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Original article

Safety and Efficacy of Different Paclitaxel-eluting Balloons in a Porcine Model

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A B S T R A C T

Introduction and objectives: Paclitaxel-eluting balloons have shown high antiproliferative efficacy in the treatment and prevention of restenosis. Nevertheless, not all available devices are equally effective, which makes it interesting to compare results in a preclinical model. Our objective was to assess the preclinical efficacy and safety of different devices.

Methods: We implanted 51 metallic stents (Architect®, iVascular) in 17 domestic swine (mean, 25 [3] kg), inserting 1 stent per major coronary artery. Stent postdilatation was performed with different control balloons (n = 10) or paclitaxel-eluting balloons: paclitaxel-eluting balloon 1 (iVascular) (n = 15); paclitaxel-eluting balloon 2 (iVascular) (n = 16) and In.Pact Falcon® (Medtronic) (n = 10). The restenosis rate (using angiography and histomorphometry) and vascular healing parameters (balloon-related vascular injury score, endothelialization rate, and fibrin and inflammation scores) were analyzed at 28 days.

Results: The distinct paclitaxel-eluting balloons showed a similar degree of stenosis at follow-up, which was significantly lower than that in the control group: diameter stenosis was 9% (12%) vs 34% (18%) by angiography ($P < .0001$) and was 22% (8%) vs 51% (18%) by histomorphometry ($P < .0001$). Scores for vascular injury (mean, 0.6 [0.5]) and inflammation (mean, 0.8 [0.3]) were uniformly low across all groups. Drug effect markers differed significantly between the paclitaxel-eluting balloons and control groups, with lower endothelialization rates (87% [10%] vs 99% [2%]; $P = .0007$) and higher fibrin scores (2.1 [0.7] vs 0.4 [0.5]; $P < .0001$) in the paclitaxel-eluting balloons groups. There were no differences between the different paclitaxel-eluting balloons.

Conclusions: In this preclinical model, the paclitaxel-eluting balloons studied significantly reduced in-stent restenosis compared with the control balloons. Although there were no findings of persistent vascular injury or inflammation, delayed endothelialization and fibrin aggregate suggest a drug deposition response.

Análisis de la eficacia y la seguridad de distintos balones liberadores de paclitaxel en un modelo animal

Palabras clave:
Modelo animal
Stent
Balón liberador de paclitaxel
Restenosis
Reparación vascular

R E S U M E N

Introducción y objetivos: Los balones liberadores de paclitaxel tienen demostrada eficacia en el tratamiento y la prevención de la restenosis. Sin embargo, no todos los dispositivos comercializados son igualmente efectivos; por ello es importante comparar los resultados en un modelo preclínico. Nuestro objetivo es analizar la seguridad y la eficacia preclínicas de distintos dispositivos.

Métodos: En 17 cerdos domésticos (25 ± 3 kg) se implantaron 51 *stents* metálicos (Architect®, iVascular), uno en cada rama coronaria principal, y se sobredilataron con distintos balones de control (n = 10) o liberadores de paclitaxel: balón liberador de paclitaxel 1 (iVascular) (n = 15); balón liberador de paclitaxel 2 (iVascular) (n = 16) e In.Pact Falcon® (Medtronic) (n = 10). Tras 28 días, se analizaron los resultados de restenosis (angiografía e histomorfometría) y de reparación vascular: daño vascular, endotelización, persistencia de fibrina e inflamación.

Resultados: Los distintos balones liberadores de paclitaxel mostraron valores similares de estenosis en el seguimiento significativamente menores que los controles: angiografía, el 9 ± 12% frente al 34 ± 18% (p < 0,0001); histomorfometría, el 22 ± 8% frente al 51 ± 18% (p < 0,0001). Los grados de daño vascular (0,6 ± 0,5) e inflamación (0,8 ± 0,3) fueron bajos, sin diferencias entre los grupos. Los marcadores del efecto farmacológico fueron significativamente distintos entre los dispositivos liberadores de paclitaxel (sin diferencias entre ellos) y los controles: superficie endotelizada, el 87 ± 10% frente al 99 ± 2% (p = 0,0007); grado de fibrina, 2,1 ± 0,7 frente a 0,4 ± 0,5 (p < 0,0001). No hubo diferencias entre los distintos balones liberadores de paclitaxel.

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Conclusiones: En este modelo preclínico, los balones liberadores de paclitaxel analizados mostraron una reducción significativa de la restenosis. Aunque no se observaron datos de daño vascular o inflamación persistentes, sí se apreciaron los efectos de la acción farmacológica en forma de endotelización retrasada y acumulación de fibrina.

