4×40 mm DCB was inflated in the infrarenal aorta for 180 seconds. Rabbits were euthanised two hours after inflation of the DCB. The infrarenal aorta, a blood sample and three left hind leg muscles (tensor fasciae latae [TFL], vastus lateralis [VL], and tibialis anterior [TA] muscles) were harvested for blind measurement of PTX concentrations and histological analysis (PTX emboli count).

Results: In the TA muscle (the most distal), concentrations of PTX were significantly lower for the Ranger (0.067 ng/mg) than for the Lutonix (0.342 ng/mg; $p = .008$), In.Pact (0.370 ng/mg; $p = .012$), and Passeo-18-Lux (0.160 ng/mg; $p = .021$) DCBs. Similarly, concentrations of PTX were significantly lower for the Passeo-18-Lux than for the In.Pact ($p = .028$). Concentrations of PTX were not significantly different between DCBs in the TFL and VL muscles. Concentrations of PTX were found to be significantly higher in the plasma and lower in the aorta and on the DCBs after use of Lutonix compared with the four other DCBs. Histological analysis revealed evidence of embolised PTX crystals in small arterioles of all muscle tissue samples without any significant difference between the DCBs.

Conclusions: This study suggests some differences regarding distal embolisation profiles between the five assessed DCBs. Although clinical implications remain to be demonstrated, the present results may have implications when choosing a DCB, especially in a critical limb ischaemia setting.

Keywords: Angioplasty, Drug-coated balloon, Embolization, Paclitaxel

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INTRODUCTION

Drug coated balloons (DCB) improve the results of lower limb plain balloon angioplasty (PBA) for femoropopliteal disease.^{1–15} As a result, the European Society of

Cardiology/European Society for Vascular Surgery (ESC/ESVS) concluded that DCBs may be considered for short lesions (<25 cm) (Class IIb, Level A) or in stent restenosis (Class IIb, Level B).¹⁶ Their main action is to reduce cellular proliferation secondary to the initial angioplasty injury through paclitaxel (PTX) deposition in the arterial wall.¹⁷ This deposition in the arterial wall is driven by a balloon platform, a carrier (or excipient), and a local amount of PTX. In particular, a certain quantity of crystalline PTX form is required to maintain solid phase PTX reservoirs in the arterial wall for sustained antiproliferative effects.^{18–20}

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At the same time, drug nanocrystals may act as solid thrombi with a subsequent risk of embolisation and thrombosis. Worrying cases of diffuse distal fibrinoid necrosis were reported following DCB use at femoropopliteal level,^{21,22} in which PTX emboli were identified. Similarly, one large randomised controlled trial comparing PBA + DCBs to PBA alone in the tibial arteries for critical limb ischaemia (CLI) had to be stopped prematurely because of a trend towards an increased major amputation rate at 12 months in the DCB group.²³ One suspected cause was PTX particle downstream effects in the distal arterial bed, which could lead to microvessel occlusions and non-healing wounds.¹⁹ This DCB is no longer available for below knee use.

As DCBs are different regarding balloon platform, excipient, PTX formulation, and dosage, the aim of this study was to compare experimentally five DCBs in terms of distal embolisation of paclitaxel.

MATERIALS AND METHODS

This study was conducted in accordance with the requirements and guidelines of the European Union legislation and the French Animal Protection Act. The animal experiments were approved by the French animal protection committee (Project n° 2016101009413104 – V8 #8423) and took place in the UMR 1148 lab (Inserm-Paris7 - Denis Diderot University, Xavier Bichat Hospital, Paris, France), along with the histological analyses. Paclitaxel dosages were performed in the mass spectrometry platform MasSpecLab (UMR 1173, Inserm-Paris11 - Faculty of Health Sciences Simone Veil, Versailles Saint-Quentin-en-Yvelines University, Paris-Saclay University, Montigny-le-Bretonneux, France).

Animals

Twenty-five six month old New Zealand male white rabbits (CEGAV, Saint-Mars d'Egrenne, France) were used for the present study. They were fed with a normal diet and could drink ad libitum. To decrease the animal's stress, an acclimatisation period of one week was allowed before the procedure.

Drug coated balloons

All DCBs used were coated with PTX and were provided free of charge by DCB companies. The study was performed between March 2017 and August 2017.

The following DCBs were assessed: Lutonix (Bard), In.Pact (Medtronic), Ranger (Boston Scientific), Stellarex (Spectranetics), and Passeo 18 Lux (Biotronik) (Table 1). All DCBs had a diameter of 4 mm and a length of 40 mm. These dimensions were chosen because they were available for all the balloons, and because the aortic diameter is around 3.5 mm in rabbits.

