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Original article

Safety and Efficacy of New Biodegradable Polymer-based Sirolimus-Eluting Stents in a Preclinical Model

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A B S T R A C T

Introduction and objectives: New drug-eluting stents (DES) designed to overcome the limitations of existing devices should initially be tested in preclinical studies. Our objective was to analyze the safety and efficacy of new biodegradable polymer-based DES compared with bare-metal stents (BMS) and commercially available DES in a model of normal porcine coronary arteries.
Methods: We randomly implanted 101 stents (BMS and biodegradable polymer-based sirolimus-eluting stents: 3 test stent iterations [BD1, BD2, and BD3], Orsiro, Biomime and Biomatrix) in the coronary arteries of 34 domestic pigs. Angiographic and histomorphometric studies were conducted 1 month (n = 83) and 3 months (n = 18) later.
Results: The stents were implanted at a stent/artery ratio of 1.31 ± 0.21, with no significant differences between groups. At 1 month, the new test stents (BD1, BD2 and BD3) showed less late loss and angiographic restenosis, as well as lower histologic restenosis and neointimal area ($P < .0005$), than the BMS. There were no differences in endothelialization, vascular injury, or inflammation between the new test stents and BMS, although the new stents showed higher fibrin deposition ($P = .0006$). At 3 months, all these differences disappeared, except for a lower neointimal area with the new BD1 stent ($P = .027$). No differences at any time point were observed between the new test stents and commercially available controls.
Conclusions: In this preclinical model, the new biodegradable polymer-based DES studied showed less restenosis than BMS and no significant differences in safety or efficacy vs commercially available DES.

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

Palabras clave:
Modelo preclínico
Stent farmacoactivo
Reestenosis
Reparación vascular

R E S U M E N

Introducción y objetivos: Los nuevos *stents* farmacoactivos (SFA), diseñados para solventar las limitaciones de los existentes, han de someterse inicialmente al análisis preclínico. El objetivo es analizar la eficacia y la seguridad de nuevos SFA con polímero biodegradable en comparación con *stents* convencionales (SC) y SFA comercializados en el modelo de arteria coronaria sana porcina.
Métodos: Se implantaron aleatoriamente 101 *stents* (SC y *stents* liberadores de sirolimus con polímero biodegradable: 3 formulaciones test [BD1, BD2 y BD3], Orsiro, Biomime y Biomatrix) en las arterias coronarias de 34 cerdos domésticos. Se completó estudio angiográfico e histomorfométrico al mes (n = 83) y a los 3 meses (n = 18).
Resultados: Los *stents* se implantaron en proporción *stent*/arteria de 1,31 ± 0,21, sin diferencias entre grupos. Al mes, los nuevos *stents* (BD1, BD2 y BD3) mostraron menos pérdida tardía y reestenosis angiográfica, así como menor área neointimal y reestenosis histológica ($p < 0,0005$) que los SC. No se observaron diferencias significativas entre los nuevos *stents* y los SC en endotelización, daño vascular o inflamación; solo se encontró mayor persistencia de fibrina en los nuevos ($p = 0,0006$). A los 3 meses, todas estas diferencias desaparecieron, excepto una menor área neointimal con el nuevo *stent* BD1 ($p = 0,027$). No hubo diferencias en ningún parámetro al mes ni a los 3 meses entre los nuevos *stents* y los comercializados.

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Conclusiones: En este modelo preclínico, los nuevos SFA con polímero biodegradable estudiados presentan menos reestenosis que los SC, sin diferencias significativas en seguridad y eficacia respecto a SFA comercializados.

Abbreviations

BMS: bare-metal stents
DES: drug-eluting stents
MLD: minimal luminal diameter

INTRODUCTION

Drug-eluting stents (DES) have consistently demonstrated lower rates of revascularization than bare-metal stents (BMS) in a wide range of clinical situations[1] and thus their use has become widespread, far surpassing that of BMS in Spain.[2] The risk of late thrombosis of first-generation DES has been a serious cause of concern.[3] This phenomenon has been associated with the deleterious effect of the drug, the drug delivery polymer, the stent platform, or a combination of these in the vessel wall, which leads to incomplete endothelialization and persistent hypersensitivity and inflammatory reactions.[4–8]

New-generation DES have demonstrated much lower rates of late thrombosis,[9,10] which is probably associated with the use of improved polymers. The use of biodegradable polymers has demonstrated an excellent safety profile in preclinical studies[12] and clinical studies.[13–15] Although these advances are very important, unwanted phenomena persist, such as the appearance of neosclerosis,[16] which has prompted the development of new devices that eliminate all such problems.

