LABORATORY INVESTIGATION

Comparison of Particulate Embolization after Femoral Artery Treatment with IN.PACT Admiral versus Lutonix 035 Paclitaxel-Coated Balloons in Healthy Swine

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ABSTRACT

Purpose: Different carrier excipients unique to individual drug-coated balloons (DCBs) may influence embolic safety characteristics in peripheral vascular territories through embolization of released particulates. A comparator study of IN.PACT Admiral vs Lutonix 035 balloons in healthy swine was therefore performed to assess which balloon produces more downstream emboli.

Materials and Methods: Single or overlapping 80-mm IN.PACT and Lutonix 035 DCBs were assessed in the femoral arteries of 21 swine with 28- and 90-day follow-up, with standard balloon angioplasty as a control. Histologic analysis of arterial wall and downstream skeletal muscle and coronary band was performed. This analysis was supported by an analytic measurement of paclitaxel levels.

Results: IN.PACT DCBs demonstrated a more pronounced change in medial wall composition, characterized by a paclitaxel-induced loss of medial smooth muscle cells accompanied by increased proteoglycans. The percentage of sections with arterioles exhibiting paclitaxel-associated fibrinoid necrosis in downstream tissues was higher at 90 days with overlapping IN.PACT DBCs compared with Lutonix 035 DCBs (46.2% [interquartile range, 19.2–57.7] vs 0.0% [0.0–11.5]; $P = .01$), with similar trends noted for 28-day single and overlapping DCBs. Drug analysis in parallel tissues further confirmed higher paclitaxel concentrations in nontarget tissues for IN.PACT than Lutonix 035 balloons for single and overlapping configurations at both time points. Rare embolic crystalline material was observed in downstream tissues, but only for IN.PACT balloons.

Conclusions: There was more fibrinoid necrosis in tissues treated with IN.PACT DCBs compared with Lutonix DCBs, suggesting increased emboli debris with higher paclitaxel levels.

ABBREVIATIONS

CLI = critical limb ischemia, DCB = drug-coated balloon, DES = drug-eluting stent, IQR = interquartile range, PAD = peripheral arterial disease, PTA = percutaneous transluminal angioplasty, SFA = superficial femoral artery, SMC = smooth muscle cell

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Appendix A and Table E1 are available online at *www.jvir.org*.

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Femoropopliteal disease treated by endovascular therapy with adjunctive local drug delivery via recently developed drug-eluting stents (DESs) or drug-coated balloons (DCBs) has led to further improvements in early clinical outcomes (1–3). However, limitations unique to each of these drug-delivery platforms may impair their long-term clinical effectiveness, particularly for relatively challenging territories such as the occlusion-prone superficial femoral artery (SFA). This target vessel is uniquely one of the longest and most dynamically active arteries, continuously exposed to torsion, compression, flexion, and extension caused by hip and knee motion during walking (4,5). Lower-limb vessels such as the SFA are also more susceptible to atherosclerosis because of low shear stress and spiral flow, which is most appreciated in the long segment of its lesser curvature (6). The stentless technology of DCBs

offers a unique advantage by providing the same antiproliferative agent through more rapid transfer of drug with a presumably more homogeneous distribution on the luminal surface, as opposed to confined to struts on a scaffold platform. Moreover, unlike stents, there is no durable or biodegradable polymer carrier or rigid metallic frame with a DCB, thereby avoiding a potential unfavorable chronic foreign body response that could contribute to in-stent restenosis.

To date, the most commonly used drug for DCB technology is paclitaxel, which has high lipophilic physiochemical properties, allowing passive absorption through the cell membrane and a sustained effect within the treated vessel wall (7). Drug delivery to the luminal surface is facilitated by markedly different carrier excipients such as iopromide, urea, or polysorbate/sorbitol. Therefore, each DCB technology is unique and should be evaluated separately (8). Of the two most current leading devices, the Lutonix 035 DCB (Lutonix, New Hope, Minnesota) is a low-dose (2 μg/mm^2) paclitaxel-coated balloon with a polysorbate/sorbitol carrier, whereas the IN.PACT Admiral DCB (Medtronic, Santa Rosa, California) is loaded with a higher concentration of paclitaxel (3.5 μg/mm^2) and uses a urea-based excipient, in a combination referred to as FreePac. The excipient coating and crystallinity of the drug/excipient combination is the main proprietary feature separating the various DCB technologies, and it is of great importance considering that its function is to facilitate the release and transfer of paclitaxel into the arterial wall.