Abbreviations

PEB: paclitaxel-eluting balloon

INTRODUCTION

Coronary stents provide coating and luminal support, virtually eliminating the phenomenon of elastic recoil and subsequent negative vascular remodeling. As a result, the incidence of restenosis is 30% lower than in balloon angioplasty procedures.[1,2] However, metallic stents do not reduce intimal hyperplasia and they also trigger hyperproliferation. Drug-eluting stents have virtually eliminated restenosis caused by neointimal proliferation.[3,4] The drawback is that they have been found to delay and impair vascular healing,[5–8] the clinical implications of which may be stent thrombosis[5–7] and neoatherosclerosis.[9,10] Permanent polymer coating has been associated with persistent inflammation, hypersensitivity, and deficient vascular healing in experimental models[11,12] and human autopsy studies alike.[5,6,13]

To prevent these undesirable effects, alternative antiproliferative drug administration systems have been proposed, such as paclitaxel-eluting balloons (PEBs), which have proven efficacy in the prevention and treatment of restenosis in animal models[14,15] and in clinical trials.[16,17] However, not all currently-available PEBs yield the same results,[18–22] and it would therefore be interesting to conduct a comparative analysis of various devices. This study aimed to compare the safety and efficacy results of various PEBs in the recommended[23,24] porcine healthy coronary artery model, and to determine drug release kinetics and arterial drug deposition.

METHODS

Animal Model

In this experimental, randomized, controlled study with blinded final sample analysis, we used 17 domestic large white pigs, aged 2-3 months, weighing 25 (3 kg), from the experimental farm of our center. All procedures were carried out according to current Spanish regulations (Royal Decree 53/2013, of February 1, laying down the basic standards for the protection of animals used for experimental and other scientific purposes, including teaching) and European Directive 2010/63/EC. The local ethics committee approved the study protocol before we started any procedures.

All the pigs were given antiplatelet pretreatment with acetylsalicylic acid (325 mg) and clopidogrel (300 mg) 24 h before the procedure. The anesthetic protocol and surgical preparation of the animals have been previously described in the literature.[25,26] Briefly, the animals were prepared and then administered heparin 5000 IU intravenously. A left carotid artery approach was used to perform angiography in both coronary arteries, with prior administration of intracoronary nitroglycerin.

Coronary Procedure

With the aim of implanting the devices to achieve a stent-to-artery ratio of 1.1 to 1.2, the best segment was located in each of the 3 major coronary arteries. After passing the angioplasty guidewire, a cobalt-chromium stent (Architect®, iVascular) was implanted in each major coronary artery. The stents were 14 mm in length, with a diameter of 3.5 mm (left anterior descending and right coronary artery) or 3 mm (in the circumflex). We adjusted balloon inflation pressure to achieve the desired overstretching. After stent deployment, we performed postdilatation with various balloons, using the same diameter as the implanted stent and a length of 20 mm, following a randomization table. We inflated the balloons at the manufacturers' recommended nominal pressure for 1 or 2 min (26 and 25 balloons, respectively) in a randomized manner, to analyze any differences in drug release by device type.

Devices Analyzed

The following balloons were used (numbers in parentheses):

1. Conventional plain balloon angioplasty control (n = 10): Xperience® (iVascular).
2. PEB 1 (n = 15): experimental formulation 1 (iVascular). The Xperience® balloon is coated with paclitaxel (3 $\mu g/mm^2$ balloon surface) in a nanocrystalline formulation combined with a biocompatible plasticizer using TransferTech® ultrasonic deposition technology. This results in a homogeneous thin coating. The manufacturer estimates a theoretical drug release time of 30 to 60 s, which means that balloon inflation for longer than 60 s would not lead to any additional drug release.
3. PEB 1 (n = 16): experimental formulation 2 (iVascular). This is similar to PEB 1, with a more hydrophilic drug carrier matrix. The combination of the hydrophilic groups in this new matrix with hydrophobic groups already present in the backbone provides increased polarity in the coating, which potentially increases the solubility of the drug itself.
4. PEB 3 (n = 10): Marketed PEB In.Pact Falcon® (Medtronic). The paclitaxel formulation (3 $\mu g/mm^2$ balloon surface) is also crystalline. The excipient, urea, is applied to the balloon using FreePac® technology.

All materials were supplied by iVascular, including PEB 1 and PEB 2, which are not yet available in the market. After the treatment had been applied, the balloons were then analyzed to determine the quantity of paclitaxel remaining in them, using high performance liquid chromatography.

Angiographic Analysis

After completing the above-described procedure on each artery, we then repeated the coronary angiography (with prior administration of intracoronary nitroglycerin) to determine the minimal luminal diameter in the stent. A control coronary angiography was performed at 28 days to determine the follow-up minimal luminal diameter. We measured the 2 variables and the reference diameters of the treated artery (mean diameter of the arterial segments located 5 mm proximal and distal to the stent edges) using the automatic quantitative coronary analysis software Medis QCA-CMS ®, version 6.1. The following angiographic restenosis parameters were calculated: