Short- and Intermediate-Term Results of ^{32}P Radioactive β-Emitting Stent Implantation in Patients With Coronary Artery Disease

The Milan Dose-Response Study

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Background—Radioactive ^{32}P β-emitting stents have been shown to reduce intrastent neointimal hyperplasia in a substantial dose-related manner in the animal model. The aim of this dose-response study was to evaluate, in the clinical setting, the safety and efficacy at 6-month follow-up of this approach to reducing restenosis.

Methods and Results—A total of 122 ^{32}P radioactive β-emitting stents (initially the Palmaz-Schatz and later the BX Isostent) with an activity level of 0.75 to 3.0 μCi (group 1), 3.0 to 6.0 μCi (group 2), and 6.0 to 12.0 μCi (group 3) were implanted in 91 lesions in 82 patients. There were no procedural events. At 6-month follow-up, no deaths had occurred, and only 1 patient had stent thrombosis. Pure intrastent binary restenosis was 16% in group 1, 3% in group 2, and 0% in group 3. However, intralesion restenosis was 52% in group 1, 41% in group 2, and 50% in group 3.

Conclusions—The use of ^{32}P radioactive β-emitting stents in patients with CAD is feasible. At 6-month follow-up, intrastent neointimal hyperplasia was reduced in a dose-related manner. However, in the 3 groups, intralesion restenosis was high because of a high late lumen loss in the reference segments at the stent edges, possibly as a result of a low activity level of radiation at the edges of the stent combined with an aggressive approach to stenting. We called this "edge effect" the "candy wrapper." **(*Circulation*. 2000;101:18-26.)**

Key Words: radioisotopes ■ stents ■ restenosis ■ coronary disease

Restenosis after PTCA is a major limitation of this revascularization technique, occurring in 30% to 50% of patients.[1] Although Palmaz-Schatz stent placement in selected lesions has demonstrated a 30% relative reduction in restenosis rate[2,3] compared with balloon angioplasty, intrastent restenosis remains a major clinical problem. As demonstrated by serial intravascular ultrasound (IVUS) studies,[4] intrastent restenosis is mostly a result of intimal hyperplasia.

See p 3

Catheter-based endovascular delivery of both β- and γ-radiation have been shown to reduce neointimal formation in the animal model[5–8] and in patients with coronary artery disease (CAD).[9,10] Animal studies in rabbit iliac arteries[11] and in porcine coronary arteries[12] have shown that implantation of a β-particle–emitting radioactive stent has a similar efficacy in the inhibition of subsequent intrastent neointimal cell proliferation.

The safety and feasibility of ^{32}P radioactive β-emitting stent implantation in patients with symptomatic de novo or restenotic native coronary lesions has been evaluated in the low-dose IRIS 1A (0.5 to 1.0 μCi, n=32 patients)[13] and IRIS 1B (0.75 to 1.5 μCi, n=25 patients) trials.[14–16] These pilot clinical trials have found that ^{32}P radioactive Palmaz-Schatz stents can be safely implanted with a high short-term success rate. However, coronary angiography, performed in 52 of 57 patients (92.9%) at 6-month follow-up, showed a binary intralesion restenosis, both within the stent and at the edges, in 21 of 52 patients (40.4%), not different from or perhaps higher than that of currently available nonradioactive stents.

The purpose of this single-center, nonrandomized, dose-response study was to evaluate the safety and the efficacy for prevention of restenosis at 4- to 6-month follow-up of ^{32}P radioactive stent implantation with 3 increasingly higher activity levels: 0.75 to 3.0 μCi, 3.0 to 6.0 μCi, and 6.0 to 12.0 μCi, in patients with CAD.

Methods

From October 1997 through October 1998, at Centro Cuore Columbus in Milan, Italy, 82 patients (with 91 lesions) were enrolled in this dose-response study. Two type of stents (Fischell Isostent) were implanted: initially the Palmaz-Schatz 0.75 to 3.0 μCi (group 1, n=23 patients, 27 lesions, 31 stents), and later the BX stent with increasing activity levels of 3.0 to 6.0 μCi (group 2, n=29 patients,

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TABLE 1. Clinical Characteristics