Experimental design

Rabbits were divided into five groups, according to the DCB used: the Lutonix group ($n = 5$), the In.Pact group ($n = 5$), the Ranger group ($n = 5$), the Stellarex group ($n = 5$), and the Passeo 18-Lux group ($n = 5$). One DCB was used for each animal.

General anaesthesia was induced with intramuscular xylazine at a dose of 20 mg/kg, ketamine hydrochloride at a dose of 4.5 mg/kg, and acepromazine at a dose of 1 mg/kg. The intramuscular injections were done in the right thigh. In a first step, a laparotomy was done and the aorto-iliac vessels were dissected from the renals to the iliac bifurcations. The external aortic diameter was measured. The right common iliac artery was ligated at its origin with a non-absorbable 5–0 nylon suture. The aim of this manoeuvre was to direct all the aortic flow toward the left side for precise measurement of the downstream PTX emboli following DCB inflation in the aorta. The abdomen was further closed with a 4–0 polypropylene running suture. In a second step, arterial access was obtained via the right common carotid artery through neck cutdown. The common carotid was clamped. An oblique arteriotomy was performed to allow retrograde insertion of an angiography catheter (Vertebral Radifocus Glidecath 4 F - Hydrophilic Angiographic Catheter; Terumo, Leuven, Belgium), a guidewire (0.035 wires [Terumo Glidewire Hydrophilic Coated Guidewire Straight 180 cm, Terumo Leuven, Belgium] for Lutonix, In.Pact, and Stellarex, and 0.018 wires [V-18 ControlWire Guidewire, 150 cm, Boston Scientific] for

Table 1. Features of the main drug coated balloons (DCB) available in France ($n = 5$)

	Lutonix Bard	IN.Pact Medtronic	Ranger Boston	Stellarex Spectranetics	Passeo-18 Lux Biotronik
PTX dose, $\mu\text{g}/\text{mm}^2$	2	3.5	2	2	3
Excipient	Polysorbate sorbitol	Urea	Citrate ester	Polyethylene glycol	Butyryl-tri-n-hexyl citrate (BTHC)
PTX formulation	Hybrid (crystalline + amorphous)	Crystalline	Microcrystalline	Hybrid (microcrystalline + amorphous)	Microcrystalline
Technique of PTX deposition	Pulverisation	Micro-pipetting	Pulverisation	Pulverisation	Micro-pipetting
Balloon state during PTX deposition	Inflated	Inflated	Deflated	Inflated	Deflated

BTHC = butyryl-tri-n-hexyl citrate; DCB = drug coated balloon; PTX = paclitaxel.

Ranger and Passeo 18-Lux), and a short sheath (Radifocus Introducer II Terumo, Leuven, Belgium). The diameter of the sheaths was 4 F for Passeo 18-Lux, 5 F for Lutonix, In.Pact, and Ranger, and 6 F for Stellarex. A 2000 IU bolus of heparin was injected through the sheath. Baseline angiography was performed through the angiography catheter to locate the renal arteries. A guidewire was pushed down to the distal left limb vessels and a DCB was positioned in the infrarenal aorta. Navigation time between DCB insertion and inflation in the infrarenal aorta was <30 seconds. The DCB was then inflated in the infrarenal aorta just below the renal arteries with an inflation pressure of 10 atmospheres for 180 seconds. The DCB was collected following retrieval. Two hours after the DCB inflation, the rabbits were euthanised by an intravenous pentobarbital injection at a dose of 120 mg/kg. The infrarenal aorta, a 10 mL blood sample, and a sample of three left hind leg muscles (tensor fasciae latae [TFL], vastus lateralis [VL], and tibialis anterior [TA] muscles) was harvested for measurement of PTX concentrations. Another sample of the same three left hind leg muscles was harvested for histology.

Paclitaxel analysis

Blood samples were centrifuged at 2000 *g* for 15 minutes to obtain the supernatant, which was again centrifuged at 2000 *g* for 10 minutes to purify the plasma. With the exception of the DCBs, aortas, muscles, and blood samples were frozen at -20°C .

