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A Novel Platinum-Iridium, Potentially Gamma Radioactive Stent: Evaluation in a Porcine Model

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In-stent restenosis (ISR) is a major problem within stented arteries. Surface treatment of stents with platinum and gold were found to have the maximum charge with least neointima formation (NF). This study was designed to evaluate platinum (maximum electrical charge) as a material to make stents to reduce NF. Iridium was added to make an alloy suitable for stent manufacture, with the potential to make the stent radioactive. We implanted the novel platinum-iridium (PI) stent in 10 porcine coronaries and compared to the Palmaz-Schatz (PS) stent implanted in 8 coronary arteries. Six weeks after implantation, angiography of the stented vessel was performed before sacrifice. The coronaries were perfusion-fixed and stained, and vessel parameters were analyzed by computer-aided histomorphometry. The thrombus formation and the inflammatory response was less in the PI stent (0.04 ± 0.1 vs. 0.24 ± 0.2, $P = 0.005$; and 1.1 ± 0.5 vs. 2.4 ± 0.3, $P < 0.001$). The NF from PI-stented arteries was smaller in size than the PS controls (1.9 ± 0.6 mm^2 vs. 2.4 ± 0.4 mm^2, $P = 0.06$). However, PI stents presented with higher recoil than the PS stent (16% vs. 5%, $P < 0.001$). Platinum-iridium is a highly biocompatible material with high performance, low inflammatory response with small NF. This stent does not lead to thrombus formation and has the potential (due to the presence of iridium) to be irradiated to form a gamma radioactive stent. *Cathet. Cardiovasc. Intervent. 51:364–368, 2000.*

Key words: angioplasty; stents; restenosis; platinum-iridium alloys; gamma stent

INTRODUCTION

In-stent restenosis (ISR), a major problem with stents, is a consequence of neointimal smooth-muscle proliferation through the stent struts [1,2]. Several metals, coatings, drugs, and different stent designs have been tested to reduce neointimal hyperplasia [3–5]. The metals tested in the development of stents include stainless steel (316 L), tantalum, and nitinol. No local or distant toxicity has been demonstrated with any of these alloys [6]. Surface treatments of stents with platinum and gold have been shown to modify the performance of stents. Low stent electrical charge correlates with an increased neointima formation (NF). Platinized or gold-coated stents were found to have the maximum charge with least NF [7]. This study was designed to evaluate platinum as a material to make stents; iridium was added to make an alloy suitable for stent manufacture, with the potential to make the stent gamma radioactive. We compared the platinum-iridium (PI) stent to the Palmaz-Schatz (PS) stent implanted in porcine coronaries.

MATERIALS AND METHODS

Stents

The stents were made of platinum-iridium wire (0.15 mm, 90%:10% ratio). Alloying and manufacturing were done by Touchstone, Bombay, India. The alloy was passed through a diamond eye and manually drawn into wire. This wire was mechanically twisted in a zigzag shape forming the special design. This design allows folding on any conventional balloon, resulting in a low-profile 6 Fr guiding catheter compatible stent delivery

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system. The percentage of shortening is limited (< 5%) and the stent is available in a large variety of lengths from 12 to 40 mm, allowing customized stenting.

Procedures

All animals were treated and cared for in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals in Belgium. Sedation, anesthesia, and stent implantation details have been described [8]. Ten PI stents were implanted in the right coronary artery in 10 pigs. The stents were hand-crimped on a conventional angioplasty balloon catheter and deployed using an inflation pressure of 8 atm for 30 sec. Angiography (after 0.25-mg nitroglycerin) confirmed vessel patency in all animals. No antiplatelet agents or additional anticoagulants were administered during follow-up. As a control group, 8 Palmaz-Schatz stents, 15 mm, were implanted under similar conditions in eight right coronary pig arteries. Six weeks after implantation, control angiography of the stented vessel was performed before sacrifice.

Quantitative Coronary Angiography

Angiographic analysis of stented vessels was performed before, immediately after stenting, and at follow-up using Polytron 1000 system [8,9]. The diameters of the stented vessel segments were measured before, immediately after stent implantation, and at follow-up. Recoil was expressed as measured maximum balloon size minus minimal stent lumen diameter measured 15 min after stent implantation divided by measured maximum balloon size.