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	P
No. of patients	23	29	30	
Age, y	60±10	61±8	59±7	NS
Ejection fraction, %	65±9	61±11	65±11	NS
Male, n (%)	21 (91)	28 (96)	24 (80)	NS
Prior MI, n (%)	9 (39)	16 (55)	15 (50)	NS
Prior PCI, n (%)	6 (26)	7 (24)	14 (47)	NS
Prior CABG, n (%)	6 (26)	6 (21)	4 (13)	NS
No. of diseased vessels, n (%)				NS
1	7 (30)	13 (45)	14 (47)	
2	9 (40)	7 (24)	11 (37)	
3	7 (30)	9 (31)	5 (16)	
Unstable angina, n (%)	7 (30)	14 (48)	11 (37)	NS
Smokers, n (%)	2 (9)	8 (27)	9 (30)	NS
Hypercholesterolemia, n (%)	13 (56)	19 (65)	19 (63)	NS
Family history, n (%)	12 (52)	14 (48)	12 (40)	NS
Hypertension, n (%)	15 (65)	16 (55)	9 (30)	0.03
Diabetes, n (%)	1 (4)	4 (14)	2 (7)	NS

PCI indicates percutaneous coronary intervention. Data are mean±SD or number (%) of patients.

32 lesions, 39 stents) and 6.0 to 12.0 μCi (group 3, n=30 patients, 32 lesions, 53 stents).

Inclusion criteria for enrollment were the presence of a de novo or restenotic lesion of a major, native coronary artery with a reference artery size visually estimated to be appropriate for the available stent diameters (3.0 to 3.5 mm). The lesion had to be treated with 1 or 2 tandem 15-mm stents with a target lesion length visually estimated as ≤28 mm.

The trial was approved by the Columbus Hospital Ethical Committee. Written informed consent to the procedure and to return for repeat angiography and IVUS at 4 or 6 months was obtained from each patient.

Description of the Fischell Isostent

The Fischell radioactive stent used in this study initially consisted of a Palmaz-Schatz (PS 153) stent and later of a BX stainless steel stent (Isostent, Inc) mounted on a compliant balloon covered with an integral sheet (delivery system), and with a lucite radiation shield attached to the distal end of the stent delivery system, which prevents operator exposure to the radiation. The BX stent, designed by computer-aided technique, provides flexibility, without a central articulation, with a homogeneous dosimetry along the length of the stent and has been demonstrated to favorably influence the vascular response in normal porcine coronary arteries compared with the Palmaz-Schatz stent.[17] The radioisotope ^{32}P, a pure β-particle emitter with a half-life of 14.3 days and maximum energy of 1.71 MeV, was embedded beneath the surface of the stent. Activity levels of 0.75 to 12 μCi deliver a total dose to the tissue at 0.5 mm from the stent surface of ≈8 to 140 Gy over a 28-day period. The total dose to tissue is higher than with catheter-based radiation therapies, which range from 8 to 50 Gy at 2 mm from the source. However, this dose is delivered at a lower dose rate over a much greater length of time. The β-particle ^{32}P also has a short distance of tissue penetration: at 2 to 3 mm from the stent, the activity drops off significantly and is almost negligible. In addition, 1 of the potential problems associated with β-radiation is shielding by previously implanted stents, which may reduce the tissue exposure further.[18]

Stenting Procedure and Medical Regimen

Patients received aspirin 325 mg daily continued long-term plus ticlopidine 250 mg twice daily continued for 3 months after the procedure. In this group of patients, there were no adverse consequences of ticlopidine therapy. The technique used for implantation of a radioactive stent is nearly identical to that required for optimal placement of a nonradioactive stent. After lesion predilatation, usually with a 20-mm-long balloon, the delivery system was advanced to the target lesion site, and the 15-mm-long stent was delivered at the recommended pressure of 8 to 10 atm (mean 9 atm, range 5 to 12 atm). The stent was premounted on a 20-mm-long compliant balloon so that 2.5 mm of the length of the delivery balloon emerged beyond each stent edge. Further stent expansion with a larger and usually shorter balloon at higher pressure was used to achieve an optimal angiographic result. After high-pressure inflation, IVUS was performed. Further expansion was indicated if the stent was not fully apposed to the vessel wall or the cross-sectional area (CSA) was not appropriately large compared with the adjacent reference segments.

