Preventive role of palladium-103 radioactive stent on in-stent restenosis in rabbit iliac arteries

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Abstract The abilility of γ-emitting palladium-103 stent implantation to inhibit in-stent restenosis in rabbit iliac arteries was investigated. Quantitative histomorphometry of the stented iliac segments 28 days after the implantation indicated that palladium-103 stents made a significant reduction in neointimal area and percent area stenosis compared with the nonradioactive stents. Lumen area in the palladium-103 stents treatment group was larger than the control group. However, the reduction of neointima formation by palladium-103 stents implantation was in a non-dose-dependent fashion. Low ionizing radiation doses via γ-emitting palladium-103 stent are effective in preventing neointimal hyperplasia in iliac arteries of rabbits. Palladium-103 stents can be employed as a possible novel means to prevent in-stent restenosis.

Keywords Restenosis, Palladium-103, Radiation, Stent, Radioisotopes

CLC number R817.5

1 Introduction

Neointimal hyperplasia is the predominant feature of human restenosis after percutaneous transluminal coronary angioplasty (PTCA) or stent implantation. Migrating and proliferating smooth muscle cells (SMCs) responding to the initial vascular injury accompanied by the deposition of extracellular matrix are thought to be key events in this process.[1-3]

It was well known that proliferating cells are more susceptible to radiation than quiescent cells.[1-8] Therefore, the radiosensitivity of an injured vessel wall may be much higher than that of an intact vessel. This study was to investigate whether low-dose gamma-ray irradiation from a palladium-103 electroplated stent could inhibit neointimal proliferation after implantation in rabbit iliac arteries.

Radioactive stents (RS) with very low activity were implanted in rabbit iliac arteries, and the resulting neointimal hyperplasia was compared with that from nonradioactive stents (NRS).

2 Experimental

2.1 Stent preparation

The stents used in the present study are made of 316L stainless tube, 2.5 in diameter, carved into a flexible mesh tube by laser (Shanghai Microport Medical Corp.). The stents were 15 mm long with an expanded diameter of 5.0 mm. After stent fabrication, palladium-103 (China Institute of Atomic Energy, Beijing) was electroplated on the surface of the nonradioactive stents. This technique results in even distribution of palladium-103 within the stent wire, which ensures uniform delivery of γ-ray irradiation into the vessel wall. The radioactive stents were mounted onto a 3.0mm balloon catheters (Shanghai Microport Medical Corp.). The assembly was then packaged and sterilized in the conventional manner. The control stents were fabricated in a manner identical to the radioactive stents except that they were not electroplated. The use of a 15 mm long stent with an activity level of 3.7MBq (100μCi) resulted in a calculated total radiation dose at the surface of the stent wires (over the lifetime of palladium-103) of approximately 8.6 Gy. The radiation dose delivered over the

Received date: 2004-03-30

28-day study period was equivalent to about 70% of the total radiation dose. This calculating method is based on the assumption that the source has a shape of uniform line.[9-10]

2.2 Animal preparation

Twenty stents (ten control, ten palladium-103 electroplated) were implanted in the right and left iliac arteries of ten New Zealand rabbits of both sexes (weight, 2.5 to 3.0 kg) fed on a high fat chow diet. The animals were anesthetized with sodium pentobarbital (30 mg/kg) IV. Both femoral arteries were exposed and ligated, and two 4F pediatric sheaths were introduced via arteriotomy. Heparin 500 IU and aspirin 60mg were given IV before the stent implantation. A radioactive stent was introduced retrograde in one common iliac artery and expanded at 1 MPa for 1 minute. A nonradioactive stent was implanted likewise in the contralateral iliac artery. The iliac arteries had diameters of 2.5 mm; therefore, the ratio of balloon-expanded stent to artery was 1.2:1. The femoral artery was ligated, the wounds were closed, and the animals received 60 mg of aspirin IM every third day for 4 weeks. Rabbits were divided into six groups on the basis of stent radioactivity (2.2 MBq (n=3), 5.6 MBq (n=4), 9.3 MBq (n=4), 14.8 MBq (n=3), 22.2 MBq (n=3) and 33.3 MBq (n=3)).

2.3 Quantitative histomorphometry

After a lethal dose of sodium pentobarbital (120 mg/kg) was given to the rabbits, the abdominal aorta was cannulated and the animals were exsanguinated by flushing with lactated Ringer's solution at 13.3 kPa pressure. The iliac arteries were harvested, and immersed in 1.5% formaldehyde and 1.5% glutaraldehyde overnight. The specimens were stepwise dehydrated with graded alcohol and embedded in epoxy resin. Thereafter, stented arteries were sectioned into 100 μm slices with a rotating diamond-coated saw. The sections were stained with Heidenhain azan stain. The vessel parameters including external elastic lamina (EEL), internal elastic lamina (IEL), media, and residual vessel lumen were measured by computer assisted morphometry using a light microscope (Olympus) connected to a video camera (Sony) and a computer-based digitizing imaging analyzer. The area within the IEL was considered the normal lumen area. The percent area stenosis was defined as: [(IEL area-lumen area) / IEL area]×100%. Neointimal area was determined by subtracting the residual lumen area from the area within the IEL.