The PTX concentrations were assessed using a standardised method of high performance liquid chromatography (HPLC) tandem mass spectrometry. Dosages were performed blindly by a single operator (SGD). Briefly, 50 μL of internal standard (docetaxel 1 mg/L) and 1 mL of methyl tert-butyl ether(-MTBE)/hexane (50/50 v/v) were added to 100 μL of plasma or 25 mg of tissue samples (aorta and muscles). Plasma samples were agitated for 20 minutes and tissue samples were crushed for 20 minutes. Then, all the samples (tissue and blood samples) were centrifuged and supernatants were vacuum evaporated. Ammonium formate/methanol (100 μL , 20/80 v/v) was added to reconstitute the dry residues. The remaining PTX on the DCBs after use was analysed after extraction with 10 mL of methanol. Dilutions in the 1/100th and in the 1/1,000th were directly injected after adding 50 μL of internal standard. With each series, a curve of calibration in 9 points was created from 0.1 ng/mL to 1000 ng/mL. The samples were analysed with Ultimate 3000 on a Hypersil Gold C18 column (1.9 μm , 150 \times 2.1) (ThermoFisher, France) using 20/80 (v/v) ammonium formate 2 mM/methanol as the mobile phase. Paclitaxel detection was made with a Quantiva mass spectrometer operating with electrospray ionisation in the positive mode, with specific MRM transitions for PTX and internal standard. The lower and upper limits of quantification were 0.1 and 1000 ng/mL, respectively.

Histological analysis

After euthanasia, one piece of 1 cm^3 each of TA, VL, and TFL muscles was isolated and fixed in formalin 10% over 24

hours for histological analysis. Briefly, muscles were dehydrated, embedded in paraffin, and 6 μm sections were cut. Sections were then deparaffinised in toluene and hydrated in ethanol baths. Several stains were used: haematoxylin eosin or Masson's trichrome to explore the structure of muscles. The histological slides were scanned using NanoZoomer 2.1 (Hamamatsu Photonics KK, Hamamatsu City, Japan). Histological analyses focused on paclitaxel crystal detection in the microvessels. Two slides were randomly studied for each muscle piece. In each slide, the number of arteries with paclitaxel crystal emboli was counted. This analysis was performed blind.

Statistical analysis

Stata/SE software (Version 13.0 for Mac) was used for statistical analysis. Data are given as median and interquartile range (IQR) for non-parametric distribution or mean \pm standard deviation for parametric distribution. For global comparison of the five groups (independent non-parametric samples), the Kruskal–Wallis test was used. When the Kruskal–Wallis test was significant, differences were assessed by comparing groups two by two using the Mann–Whitney *U* test. A *p* value < .05 was considered to indicate statistical significance.

RESULTS

Surgical procedures

In total, complete procedures were achieved in 25 rabbits (weight 3.84 ± 0.36 kg, aortic diameter 3.6 ± 0.1 mm). Inflation pressure of DCBs was 10.3 ± 0.5 atm for 180 seconds. Duration between DCB inflation in the infrarenal aorta and animal sacrifice was 122.5 ± 11.2 minutes. A retroperitoneal haematoma was found in one case during the autopsy but it did not lead to the death of the rabbit.

Paclitaxel analysis

In the TA muscle (the most distal muscle), concentrations of PTX were significantly lower for the Ranger (0.067 ng/mg) DCB than for the Lutonix (0.342 ng/mg; *p* = .008), In.Pact (0.370 ng/mg; *p* = .012), and Passeo-18-Lux (0.160 ng/mg; *p* = .021) DCBs. Similarly, concentrations of PTX were significantly lower for the Passeo-18-Lux than for the In.Pact DCB (*p* = .028) (Tables 2 and 3, Fig. 1).

Concentrations of paclitaxel were not significantly different between DCBs in TFL and VL muscles (Table 2, Fig. 1).

In the plasma, concentrations of PTX were significantly higher for Lutonix (9.00 ng/mL) than In.Pact (1.00 ng/mL; *p* = .008), Ranger (0.05 ng/mL; *p* = .007), Stellarex (0.08 ng/mL; *p* = .014), and Passeo-18-Lux (0.90 ng/mL; *p* = .014), and significantly lower for Ranger than In.Pact (*p* = .011) and Passeo-18-Lux (*p* = .011) (Tables 2 and 4, Fig. 1).