Angiographic Analysis

Quantitative coronary angiography (QCA) was performed at our institution with an automated computer-based system by experienced angiographers not involved in the stenting procedure as previously described.[19] Lesions were characterized according to the American College of Cardiology/American Heart Association classification.[20] Image calibration was performed with a contrast-filled catheter. The external diameter of the catheter was used as the calibration standard. Reference diameter, minimum lumen diameter (MLD), percent diameter stenosis (%DS), and lesion length were measured for each lesion from coronary end-diastolic matched frames in the single worst view obtained on initial, final, and follow-up angiograms by use of a contour-detection minimum-cost algorithm (QCA-CMS version 3.0, MEDIS). Lesion length was measured from the first narrowing of the vessel. In addition, after stenting and at follow-up, MLD was measured in 3 different segments of the lesion: at the stent level and in the 10 mm proximal and the 10 mm distal to the stent edges. Acute lumen gain, late lumen loss, and loss index were defined as previously reported.[21]

IVUS Equipment and Measurement

IVUS imaging was performed by use of the Cardiovascular Imaging System (CVIS) with a 3.2F catheter. The ultrasound catheter was advanced ≈10 mm distal to the distal stent edge, and an automatic pullback at 0.5 mm/s was performed. Data were stored on 0.5-in high-resolution Super VHS videotape for offline analysis. Quantitative IVUS analysis was performed to measure stent/external elastic membrane (EEM) CSA, lumen CSA, and plaque CSA and in 15 segments inside the stent and, when feasible, in 10 reference segments proximal and distal to the stent. The image cross sections analyzed were 1 mm apart. Intrastent plaque volume was calculated at follow-up according to Simpson's rule and was therefore the product of the 15 plaque CSAs and the distance of 1 mm separating them. For each of the 15 segments inside the stent and for the reference segments, the following calculations were made: remodeling=postintervention (PI) stent or EEM CSA−follow-up (FU) stent or EEM CSA; late lumen loss=PI lumen CSA−FU lumen CSA; and tissue growth=FU plaque CSA−PI plaque CSA. Validation of quantitative measurements and pathological correlation with ultrasound measurements has been reported.[22,23] Interobserver and intraobserver reproducibility of MLD and lumen CSA measurements has been reported previously.[24,25]

Follow-Up

All patients were requested to return for clinical, angiographic, and IVUS follow-up at 4 to 6 months after the procedure (the first 10 patients in group 2 and group 3 were requested to return at 4 months, and the remainder at 6 months).

TABLE 2. Angiographic and Procedural Characteristics

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	P
No. of lesions	27	32	32	
Type of stent	PS 153	BX	BX	
Radioactivity, μCi	1.55±0.43	4.25±0.74	9.30±1.59	<0.0001
De novo lesions, n (%)	25 (93)	29 (91)	32 (100)	NS
Vessel				NS
LMCA	2 (7)	1 (3)	0 (0)	
LAD	17 (63)	17 (53)	21 (66)	
LCx	4 (15)	5 (16)	6 (19)	
RCA	4 (15)	9 (28)	5 (15)	
ACC/AHA lesion type				NS
A	2 (8)	2 (6)	2 (6)	
B1	14 (54)	18 (56)	15 (47)	
B2	7 (27)	8 (25)	8 (25)	
C	3 (11)	4 (13)	7 (22)	
Rotablator, n (%)	7 (7.7)	1 (1.1)	1 (1.1)	0.004
Final balloon size, mm	3.63±0.38	3.64±0.27	3.45±0.45	NS
Max inflation pressure, atm	14.3±3.4	14.4±2.3	14.7±3.3	NS
Balloon-to-artery ratio	1.27±0.18	1.22±0.13	1.16±0.16	0.02
No. stents/lesion	1.15±0.36	1.21±0.42	1.65±0.90	0.004

LMCA indicates left main coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; and ACC/AHA, American College of Cardiology/American Heart Association. Data are mean±SD or number (%) of lesions.

Definitions

At the follow-up angiogram, pure intrastent restenosis was defined as ≥50% luminal reduction occurring only inside the stent with absence of restenosis in the proximal and distal reference segments. Intralesion restenosis was defined as ≥50% luminal reduction occurring inside the stent or at the proximal or distal reference segments.

Death, myocardial infarction (MI) (Q-wave or non–Q-wave MI), and stent thrombosis (which were considered major adverse clinical events), CABG, and repeat percutaneous coronary intervention were defined as previously reported.[21,25]

Statistical Analysis

Statistical analysis was performed with the StatView statistical package (StatView 5, SAS Institute). Continuous normally distributed data were expressed as mean±SD. Comparisons of continuous variables between groups were performed by ANOVA. Subgroup comparisons of categorical variables were performed by the Fisher exact test or the χ^2 test. Regression analysis was used to assess the correlation among plaque volume and stent radioactivity level. Differences were considered statistically significant at $P<0.05$.