2.4 Statistical analysis

All data are presented as mean±SD. The two-tailed paired Student's t test was used to compare group means. A probability value of P<0.5 was considered significant.

3 Results

3.1 Animal follow-up

All 20 stents were deployed without complication and each of the animals survived to 28 days. Follow-up angiography demonstrated 100% patency of the stents.

3.2 Radiation dose

The dosimetry of a radioactive stent with different activities at the date of implantation is given in Table 1.

Table 1 Absorbed doses at *A* point and *B* point of palladium-103 stents.*

Stent activity (MBq)	*A* point (Gy)		*B* point (Gy)	
	Over life time	Over 28 days	Over life time	Over 28 days
2.2	5.2	3.6	2.8	2.0
3.7	8.6	6.0	4.6	3.2
5.6	12.9	9.0	6.9	4.8
9.3	21.5	15.1	11.5	8.1
14.8	34.3	24.0	18.4	12.9
22.2	51.5	36.0	27.7	19.4
33.3	77.2	54.0	41.5	29.1

* *A* point refers to the midpoint on the stent surface; *B* point refers to the endpoint on the stent surface.

3.3 Histopathology

The histological examination of arteries treated with radioactive stent compared with NRS revealed a non-dose-dependent inhibitory effect of radiation on

neointimal hyperplasia, since there were no significant differences in the percent area stenosis among groups. There was a statistical reduction in neointimal area and percent area stenosis in the radioactive stents compared to control stents (Fig.1.). Lumen area in the treatment group was larger than the control group. Table 2 gives a summary of the comparisons of IEL area, luminal area and neointimal area. Vascular thrombosis after stent implantation was minor and did not differ between treatment group and control group.

The histological sections from the treatment and control stents showed neointimal proliferation with a predominant population of spindle-shaped SMCs. These SMCs were haphazardly arrayed near the stent struts with abundant extracellular matrix. At the lumen surface, the SMCs were more circumferentially organized and had a higher density compared with cells adjacent to the stent wires. The EEL was intact in all sections, indicating an absence of deep vessel wall injury. There was mild compression of the media with minimal medial SMC necrosis.

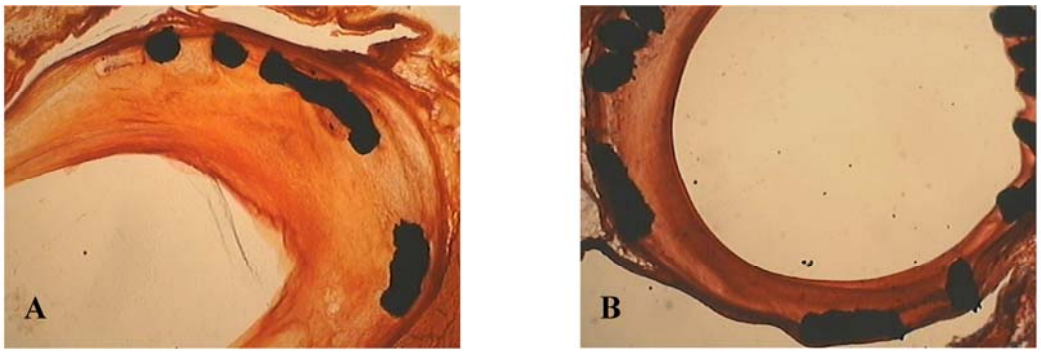

Fig.1 Histological sections.
(A) Iliac artery 28 days after nonradioactive stent implantation;
(B) Iliac artery 28 days after 9.3 MBq palladium-103 stent implantation (Azan, ×40).

Table 2 Outcome of histopathology of RS and NRS implanted iliac arteries

Activity (MBq)	*N*	Group	IEL area (mm^2)	Luminal area (mm^2)	Neointimal area (mm^2)	Percent area stenosis (%)	*P* value *
2.2	3	RS	5.77±0.37	4.12±0.52	1.65±0.49	28.7	<0.01
		NRS	5.14±0.52	2.43±0.84	2.71±0.53	52.8	
5.6	4	RS	4.63±1.84	2.79±1.88	1.84±1.02	39.8	<0.01
		NRS	4.88±1.04	2.17±1.45	2.71±0.84	55.6	
9.3	4	RS	4.71±0.71	3.43±0.27	1.27±0.47	27.1	<0.01
		NRS	4.57±0.72	2.01±0.70	2.56±0.36	55.9	
14.8	3	RS	4.15±1.10	3.23±1.04	0.93±0.34	22.4	<0.01
		NRS	4.79±0.33	1.86±0.32	2.92±0.32	61.0	
22.2	3	RS	5.36±1.65	3.76±1.36	1.60±0.30	29.8	<0.01
		NRS	5.87±1.20	2.74±1.11	3.13±1.13	53.4	
33.3	3	RS	5.27±1.03	3.88±1.13	1.40±0.82	26.5	<0.01
		NRS	5.40±1.00	2.47±0.65	2.92±0.36	54.2	

* Comparing the percent area stenosis of RS with NRS.