In the aorta, concentrations of PTX were significantly lower for Lutonix (35.2 ng/mg) than In.Pact (119.0 ng/mg;

Table 2. Paclitaxel concentrations in various tissues after aortic angioplasty in rabbits using different drug coated balloons (DCB)

	Lutonix	IN.Pact	Ranger	Stellarex	Passeo 18-Lux	<i>p</i>
Tensor fascia latae, ng/mg	0.162 (0.436–2.211)	0.450 (0.013–0.840)	0.092 (0.014–0.110)	0.047 (0.006–0.106)	0.290 (0.120–0.300)	.4115
Vastus lateralis, ng/mg	0.108 (0.322–0.395)	0.610 (0.290–0.760)	0.140 (0.110–0.200)	0.132 (0.062–0.375)	0.110 (0.030–0.440)	.3848
Tibialis anterior, ng/mg	0.342 (0.225–0.451)	0.370 (0.280–0.950)	0.067 (0.047–0.067)	0.055 (0.041–0.360)	0.160 (0.100–0.170)	.0062
Plasma, ng/mL	9.00 (7.50–10.80)	1.00 (0.70–1.10)	0.05 (0.05–0.40)	0.08 (0.05–0.50)	0.90 (0.80–1.00)	.0007
Aortic wall, ng/mg	35.2 (27.2–66.8)	119.0 (113.0–137.0)	568.0 (113.0–740.0)	113.5 (76.5–132.5)	77.0 (75.0–155.0)	.0123
DCB after use, µg	1364.1 (587.5–2013.0)	3643.5 (3613.1–3803.8)	2500.9 (2467.8–3214.3)	1335.85 (1219.9–2075.1)	2522.50 (2259.0–2896.1)	.0022

Data are reported as medians (interquartile ranges). *p* values correspond to the results of the Kruskal–Wallis test. *p* < .05 indicates a statistically significant difference between at least two groups for the variable assessed. DCB = drug coated balloon.

Table 3. Differences between drug coated balloons (DCB) regarding paclitaxel (PTX) concentrations found in rabbit tibialis anterior muscle after aortic angioplasty

Group/tibialis anterior	Lutonix	IN.Pact	Ranger	Stellarex
In.Pact	0.792	–	–	–
Ranger	0.008	0.012	–	–
Stellarex	0.165	0.110	0.902	–
Passeo-18-Lux	0.052	0.028	0.021	0.268

Table reports *p* values from Mann–Whitney U tests comparing groups of rabbits treated with different DCBs. *p* < .05 indicates a statistically significant difference between the two groups for the PTX concentration in the tibialis anterior muscle. PTX = paclitaxel; DCB = drug coated balloon.

p = .004), Ranger (568.0 ng/mg; *p* = .009), Stellarex (113.5 ng/mg; *p* = 0.038), and Passeo-18-Lux (77.0 ng/mg; *p* = .030) (Tables 2 and 5, Fig. 1).

Remnant amounts of PTX after DCB use were significantly lower for Lutonix (1364.1 µg) than In.Pact (3643.5 µg; *p* = .004), Ranger (2500.9 µg; *p* = .017), and Passeo-18-Lux (2522.50 µg; *p* = .017), and significantly higher for In.Pact than Lutonix (*p* = .004), Ranger (*p* = .032), Stellarex (1335.85 µg; *p* = .016), and Passeo-18-Lux (*p* = .016) (Tables 2 and 6, Fig. 1).

Histological analysis

Histological analysis of muscle tissue samples revealed evidence of embolised PTX with some crystals in small arterioles with all DCBs (Fig. 2). PTX crystals were identified in one to eight arteries per slide, with a mean of 4.30 ± 2.08 emboli. The number of PTX emboli was not significantly different between the DCBs (*p* = .141).

DISCUSSION

The present study was designed to evaluate the embolic profiles of the five main DCBs used in France. To assess downstream tissue PTX emboli and PTX distribution during and immediately after DCB use, the muscle tissue samples,

the aorta, the plasma, and the DCBs used were analysed. Histological analysis showed some PTX crystals in several muscle tissue samples, highlighting the reality of distal embolisation after inflation of DCBs in the arteries. Some significant differences were found in terms of concentrations of PTX in the muscles between the five DCBs, which can be explained by the differences between the PTX formulations (crystalline, microcrystalline, or amorphous), the technique of PTX deposition (pulverisation or micro-pipetting), the balloon state during PTX deposition (inflated or deflated), the dose of PTX on the DCBs, and the excipient (Table 1). Crystals enter the arterial wall and serve as a long-term PTX reservoir, allowing sustained anti-proliferative effects,¹⁸ but distal embolisation of crystalline PTX can cause fibrinoid necrosis with serious clinical consequences.^{21,22} The anti-proliferative effects may have an impact on wound healing in the setting of ischaemic ulcers, especially when ulcers are secondary to below knee lesions.²⁴

Endovascular treatment became the first line therapy in peripheral vascular disease but the one year primary patency of PBA can be as low as 50% in the femoropopliteal segment, with subsequent target lesion re-interventions (TLR).^{1–15} DCBs are now considered a valuable alternative to stents because they decrease the rate of restenosis by intimal hyperplasia without leaving a permanent scaffold in place. Several randomised controlled trials (RCTs)^{1–15} concluded that primary patency and TLR were better after DCB angioplasty than PBA in femoropopliteal disease. Cost effectiveness studies also support DCB use. However, results of RCTs are more heterogeneous when looking at infrapopliteal lesions. There is the potential for bio-resorbable scaffolds to be used in association with DCBs in future^{25,26} to avoid permanent scaffolding of the treated arteries.