TABLE 3. Baseline and Postprocedure Quantitative Angiographic Results

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	P
No. of lesions	27	32	32	
Preprocedure				
Reference vessel diameter, mm	2.91±0.55	3.0±0.36	3.08±0.44	NS
MLD, mm	0.92±0.39	0.77±0.38	0.74±0.47	NS
%DS	68±11	74±13	76±15	NS
Lesion length, mm	12.7±8.5	13.8±6.2	17.6±7.5*	0.05
Postprocedure				
Reference diameter, mm	3.16±0.48	3.24±0.38	3.19±0.46	NS
MLD, mm	3.07±0.48	3.11±0.37	2.87±0.49	NS
%DS	1.7±5.2	3.2±10.4	9.7±9.9*†	0.002
Acute gain, mm	2.15±0.45	2.34±0.50	2.13±0.58	NS

Data are mean±SD.
*Significant difference between group 3 and group 1.
†Significant difference between group 3 and group 2.

TABLE 4. Clinical Events at 6-Month Follow-up

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	P
No. of patients	23	29	30	
Stent thrombosis, n (%)	0	0	1 (3.3)	NS
MI, n (%)	0	0	1 (3.3)	NS
Death, n (%)	0	0	0	NS
CABG, n (%)	0	1 (3.4)	2 (6.6)	NS
Repeat PCI, No. of lesions	10/19 (52%)	12/29 (41%)	13/26 (50%)	NS
Any repeat revascularization, No. of lesions	10/19 (52%)	13/30 (43%)	14/27 (52%)	NS

Data are mean±SD or number (%) of patients.

Results

Patient, Baseline Angiographic, and Procedural Characteristics

The patients' clinical data are shown in Table 1. There was no difference in the clinical characteristics between the groups except for a lower percentage of patients with hypertension in group 3. Baseline angiographic and procedural characteristics are shown in Table 2. Procedure success was 100%. More than 90% of the treated lesions were de novo lesions. A higher percentage of lesions were treated with rotational atherectomy (Rotablator) before stenting in group 1. In addition, the balloon-to-artery ratio was significantly lower in group 3 because of a less aggressive stent implantation strategy in the late phase of the study. Finally, the number of stents per lesion was higher in group 3 because of a significantly longer lesion length in this group, as shown in Table 3.

Quantitative Angiographic Analysis

Table 3 summarizes the baseline and postprocedure quantitative angiographic results. Reference vessel diameter, MLD, and %DS immediately before stenting were similar in the 3 groups. Final %DS was significantly higher in group 3 than in the other 2 groups because of the above-mentioned less aggressive stent implantation strategy in the late phase of the study. However, there was no difference in final MLD and acute gain between the groups.

Clinical Events

As shown in Table 4, at 6-month follow-up there had been no deaths, and only 1 patient in group 3 had a subacute stent thrombosis with a Q-wave MI 1 week after he had stopped both aspirin and ticlopidine 3 months after stenting. A repeat percutaneous coronary intervention was performed in all the lesions with angiographic restenosis even if the patients were asymptomatic and had no objective evidence of ischemia. Three patients underwent elective CABG during the follow-up period.

Follow-Up Quantitative Angiographic Measurements

Table 5 shows the angiographic results of the 74 of 91 lesions (81% of lesions) of patients who underwent angiographic follow-up after 4 to 6 months. Reference vessel diameter, MLD, %DS, acute gain, late loss, and loss index were similar in the 3 groups. A longer lesion length was observed in group 3, a result similar to that observed before stenting. Intralesion restenosis rate was 52% in group 1, 41% in group 2, and 50% in group 3 (average 47%). As shown in Table 5 and Figure 1, the increase in the stent activity level resulted in a progressive reduction of pure intrastent restenosis: 16% in group 1, 3% in group 2, and 0% in the 6- to 12-μCi group. However, restenosis in 1 or both edges of the stent or at the edges plus in the first 1 to 4 mm inside the stent was present in 31% to 39% of the lesions. Moreover, in 4 lesions, a total occlusion was observed: 3 occlusions were not associated with clinical events, and only 1 of these 4 occlusions was associated with a clinical syndrome of stent thrombosis.