4 Discussion

Restenosis is the major drawback of PTCA and occurs within 6 months in 40%~60%. Neointimal formation in response to arterial injury, which has been demonstrated to be primarily caused by smooth muscle cells (SMCs) proliferation, is an important contributor to restenosis.[1-8] Radioactive stent implantation for the treatment of restenosis has been well established. Many studies have demonstrated the effective inhibition of SMCs proliferation by β-emitting stents implantation.[11-13] However, few studies have been made on γ-emitting stents so far.

Radioactive stent implantation is a new approach to the reduction of restenosis. Beta and gamma sources can be applied to prevent restenosis. Beta-emitters are characterized by a low tissue penetration, which simplifies radiation protection but complicates the achievement of a homogeneous dose distribution. By contrast, gamma-emitters are characterized by deep tissue penetration and delivery of almost the same dose to all vessel layers. Gamma rays are not shielded by stent. These make gamma energy ideal for treating large vessels and for the treatment of in-stent restenosis. However, considerable care with regard to radiation protection is required if gamma-emitters are used.

Recent articles[14-15] have identified the adventitia as a contributor to neointimal regrowth. Gamma sources are better suited for delivering a more homogenous, balanced dose to the whole vessel wall. Many approaches to intravascular brachytherapy describe not only the required dose to the intima, but, more properly, a dose to the adventitia.

^{103}Pd has features well suited to intravascular brachytherapy. ^{103}Pd decays by electron capture to excited states of ^{103}Rh, which, in turn, decays to its ground state by internal conversion. In the internal conversion process, the unstable ^{103}Rh nucleus deexcites by giving its energy to an orbital electron. The ^{103}Rh atom fills the *K* shell by emitting the characteristic X-rays of 20—23 keV.[16] The 20—23 keV X-rays interact with matter primarily by photoelectric effect in which the X-rays transmit all their energy to an electron in a single reaction.

^{103}Pd is the newer one of the two main sources widely used in prostate brachytherapy. The mean 21 keV X-rays (photons) from ^{103}Pd have a half-value layer of 11mm in water (slightly less in soft tissue), thus limiting the dose primarily to vessel wall. Furthermore, the low energy X-rays from ^{103}Pd are shielded easily by a thin, stainless steel housing. Half-value layer of ^{103}Pd is 0.035 mm in stainless steel.[16] The half-life of 16.93 days allows ^{103}Pd to deliver the dose with an acceptable dose rate for stent application. These features are extremely important for intravascular brachytherapy considerations because ^{103}Pd do not present substantial safety issues for the medical staff in the cath-lab.

Thus, from the point of view of handling and shielding, ^{103}Pd is very similar to beta sources. Also, from the point of view of dose distribution, ^{103}Pd delivers a homogeneous dose nearly identical to ^{192}Ir to the vascular structure. The relative biological effectiveness (RBE) is higher for low-energy X-rays of ^{103}Pd compared to ^{192}Ir due to the fact that energy deposition as governed by low-energy photoelectrons favors ^{103}Pd over ^{192}Ir.[17]

The EGS4/DOSRZ Monte Carlo code was used to calculate the dose distribution of ^{103}Pd stent by McLemore et al.[18] For a 2 mm outer-diameter ^{103}Pd stent, approximately 26.6 MBq was required to deliver 31.5 Gy in 28 days at a distance of 0.5 mm along the perpendicular bisector from the stent's outer surface. The dosimetry calculated by Sioshansi et al.[19] indicated that a 13.0 MBq ^{103}Pd stent delivered approximately 14 Gy at 1 mm distance over its lifetime. The dose distribution of this study given by the calculating method[9,10] is close to the results of McLemore et al. and Sioshansi et al. mentioned above.

5 Conclusions

This preliminary study reports that low ionizing radiation doses emitted by gamma-emitting ^{103}Pd stents are effective in preventing neointimal hyperplasia in iliac arteries of rabbits. However, radioactive stents were implanted only in rabbits. Further studies using other animal species are necessary to evaluate the efficacy and safety of ^{103}Pd stents. Iliac arteries are elastic arteries, and for muscular coronary arteries different radiation doses may be required to prevent neointimal hyperplasia.

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