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Original article

Safety and Efficacy of New Sirolimus-eluting Stent Models in a Preclinical Study

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ABSTRACT

Introduction and objectives: Initial preclinical studies are required during the process of improving polymers, platforms, and drug-eluting systems for new coronary stent designs. Our objective was to analyze the efficacy and safety of new drug-eluting stent models compared with a conventional stent and commercialized drug-eluting stents in an experimental model with healthy porcine coronary arteries.

Methods: Sixty stents (conventional stent, new sirolimus-eluting stents: drug-eluting stents 1, 2 and 3; Cypher® and Xience®) were randomly placed in the coronary arteries of 20 Large White domestic pigs. Angiographic and histomorphometric studies were done 28 days later.

Results: The stents were implanted at a stent/artery ratio of 1.34 ± 0.15, with no significant differences between groups. The new stents showed less late loss and angiographic restenosis than conventional stents ($P = .006$ and $P < .001$, respectively). Histologically, restenosis and neointimal area were lower with all the new platforms than with the conventional stents ($P < .001$ for each variable), and no differences were found vs the drug-eluting stents on the market. Safety data showed that endothelialization was lower with drug-eluting stents than with conventional stents, except for drug-eluting stent 3 ($P = .084$). Likewise, inflammation was lower with drug-eluting stent 3 than with other stents.

Conclusions: The new drug-eluting stent platforms studied are associated with less restenosis than conventional stents and showed no significant differences in safety or efficacy vs commercialized drug-eluting stents.

Seguridad y eficacia de nuevos modelos de *stents* liberadores de sirolimus en el modelo preclínico

Palabras clave:
Modelo preclínico
Stent liberador de fármaco
Restenosis
Reparación vascular

RESUMEN

Introducción y objetivos: En el proceso de mejora de los polímeros, las plataformas y los sistemas de liberación de fármacos en los nuevos diseños de *stents* farmacoactivos, el análisis preclínico inicial es obligatorio. El objetivo es analizar la eficacia y la seguridad de nuevos modelos de *stents* farmacoactivos en comparación con un *stent* convencional y *stents* farmacoactivos comercializados en el modelo experimental de arteria coronaria sana porcina.

Métodos: Se implantaron aleatoriamente 60 *stents* (*stent* convencional, nuevos *stents* liberadores de sirolimus: *stents* liberadores de fármaco 1, 2 y 3; Cypher® y Xience®) en las arterias coronarias de 20 cerdos domésticos raza *Large White*. Se realizó estudio angiográfico e histomorfométrico a los 28 días.

Resultados: Los *stents* se implantaron en proporción *stent*/arteria de 1,34 ± 0,15, sin diferencias significativas entre grupos. Los nuevos *stents* mostraron menos pérdida tardía y restenosis angiográfica que los convencionales (p = 0,006 y p < 0,001 respectivamente). Todas las nuevas plataformas presentaron menos área neointimal y restenosis histológica que los *stents* convencionales (p < 0,001 para cada variable), sin diferencias con los farmacoactivos comercializados. En cuanto a la seguridad, todos los *stents* farmacoactivos mostraron menos endotelización que los convencionales, salvo el *stent* liberador de fármaco 3 (p = 0,084). Asimismo, la inflamación observada fue menor con el *stent* liberador de fármaco 3 que con los demás.

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Conclusiones: Las nuevas plataformas de *stents* farmacoactivos estudiadas se asocian con menos restenosis que los convencionales, sin diferencias significativas en seguridad y eficacia respecto a los *stents* farmacoactivos comercializados.

Abbreviations

CS: conventional stent
DES: drug-eluting stent
MLD: minimal luminal diameter

INTRODUCTION

Drug-eluting stents (DES) are one of the greatest advances made in the percutaneous treatment of coronary disease. These devices have consistently provided lower rates of target vessel revascularization than conventional stents (CS) in a wide range of clinical situations.[1–4] However, the risk of late and very late thrombosis associated with these stents is still a cause for concern.[5,6] This phenomenon has been related to the deleterious effects of the drug, polymer, stent platform, or a combination of all 3 on the vessel wall, leading to incomplete endothelialization, persistent inflammatory reactions, and the development of neoatherosclerosis.[7–11]

To overcome these limitations, innovations have been made in platform design and drug-eluting systems, polymers have been developed that are more biocompatible or resorbable, and even a completely resorbable DES has been designed.[12–14] Preclinical animal studies have been deemed very useful for analyzing the differences among new devices because the sequence of biological events associated with arterial healing (injury caused by the stent, fibrin deposits, inflammation and cell proliferation) is similar to that in humans.[15–17] Experimental models with healthy porcine coronary arteries are considered suitable for evaluating biological responses after the placement of CS, DES or drug-eluting balloons.[18–20]

The purpose of this study was to evaluate the safety and efficacy of 3 new sirolimus-eluting permanent polymer stent designs in terms of vascular response in a preclinical porcine model.