TABLE 5. Follow-up Intralesion Quantitative Angiographic Measurements

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	P
No. of lesions, n (%)	19 (70)	29 (91)	26 (81)	
Follow-up				
Reference diameter, mm	3.17±0.42	3.13±0.39	3.17±0.41	NS
MLD, mm	1.60±1.08	1.90±0.90	1.74±1.15	NS
%DS	51±33	39±29	46±35	NS
Lesion length, mm	12.7±8.4	13.8±6.1	17.6±7.5*	0.048
Acute gain	1.9±0.38	2.3±0.44	2.3±0.50	NS
Late loss	1.53±0.90	1.26±0.82	1.20±1.05	NS
Loss index	0.71±0.42	0.59±0.43	0.57±0.52	NS
Intralesion restenosis, %DS≥50	10 (52)	12 (41)	13 (50)	NS
Type of restenosis, n (%)				NS
No restenosis	9 (48)	17 (59)	13 (50)	
Pure intrastent	3 (16)	1 (3)	0	
Total occlusion	1 (5)	0	3 (11)	
At the edges	5 (26)	8 (28)	9 (35)	
At the edges+intrastent	1 (5)	3 (10)	1 (4)	

*Significant difference between group 3 and group 1.

TABLE 6. Postprocedure IVUS Characteristics

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	*P*
Stent	n=13	n=31	n=31	
Minimum CSA, mm²	6.4±1.7	6.9±1.2	6.3±2.4	NS
Maximum lumen diameter, mm	3.18±0.53	3.12±0.27	3.00±0.62	NS
MLD, mm	2.64±0.44	2.79±0.28	2.61±0.54	NS
Proximal reference	n=9	n=22	n=17	
Lumen CSA, mm²	7.9±2.0	9.2±2.4	8.5±2.0	NS
Vessel CSA, mm²	13.7±3.1	15.3±3.4	14.6±4.8	NS
Area stenosis, %	40±14	38±13	36±14	NS
Distal reference	n=10	n=29	n=25	
Lumen CSA, mm²	6.8±1.8	7.6±1.8	7.6±2.6	NS
Vessel CSA, mm²	9.5±3.5	12.6±3.2	11.0±4.0	NS
Area stenosis, %	26±14	37±16	27±21	NS

Figure 2 shows the late loss calculated by QCA in the proximal reference segment, inside the stent (from edge to edge), and in the distal reference segment. A similar late loss of ≥0.8 mm was detected in the proximal reference segment in the 3 groups. Intrastent late loss was lower, although not significantly, inside the stent in group 2 (0.58 mm) and group 3 (0.56 mm) than in group 1 (0.84 mm). Note that intrastent QCA analysis was performed from edge to edge of the stent and that intrastent late loss in the proximal and distal part was higher than in the central part of the stent, as shown in Figure 4 by IVUS analysis. Finally, late loss in the distal reference segment was significantly higher (0.98 mm) in group 3 than in group 1 and group 2 (0.44 and 0.52 mm, respectively).

IVUS Quantitative Measurements

The final quantitative IVUS measurements of the 75 lesions in which IVUS was performed immediately after stenting are presented in Table 6: there were no significant differences

TABLE 7. Predictors of Edge Restenosis by Univariate Analysis

	No Edge Restenosis	Edge Restenosis	*P*
No. of lesions	43	31	
Initial activity level, μCi	5.0±3.1	5.5±3.1	NS
Final B/A ratio	1.17±0.13	1.24±0.18	0.05
Maximum longest B/A ratio	1.10±0.16	1.22±0.18	0.003
Maximum inflation pressure, atm	14.9±2.8	14.1±3.1	NS
Delivery balloon pressure, atm	9.2±1.0	8.7±1.5	NS
Lesion length, mm	14.1±6.5	16.3±9.5	NS
No. of stents/lesion	1.23±0.42	1.45±0.81	NS
Reference diameter, mm	3.17±0.45	2.82±0.42	0.001
Final MLD, mm	3.22±0.39	2.78±0.45	<0.0001
IVUS measurements			
	n=22	n=18	
Prox. ref. lumen CSA, mm²	9.5±2.5	8.5±1.4	0.04
Prox. ref. vessel CSA, mm²	16.3±4.0	12.8±2.9	0.04
Prox. ref. area stenosis, %	39.6±13.0	33.2±13.3	NS
	n=27	n=26	
Dist. ref. lumen CSA, mm²	8.3±2.2	6.8±1.9	0.01
Dist. ref. vessel CSA, mm²	12.9±3.2	9.9±3.6	0.002
Dist. ref. area stenosis, %	34.1±16.0	26.4±20.2	NS

B/A indicates balloon-to-artery ratio; Prox., proximal; Ref., reference; and Dist., distal.