Histology and Morphometry

After 6 weeks follow-up, the pigs were sacrificed and the stented coronary artery was pressure-fixed using a 10% formalin solution at 80 mm Hg. Coronary segments were carefully dissected together with a 1-cm minimum vessel segment both proximal and distal to the stent. The segment was fixed in 10% formalin solution. Tissue specimens were embedded in a cold polymerizing resin (Technovit 7100, Heraus Kulzer, Wehrheim, Germany). Sections were cut 5 microns thick with a rotary, heavy-duty microtome HM 360 (Microm, Walldorf, Germany) equipped with a hard metal knife and stained with hematoxylin-eosin, Mason's trichrome, elastic stain, and a phosphototungstic acid hematoxylin stain. Light microscopic examination was performed by a blinded experienced pathologist. Injury to the arterial wall due to stent deployment was evaluated for each stent filament site and graded as described by Schwartz et al. [10]: grade 0 = internal elastic membrane intact, media compressed but not lacerated; grade 1 = internal elastic membrane lacerated, media visibly lacerated; grade 2 = external elastic membrane compressed but intact; grade 3 = large lacerations of the media extending through external elastic membrane; grade 4 = stent filament residing in the adventitia. Inflammatory reaction at every stent filament site was carefully examined, searching for inflammatory cells, and scored as follows: I = sparsely located histolymphocytes around the stent filament; II = more densely located histolymphocytes covering the stent filament, but no lymphogranuloma and/or giant cell formation found; and III = diffusely located histolymphocytes, lymphogranuloma, and/or giant cells, also involving the media. Appearance of thrombus was evaluated for every stent filament on the phosphotungstic acid hematoxylin-stained slides and graded as follows: 1 = small thrombus adjacent to the stent filament; 2 = thrombus totally covering the stent filament; 3 = big thrombus resulting in area stenosis of < 50%; 4 = big thrombus resulting in area stenosis of > 50%. The mean score of every factor was calculated as follows: mean score = sum of score for each filament/number of filaments present.

Finally, morphometric analysis of the coronary segments harvested was performed using a computerized morphometry program (Leitz CBA 8000). Measurements of lumen area, lumen area inside the internal elastic lamina, and lumen inside the external elastic lamina were performed on those arterial sites visually appreciated as being the most proliferative. Furthermore, area stenosis and neointimal hyperplasia were calculated.

Statistics

Arteriographic measurements at 6 weeks following PI stent deployment were compared with the same measurements obtained for PS stents using unpaired two-tailed student's *t*-test. Data are presented as mean value ± SD. Significance was established at the 95% confidence level ($P < 0.05$).

RESULTS

Quantitative Coronary Analysis

Ten pigs had a good angiographic result 20 min after the PI stent placement. An additional eight animals had the PS stent implanted in eight arteries. All these pigs had a follow-up angiogram at 6 weeks. Stented vessel segments were processed for histopathology. The results of the quantitative angiography are shown in Table I. These results show that the PI stent can be crimped easily on the balloon and can be deployed well. However, it presents with higher recoil than the PS stent (16% vs. 5%, $P < 0.001$)

Histopathology and Histomorphometry

Hematoxylin-eosin (H&E) and Verhoff van-Giesson alashi (VVG)-stained sections of all arterial segments

TABLE I. Quantitative Coronary Analysis, Histopathologic Findings (Schwartz Criteria), and Morphometric Analysis

	Platinum-iridium stent (n = 10)	Palmaz-Schatz stent (n = 8)	P
Quantitative coronary analysis			
Prestenting (mm)	2.49 ± 0.14	2.90 ± 0.20	<0.001
Balloon size (mm)	3.03 ± 0.04	3.48 ± 0.14	<0.001
Poststenting (mm)	2.54 ± 0.16	3.30 ± 0.13	<0.001
Oversizing (%)	21.7 ± 6.2	20.0 ± 6.0	0.566
Recoil (%)	16.0 ± 4.0	5.0 ± 3.0	<0.001
Six-week follow-up (mm)	2.43 ± 0.21	3.44 ± 1.00	0.006
Histopathologic findings			
Injury score	0.62 ± 0.35	0.54 ± 0.35	0.590
Thrombus	0.04 ± 0.10	0.24 ± 0.16	0.005
Inflammatory response	1.12 ± 0.54	2.40 ± 0.31	<0.001
Morphometric analysis			
Lumen area (mm^2)	1.38 ± 0.46	0.94 ± 0.58	0.091
IEL area (mm^2)	3.28 ± 0.64	3.33 ± 0.37	0.847
EEL area (mm^2)	4.94 ± 1.45	5.29 ± 0.67	0.539
Neointimal hyperplasia (mm^2)	1.90 ± 0.64	2.40 ± 0.36	0.067
Area stenosis (%)	58.0 ± 16.0	71.0 ± 12.0	0.075