The findings of embolic debris from DCB coatings may be further compounded in patients with claudication and more complex critical limb ischemia (CLI) with limited flow reserve. Therefore, the purpose of the present study was to perform a direct comparison of two leading paclitaxel DCBs (IN.PACT Admiral and Lutonix 035) recently approved by the Food and Drug Administration in a preclinical porcine model by a histologic examination of femoral arteries and associated distal nontarget territories to determine the local tissue reaction of the treated artery and embolic safety characteristics.

MATERIALS AND METHODS

Animals and Animal Care

The animal care protocol was reviewed and approved by the institutional animal care and use committee. A total of 21 Yorkshire Cross domestic swine (mean weight, 49 kg ± 2.74) received DCB or percutaneous transluminal angioplasty (PTA) treatments to the external right and left femoral arteries. Detailed methods are described in **Appendix A** (9) (available online at *www.jvir.org*).

Porcine Femoral Artery Balloon Angioplasty

DCB treatment groups consisted of single therapeutic dosing (ie, single balloon) with paclitaxel-coated balloons or control (ie, balloons with no drug coating), whereas safety margin dosing consisted of similar overlapping balloons (n = 3 balloons). For repeat inflations, three sequential/independent balloons were used whereby each DCB was aligned by using fiducial point(s) as visualized by angiography to achieve an ~100% margin of coverage with matching lengths of 80-mm overlap (**Fig 1**).

Lutonix 035 DCBs (paclitaxel 2.0 μg/mm^2 with polysorbate/sorbitol carrier; Lutonix), IN.PACT Admiral balloon catheters (paclitaxel 3.5 μg/mm^2 with urea carrier; Medtronic), and uncoated PTA balloon catheters (RIVAL; Bard Peripheral Vascular, Tempe, Arizona) were provided in diameters of 4.0, 5.0, or 6.0 mm and lengths of 80 mm. A maximum of two treatment sites per animal (right and left external or internal femoral arteries) were treated. Balloon inflations were performed within 1 minute of insertion at a target overstretch of 10%–15% (balloon-to-artery ratio of 1.1–1.2:1.0) for 30 seconds. For single and overlapping DCBs, a new balloon was used for each treatment, whereas the same control PTA balloon was used for vessels with repeated dilations. There were five arteries treated with single DCBs and five arteries treated with 3× overlapping DCBs for each device in the 28-day survival animals, for a total of 14 animals. Only overlapping balloons (ie, 3×; five arteries for each DCB type) were used to treat the seven pigs that survived for 90 days (**Table 1**).

Collection of Porcine Tissues

Animals survived to their scheduled euthanasia time point of 28 or 90 days. On the day of euthanasia, animals were anesthetized before euthanasia, and necropsies and gross examinations were performed afterward. All treated femoral arteries were flushed with 1 L of lactated Ringer solution, followed by perfusion fixation with 10% neutral-buffered formalin at 80–120 mm Hg pressure for 10 minutes. The treatment site was marked in situ, and the femoral arteries were sharply dissected with flanking nontreated segments ~2.0–2.5 cm in length.

The skeletal muscle and coronary band samples downstream from the external or internal femoral arteries were examined for distal particulates consistent with balloon coatings; in total, six skeletal muscle territories and a coronary band sample were collected from each leg and immersion-fixed in 10% neutral-buffered formalin for histologic examination. The gastrocnemius, gluteal, and gracilis are skeletal muscle territories distal to the external femoral artery, and the rectus femoris, semitendinosus, and semimembranosus