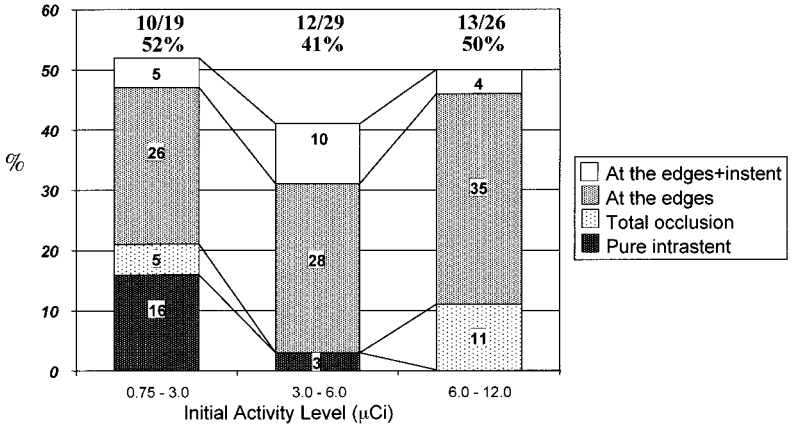

Figure 1. Pattern of restenosis in 35 of 74 lesions of patients who underwent angiographic follow-up. Increase in stent activity resulted in a progressive reduction of pure intrastent restenosis. Edge restenosis was present in 31% to 39% of lesions without difference between 3 groups.

between the 3 groups. In the 36 lesions in which a single 15-mm-long radioactive ^{32}P β-particle–emitting stent was implanted, a direct correlation was observed at follow-up between the decrease in intrastent intimal hyperplasia, measured as plaque volume, and the increase in the initial stent radioactivity level, as shown in Figure 3. By regression statistical analysis, we tried to fit the points of this correlation. These points were best fitted (r=0.64, P=0.0007) by a polynomial model of third order, which graphically looks sigmoidal and by which a prediction can be made that with an initial stent radioactivity level >11 μCi, there should be an almost complete inhibition of intimal hyperplasia inside the stent. Figure 4 shows late lumen loss, remodeling, and tissue growth, obtained by serial IVUS analysis and measured in slices 1 mm apart inside the stent and in the proximal and distal reference segments, in the 13 lesions with restenosis at follow-up, in which a single 15-mm radioactive stent with an initial activity level ≥3 μCi was implanted. Late lumen loss in the proximal and distal reference segments was higher than inside the stent and was mainly a result of tissue growth (intimal hyperplasia) in the first 2 to 3 mm and of remodeling (shrinkage of the vessel) in the last 4 to 10 mm from the edges of the stent. Inside the stent, no remodeling was observed, and late lumen loss was only a result of tissue growth, which was lower in the central 5 mm than in the 5 mm adjacent to the margins of the stent.

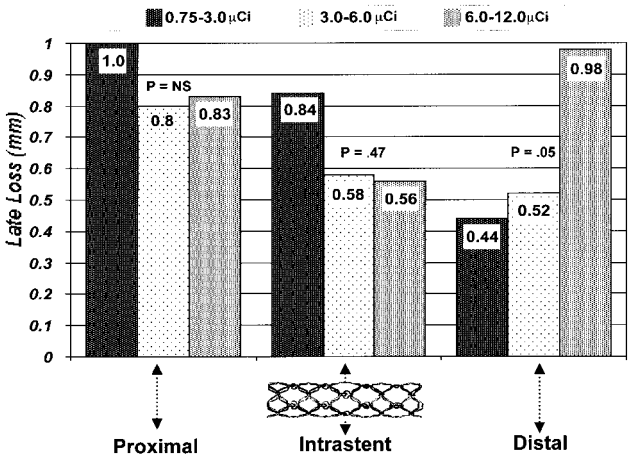

Figure 2. Late loss calculated by QCA in proximal reference segment, inside stent, and in distal reference segment in 3 groups of lesions (n=74) in patients with angiographic follow-up.

Comparison of Lesions With and Without Edge Restenosis

Edge restenosis was documented in 31 of 74 lesions of patients with angiographic follow-up. As shown in Table 7, by univariate analysis the final balloon-to-artery ratio and the ratio of the maximum diameter of the longest balloon (used to predilate, deploy, or postdilate the stent) to the reference vessel diameter were significantly higher in the edge restenosis group than in the lesions without edge restenosis. In addition, the edge restenosis group had a significant smaller reference lumen diameter and a smaller final MLD by angiography and a smaller distal and proximal lumen and vessel CSA by IVUS, with a nonsignificant lower percent area stenosis at these sites. The initial stent activity level, the number of stents per lesion, the maximum inflation pressure, the delivery balloon pressure, and the lesion length were not different between the 2 groups.