The DEBATE-BTK study²⁷ found lower restenosis and TLR rates after DCB use in diabetic patients with CLI. In contrast, the BIOLUX P-II²⁸ and IN.PACT DEEP²³ studies showed no significant differences between DCB and PBA in terms of restenosis, TLR, or occlusion. Of interest, the IN.PACT DEEP

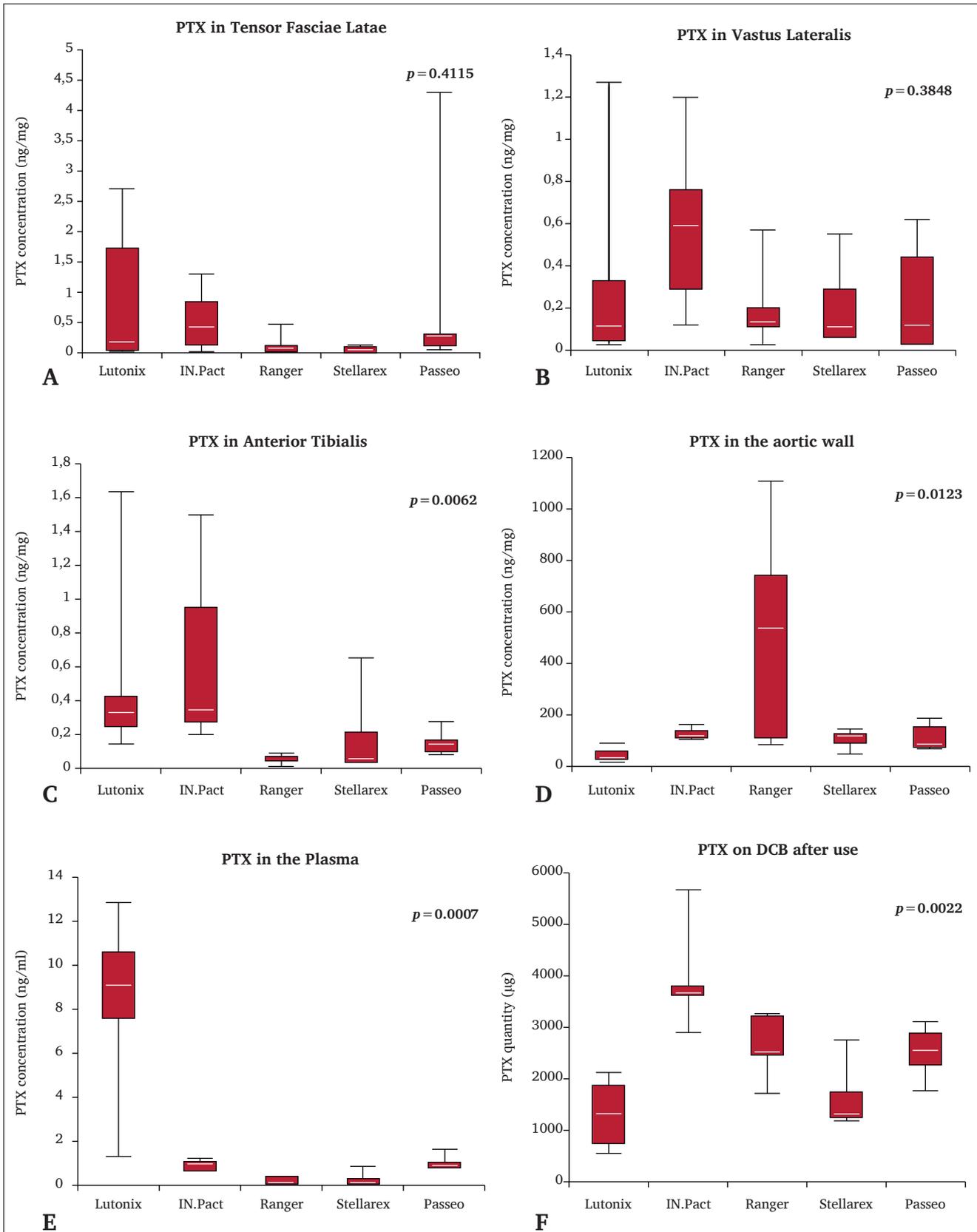


Figure 1. Concentrations of paclitaxel per group in the three analysed muscles (A, B, C), the aortic wall (D), the plasma (E), and the DCBs after use (F). The bands inside the boxes correspond to the medians. Box plots correspond to interquartile ranges. Whisker plots are the minimums and the maximums. The p value is from the Kruskal–Wallis test. DCB = drug coated balloon; PTX = paclitaxel; Passeo = Passeo-18-Lux.