METHODS

Animal Model

In this randomized, controlled, experimental study with a final blind analysis, we used 20 Large White domestic pigs aged 2 to 3 months old and weighing 25 ± 3 kg. All procedures were done in accordance with local regulations (RD 53/2013, February 1, which defines basic standards for the protection of animals during experimentation and other scientific purposes, such as education) and European Directive 2010/63/EC. Before any procedures were initiated, the study was approved by the local ethics committee.

The randomization method involved the stratified allocation of major coronary arteries in such a way that each stent type was implanted in the same number of arteries.

All animals received antiplatelet therapy with acetylsalicylic acid (325 mg) and clopidogrel (300 mg) 24 hours before the procedure. The anesthesia protocol and surgical preparation have been previously described.[21,22] The animals were anesthetized and received anticoagulant therapy with 5000 IU of unfractionated heparin. Coronary angiography was performed via left carotid artery access after intracoronary administration of nitroglycerin.

Angioplasty Procedure

To implant the devices and obtain a stent/artery ratio > 1.1, we selected the best location out of the 3 epicardial coronary arteries. After inserting an intracoronary guidewire, the different stent types were implanted in the selected area of each artery.

Devices Analyzed

For this study, we used the following devices (numbers in parentheses):

1. Control CS (n = 11): L605 cobalt chromium alloy stent, Architect® (iVascular). The stent is constructed of 6 crowns joined by 3 rows of concatenated connectors that create a continuous sinusoidal structure (Figure 1A).
2. DES 1 (n = 17): based on the metal Architect® stent, coated with a permanent polyacrylate polymer and loaded with 1.4 μg/mm^2 of sirolimus in a slow-release system (with an additional polymeric external layer to control drug release).
3. DES 2 (n = 10): based on the metal Architect® stent, coated with a permanent polyacrylate polymer and loaded with 1.4 μg/mm^2 of sirolimus (and no external polymer barrier).
4. DES 3 (n = 12): is the new DES by iVascular, called Angiolite®. The platform is made of L605 cobalt chromium alloy, with a strut thickness of 85 μm. The stent structure has 8 crowns joined by 3 rows of unlinked connectors that create a discontinuous sinusoidal structure (Figure 1B). This design represents a slight increase in the metal/artery ratio and provides better distribution of the drug to the artery wall. The polymer is permanent and from the polyacrylate family. It releases sirolimus at a dose of 1.4 μg/mm,[2] and more than 80% of the drug is released within 60 days.

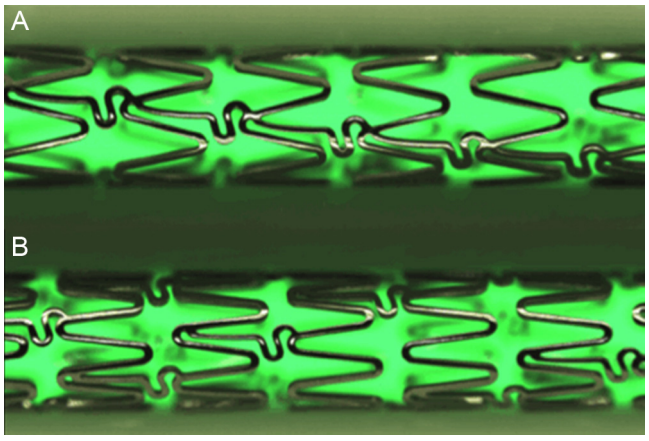

Figure 1. Stent design of the conventional cobalt chromium Architect®, the metallic control platform, drug-eluting stent 1 and drug-eluting stent 2 (A); the new metallic structural platform of the drug-eluting stent 3 has more crowns per segment and unlinked connectors to provide more uniform elution (B). High definition images using the QSix® system (Barcelona, Spain).