Discussion

The results of this study demonstrate that ^{32}P radioactive β-emitting stent implantation in patients with CAD is feasible. At 6-month follow-up, there had been no deaths, and only 1 patient had a subacute stent thrombosis with a Q-wave MI 1 week after he stopped both aspirin and ticlopidine 3 months after stenting. Moreover, radioactive β-emitting stents with

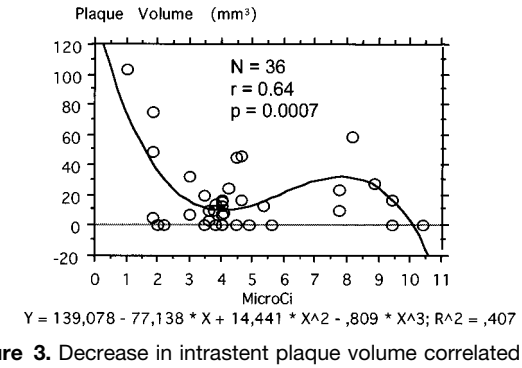

Figure 3. Decrease in intrastent plaque volume correlated with increase in radioactivity levels in 36 lesions in which a single 15-mm ^{32}P radioactive stent was implanted. Points were best fitted by a sigmoidal curve obtained by regression with a polynomial model of 3rd order.

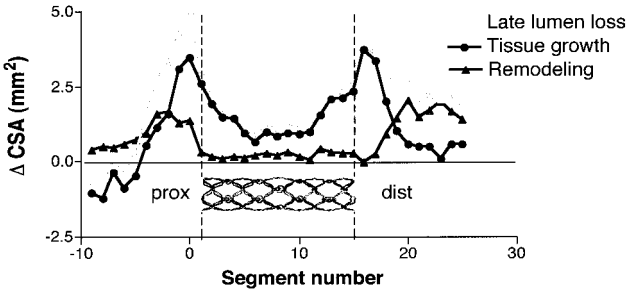

Figure 4. Plot of mean of late lumen loss, tissue growth, and remodeling (in mm^2) in 13 lesions with restenosis treated with a single BX Isostent with initial activity level ≥3 μCi. Point represents differences in CSA measured in slices 1 mm apart inside stent and in proximal and distal reference segments.

an initial activity level between 3.0 and 12.0 μCi substantially reduced intrastent neointimal hyperplasia compared with the lower-dose group. However, we observed a high intralesion restenosis rate of 41% to 52% because of restenosis in the reference segments at the stent edges. We called this "edge effect" the "candy wrapper" (Figure 5).

Comparison With Ongoing Clinical Studies Using ^{32}P Radioactive Stents

The preliminary results from 2 small clinical studies started in 1997 in Heidelberg[26] and Rotterdam[27] using ^{32}P radioactive Palmaz-Schatz or BX Isostents with low activity levels (0.75 to 3.0 μCi) have shown that clinical or angiographic restenosis was not lower than in contemporary stent trials using nonradioactive stents or than observed in the 0.75- to 3.0-μCi group in our study. At 6-month follow-up, the 11 patients enrolled in Heidelberg had a clinically driven target vessel revascularization rate of 36% (4 of 11 patients). Restenosis was found at the articulation of the Palmaz-Schatz stents and, at a lower rate, at the proximal and distal edges.[28]

Inhibition of Intrastent Intimal Hyperplasia: Potential Mechanisms

Whether the predominant mechanism by which radioactive stents prevent neointimal hyperplasia is inhibition of smooth muscle cell proliferation and migration or radiation-induced apoptosis is still unclear. In our study, the inhibition of neointimal proliferation in stents with activities >3 μCi could be, as proposed by Fischell et al,[29] a result of inhibition of the migration of smooth muscle cells and myofibroblasts from the tunica media and adventitia into the neointima as these cells pass through the "electron fence" at the plane of the stent wires. In addition, it could be that with higher activity levels, up to 12 μCi, there is a deeper effect on the media and adventitia similar to that seen with catheter-based radiation therapies, in which the cells are disabled before their attempt to migrate. Finally, Hehrlein[28] found that in the early phase of vascular injury, up to 1 week after stent implantation, the arterial media contained more apoptotic cells when the stents were radioactive.