Table 4. Differences between drug coated balloons (DCB) regarding paclitaxel (PTX) concentrations in rabbit plasma after aortic angioplasty

Group/plasma	Lutonix®	In.Pact®	Ranger®	Stellarex®
In.Pact	0.008	—	—	—
Ranger	0.007	0.011	—	—
Stellarex	0.014	0.064	0.893	—
Passeo-18-Lux	0.014	0.916	0.011	0.082

Table reports *p* values from Mann–Whitney U tests comparing groups of rabbits treated with different DCBs. *p* < .05 indicates a statistically significant difference between the two groups for the PTX concentration in the plasma. PTX = paclitaxel; DCB = drug coated balloon.

Table 5. Differences between drug coated balloons (DCB) regarding paclitaxel (PTX) concentrations in rabbit aortic wall after aortic angioplasty

Group/aortic wall	Lutonix	In.Pact	Ranger	Stellarex
In.Pact	0.004	—	—	—
Ranger	0.009	0.463	—	—
Stellarex	0.038	0.556	0.286	—
Passeo-18-Lux	0.030	0.548	0.095	0.905

Table reports *p* values from Mann–Whitney U tests comparing groups of rabbits treated with different DCBs. *p* < 0.05 indicates a statistically significant difference between the two groups for the PTX concentration in the aortic wall. PTX = paclitaxel; DCB = drug coated balloon.

Table 6. Differences between drug coated balloons (DCB) regarding paclitaxel (PTX) quantity remaining on the DCB after aortic angioplasty in rabbits

Group/aortic wall	Lutonix	In.Pact	Ranger	Stellarex
In.Pact	0.004	—	—	—
Ranger	0.017	0.032	—	—
Stellarex	0.762	0.016	0.111	—
Passeo-18-Lux	0.017	0.016	0.841	0.111

Table reports *p* values from Mann–Whitney U tests comparing groups of rabbits treated with different DCBs. *p* < .05 indicates a statistically significant difference between the two groups for the PTX quantities on DCBs after use. DCB = drug coated balloons; PTX = paclitaxel; DCB = drug coated balloon.

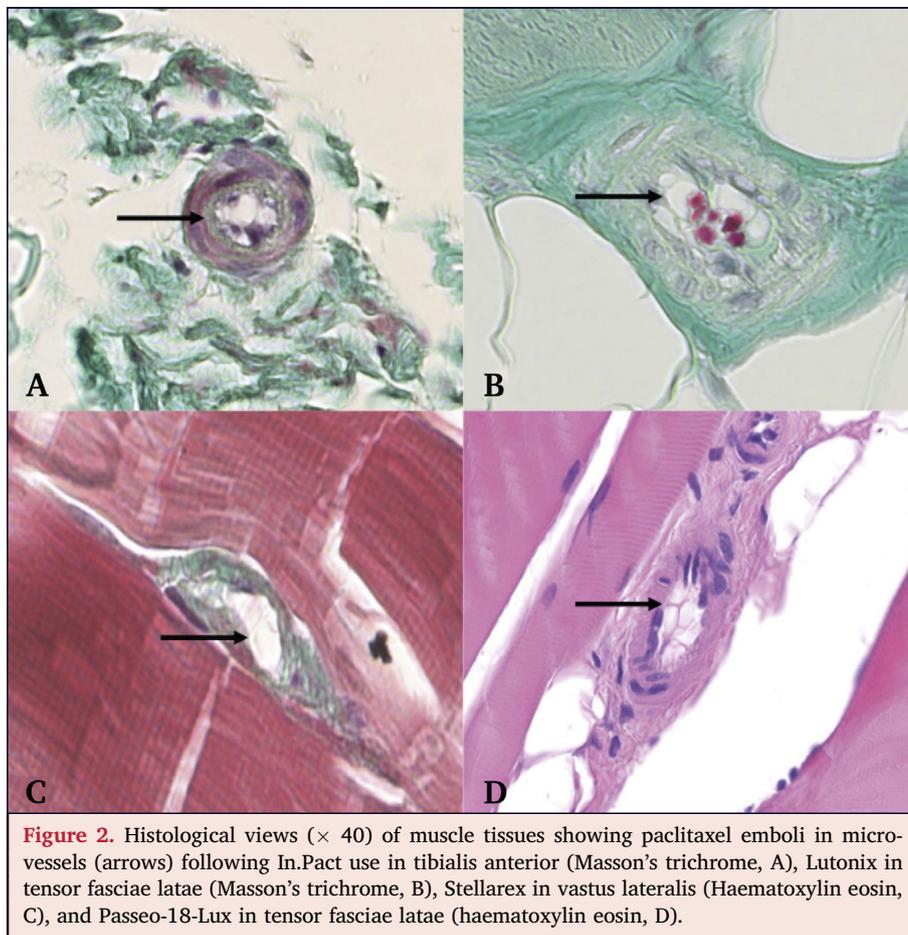
study²³ had to be stopped prematurely because of a trend towards an increase in the major amputation rate at 12 months in patients treated with DCB (8.8% vs. 3.6%; *p* = .080). One suspected cause was PTX particle embolism in distal arteries, which could lead to arterial occlusion and non-healing wounds. Kolodgie et al.¹⁹ compared Lutonix and In.Pact balloons in terms of distal embolisation in swine. Although the embolism rate was low in both groups, differences were found between DCBs (In.Pact 15.4% vs. Lutonix 7.7%; *p* = .04). In the present study, higher PTX concentrations were also found in the TA muscle after In.Pact DCB use, but embolisation rates after Lutonix were also concerning. In contrast, Ranger use was associated with significantly lower