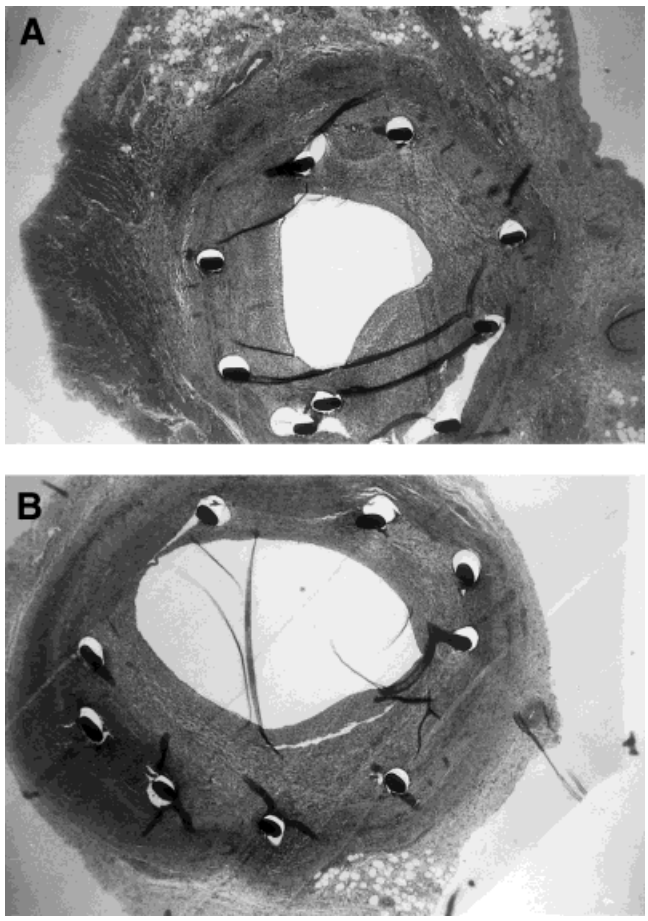

Fig. 1. Histological appearance of porcine arteries subjected to intracoronary stenting. Control PS-stented arteries (A). PI-stented arteries (B). The animals were sacrificed 6 weeks after stent placement.

were examined (Table I, Fig. 1). In injured segments of both PS- (control) and PI-stented arteries, there was a variable degree of rupture of the tunica media that resulted in a vessel wall defect. Arteries exhibited replacement of the medial defect with a substantial neointima consisting mostly of stellate and spindle-shaped cells in a loose extracellular matrix. Frequently, adventitial reaction and occasional perivascular and rare intramyocardial hemorrhages were also observed in both groups. A moderate number of sections exhibited hematomas in the media-adventitia dissection planes. In most sections, there was perivascular edema and mild to moderate round-cell infiltration. The thrombus formation and the inflammatory response (Schwartz criteria) was less in the PI compared to the PS stent (0.04 ± 0.1 vs. 0.24 ± 0.2, $P = 0.005$; and 1.1 ± 0.5 vs. 2.4 ± 0.3, $P < 0.001$).

The neointimal hyperplasia from PI-stented arteries was small (1.9 ± 0.6 mm^2 vs. 2.4 ± 0.4 mm^2 in the PS controls; $P = 0.06$). The cells of the neointima were morphologically similar. In a moderate number of samples, there were mural fibrin deposits. There was no evidence of necrosis or excess of fibrosis.

DISCUSSION

The main findings of the present study are that platinum-iridium is a highly biocompatible material with high performance, low inflammatory response with small NF as compared to the Palmaz-Schatz stent, and that this material does not lead to thrombus formation despite not using any antiplatelet drugs postprocedure.

This balloon-expandable PI stent is easy to mount on any conventional balloon catheter and easy to deploy. This stent was found to be more radiopaque than the PS stent, with a higher flexibility and deliverability. The inflammatory response as assessed by Schwartz criteria was significantly lower than the PS stent. Furthermore, the NF was also significantly lower than the PS stent.

Intrastent thrombosis was virtually nonexistent. We were unable to explain this but it may be related to the alloy. This is relevant as we see high rates of late total occlusions (thrombosis) following reintervention for in-stent restenosis with or without brachytherapy [11,12]. The recoil with the PI stent was higher than the PS stent, as seen in most coil stents and may be reduced with the use of a thicker wire [5]. A platinum stent has been tested in earlier animal studies and has been found to have a good radio-opacity with good short-term patency. The clinical results are awaited [13].

The major potential advantage of this stent is the presence of iridium, which may be irradiated to form a gamma radioactive stent. Recent animal and clinical studies have demonstrated that intracoronary radiation with Ir-192 markedly reduces neointima formation and is emerging as a potential cure for restenosis [14–16]. Furthermore, recent studies with the beta-emitting stents (Phosphorus-32) have shown mixed results, with a high rate of edge restenosis [17]. This edge restenosis is possibly due to the sudden dose fall-off at the edges, injury, and/or delayed healing. The suggested mechanisms to combat edge restenosis are: the square shouldered balloon, the cold-end stent, the hot-end stent, a hybrid radioactive stent/catheter system, a self-expanding radioactive stent, and the gamma stent [18]. Potentially, this PI stent can be activated to be used as a low-dose gamma stent with better tissue penetration and adequate clinical effect. Although exact dosimetry will vary depending on the geometry and design of the stent, an estimated activity of 30 μCi of Ir-192 can deliver 10 Gy to 1 mm from surface of the stent (based on the point source gamma factor of Ir-192) [19] and will not pose a radioactive hazard to the patient, relatives, and personnel. This study has some limitations, as the coil design PI stent was implanted in the noninjured, nonatherosclerotic porcine coronaries and compared to the tubular PS stent at only one time point.

Platinum-iridium is a highly biocompatible material with high performance, low inflammatory response with small NF as compared to the Palmaz-Schatz stent. This stent does not lead to thrombus formation and has the potential (due to the presence of iridium) to be irradiated to form a gamma radioactive stent.

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