Preclinical models have demonstrated usefulness in analyzing differences between new devices because the sequence of biological events associated with arterial repair is similar to that in humans.[17] The porcine model of healthy coronary artery has been recommended by consensus to assess biological responses after the use of coronary devices.[18–21]

The aim of this study was to assess the safety and efficacy of 3 new biodegradable polymer-based sirolimus-eluting stent designs in a preclinical porcine model.

METHODS

Animal Model

This randomized controlled experimental trial with a final blind analysis used 34 Large White domestic pigs aged 2 to 3 months old. All procedures were conducted in accordance with Spanish legal regulations (Royal Decree 53/2013, 1 February, on basic standards for the protection of experimental animals) and European Directive 2010/63EC. The study was approved by the local ethics committee prior to its inception. The randomization method involved the stratified allocation of major coronary arteries so that each type of stent was implanted in the same number of arteries. The predetermined follow-up points were at 1 month (n = 28) and 3 months (n = 6).

Aspirin (325 mg) and clopidogrel (300 mg) were administered 24 hours before the procedure. The anesthesia protocol and surgical preparation have been previously described. [19] The animals received anticoagulant therapy with 5000 IU of unfractionated heparin. To implant the devices at a stent/artery ratio > 1.2, we selected the best location out of 3 epicardial coronary arteries after the administration of intracoronary nitroglycerin.

Devices Analyzed

In this study, the following devices were used:

- Control BMS (n = 27): Conventional bare-metal stent (iVascular), L605 chromium-cobalt alloy, strut thickness 80 μm. The stent is constructed of 8 crowns joined by 3 rows of nonconcatenated connectors that form a discontinuous sinusoidal structure to provide better drug distribution.
- SFA1, BD1 (n = 32): Based on BMS, coated abluminally with 4 to 5 μm biodegradable poly(D,L)-lactic-co-glycolic polymer, loaded with 1.0 μg/mm^2 of sirolimus, with a delivery system that allows more than 60% of the drug to be released within 30 days (Figure 1).
- SFA2, BD2 (n = 6): A variant of SFA1 with 1.4 μg/mm^2 sirolimus.
- SFA3, BD3 (n = 3): A variant of SFA1 with a slower release profile, with more than 40% of the drug released within 30 days.
- SFA4 (n = 5): Commercially available DES with Biomatrix biodegradable polymer (Biosensors Interventional Technologies,

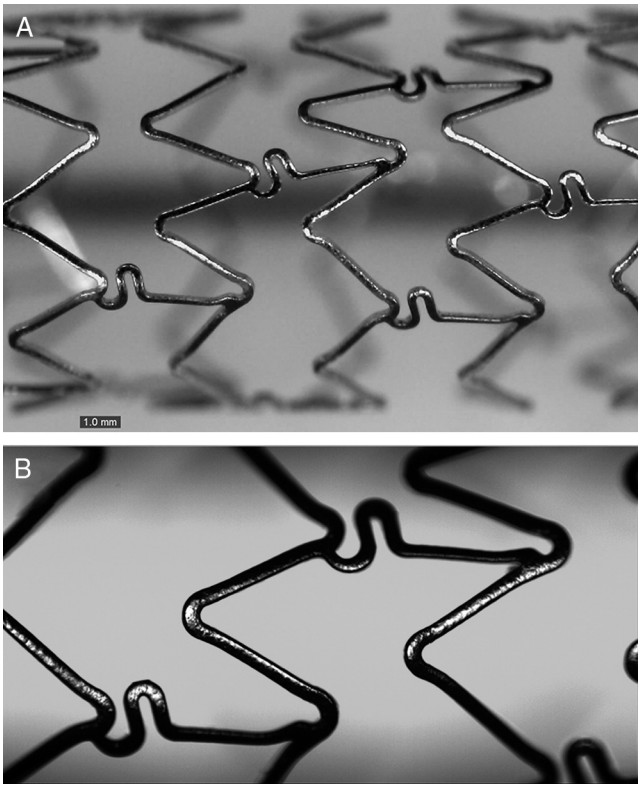

Figure 1. Structure of the BD1 drug-eluting stent, with a design optimized to allow more uniform drug release. Optical microscopy image (A) and high definition image (B) obtained using the QSix system (Sensofar, Barcelona, Spain).

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