embolisation rates. This may be explained by the characteristics of the Ranger DCB excipient and coating. The citrate ester is known to be hydrophobic and lipophilic. A hydrophobic coating may provide substantial protection against PTX loss while navigating and inflating the DCB. At the same time, the sorbitol used as the excipient of the Lutonix is known to be highly soluble in water,²⁹ which may facilitate excipient and PTX downstream washing while navigating and inflating this DCB. The In.Pact balloon has a hydrophobic coating with the urea but uses higher concentrations of macrocrystalline PTX, which could also be responsible for higher rates of distal PTX concentrations. Macrocrystals could be more susceptible to occlude distal microvessels and could be detected in the muscles.

Regarding aortic penetration of the PTX, the present study highlights significantly lower rates of PTX when using the Lutonix balloon and higher (but non-significant) PTX concentrations with the Ranger DCB. The lipophilic features of the Ranger DCB could explain the satisfactory PTX diffusion in the artery wall. One hypothesis to explain the disappointing results of the Lutonix DCB is that a lot of PTX is lost during the navigation before arrival at the target artery, as underlined by the high levels of PTX found in the plasma. In contrast, with the Ranger balloon, the lipophilic effect keeps the PTX in the artery wall because of the presence of cellular lipids in the arterial wall. The present study did not use an atherosclerosis model in rabbits, but a previous study in humans identified a fatty streak in the intima as early as during childhood, with the presence of T cells and sometimes foam cells.³⁰

The clinical relevance of the detected doses of PTX remains to be elucidated. The PTX concentrations detected in the muscle samples are low and may have no negative impact in terms of wound healing. Recently, the results of the Global Lutonix DCB Below-the-Knee (BTK) Registry in patients with Rutherford class 3 to 5 and ≥70% stenosis of native BTK arteries were reported, with high rates of freedom from primary safety events and freedom from amputation at six months.³¹ Similar results were found with the Lutonix Global SFA (Superficial Femoral Artery) Registry at 12 and 24 months,³² and with the In.Pact DCB.²⁹ Although the present study found significantly more distal emboli after Lutonix and In.Pact inflations, the results of the above mentioned clinical registries^{31–33} showed that these two DCBs are relatively safe in a clinical setting. Of note, the most severe patients (Rutherford 6) were excluded. Therefore, the impact of distal PTX embolisation on ulcer healing remains to be determined.

Another question regards the PTX concentration needed in the arterial wall to be effective on intimal proliferation. In the present study, the Lutonix DCB had the lowest PTX concentrations in the aorta and a lower efficiency could be suspected. The Lutonix DCB was assessed in a well conducted, large, randomised trial, the LEVANT II trial,⁴ and showed its superiority compared with the PBA. However, primary patency rates reported with the Lutonix DCB in the LEVANT II trial appear lower than those reported with the four other tested balloons in specific randomised



trials,^{1,2,12,13} although no head to head comparison has been published to date. A prospective trial directly comparing relevant clinical outcomes with the DCBs available in the femoropopliteal segment is needed. An analysis of the amputated or debrided tissues could assess the importance of distal PTX embolisation in humans.

This study has several limitations. First, healthy rabbits without atherosclerosis were used for this study. Rabbits were chosen for the experiments because they have a similar vascular anatomy to humans, but it is known that PTX delivery during DCB inflation is different between healthy and atherosclerotic arteries.³⁴ It would be useful to repeat this work in atherosclerotic models. Second, the number of rabbits in each group is small, which can lead to a lack of power. This may explain substantial but non-significant differences between groups. Third, DCBs were inflated in the aorta, not in below knee arteries. Flows may be different between these arterial levels and this may influence the embolisation rate. Fourth, the amount of PTX lost on the sheath during DCB insertion was not analysed. However the amount of PTX lost in the sheath can vary according to the type of sheath used. Fifth, rabbits were sacrificed two hours after DCB inflation, but PTX effects are not limited to the first hours following PTX delivery.^{17,35,36} Studies with a longer

follow up may highlight different results. Finally, only the DCBs available on the French market at the time of study were assessed. A larger study including all currently available DCBs could provide additional and valuable information.

CONCLUSION

This study suggests some differences regarding distal embolisation profiles between the five assessed DCBs. The Ranger and the Stellarex DCBs seem to have the best profiles with low distal PTX concentrations, reasonable plasma PTX loss, and satisfactory aortic penetration. In contrast, the Lutaonix DCB had the most disappointing features. Although clinical implications remain to be demonstrated, the present results may have implications when choosing a DCB, especially in a CLI setting.

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CONFLICT OF INTEREST

Raphael Coscas has been a consultant for Medtronic Inc., Spectranetics Inc. and Bard Inc. The other authors have no conflicts of interest.

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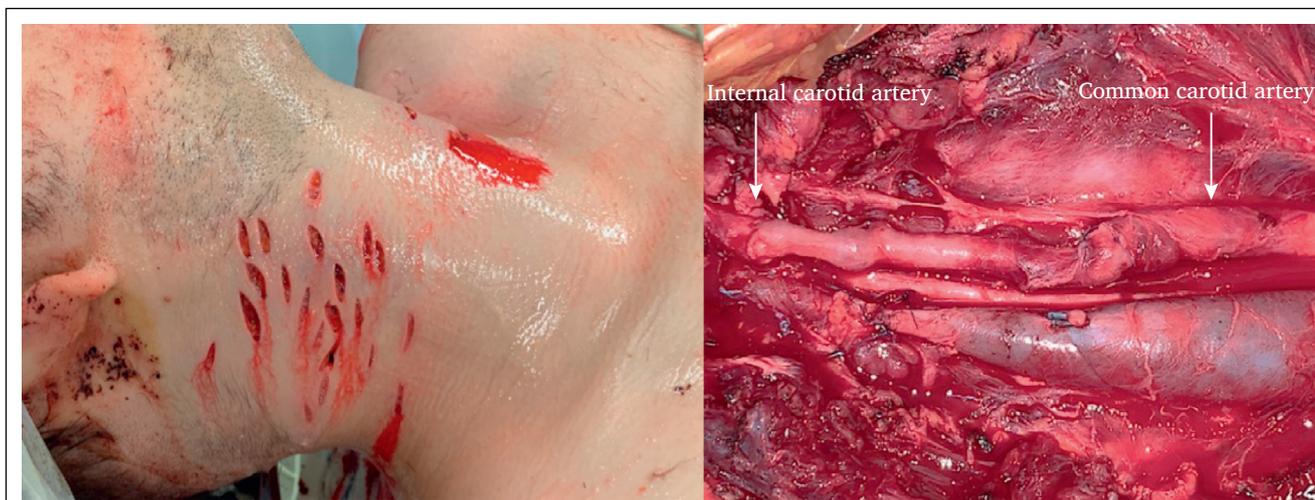
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COUP D'OEIL

Emergency Carotid Transection Treatment Following Multiple Cervical Stab Injuries

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A 25 year old man who attempted suicide was admitted with multiple cervical stab injuries. Emergency neck exploration was undertaken. When proceeding with dissection of the cervical vessels, transection of the carotid bifurcation was detected. The common carotid artery was approached and clamped before both the external and internal carotid arteries. Sacrificing the external carotid artery, it was decided to interpose a segment of great saphenous vein to create a common to internal carotid artery bypass. The patient was discharged on day 7 following an uneventful post-operative recovery.

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