The Problem of Edge Restenosis

Our study is the first to report the result of ^{32}P radioactive stent implantation with activity levels between 3.0 and 12 μCi in patients with CAD. It demonstrates an almost complete inhibition of intimal hyperplasia within the stent with activities >3 μCi, but an increased late loss and restenosis in the first 1 to 3 mm proximal and distal to the stent edges compared with the results reported in the literature with nonradioactive stents. The precise mechanism by which this phenomenon occurs remains poorly understood. It could be that the exaggerated proliferative response at the stent margins is the result of a low dose of radiation at the stent edges, due to a sharp decline of dose rate within millimeters from the stent margins,[30] in combination with the balloon injury in the segments adjacent to the stent when an aggressive stent implantation strategy with a high balloon-to-artery ratio is used, as in our population with edge restenosis. Previous studies with nonradioactive stents have demonstrated that inside a 15-mm-long Palmaz-Schatz stent, late loss was higher at the stent edges or at the central articulation than in the body of the stent. The injury at the stent margins has been advocated as 1 of the mechanisms of restenosis at these sites.[31,32]

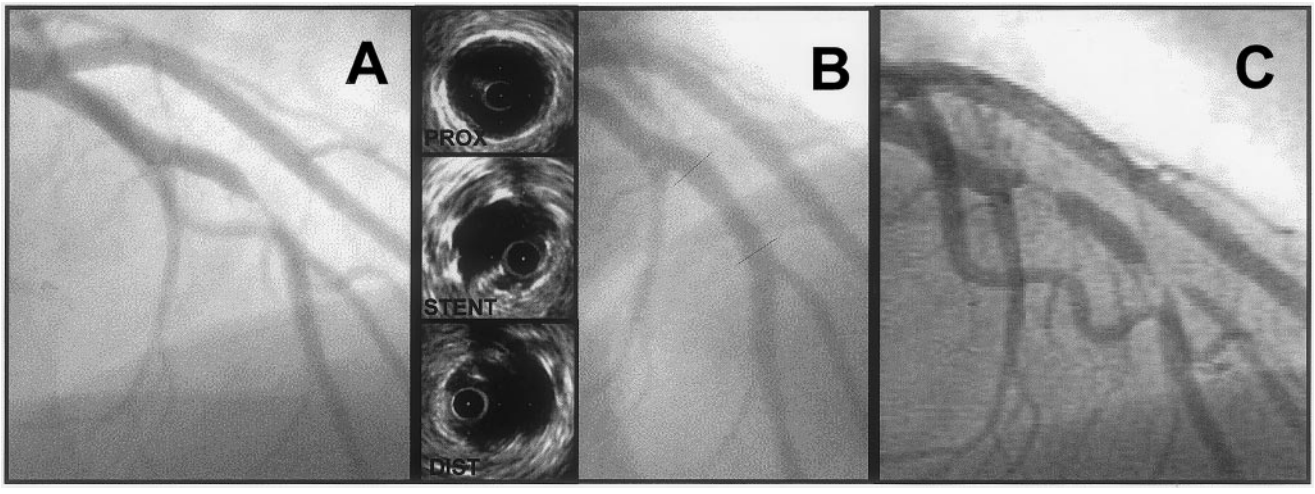

Figure 5. Representative patients with "candy wrapper" edge effect 4 months after radioactive ^{32}P β-emitting stent implantation. Baseline angiography (A) demonstrates a tight stenosis in mid left anterior coronary artery. After implantation (B) of a 15-mm BX Isostent with an activity of 8.14 μCi, IVUS images show very little plaque burden of contiguous proximal and distal reference segments. At 4 month follow-up (C), there is absence of late loss inside stent but a tight stenosis at both stent edges.

Predictors of Edge Restenosis

In a serial IVUS study by Hoffmann et al[33] of nonradioactive Palmaz-Schatz stents, the dominant periprocedural predictor of stent margin restenosis was the plaque burden of the contiguous reference segments. The same authors,[4] by serial IVUS analysis of sections sampled at a point closer to the stent edge, showed that late loss was due to a similar amount of remodeling and cellular proliferation.

The results of these studies differ from those of our study, in which we did not find that plaque burden of the contiguous reference segments was a predictor of edge restenosis. Instead, we found that the only predictors of edge restenosis were a high balloon-to-artery ratio and a small vessel size. In addition, unlike previous studies, late loss at the stent margins was mainly due to tissue growth (intimal hyperplasia) in the first 2 to 3 mm and to remodeling (shrinkage of the vessel) in the last 4 to 10 mm from the edges of the stent.

Edge Restenosis: Insights From the Animal Models

We are aware that artery models of restenosis in animal models are not really equivalent to data from a clinical investigation. However, the results from animal studies can give insights into the interpretation of the results obtained in the clinical setting.

Animal studies in rabbit iliac arteries[11] and in porcine coronary arteries[12] have shown the efficacy of a β-particle–emitting radioactive stent in the inhibition of subsequent intrastent neointimal cell proliferation. However, in some circumstances, radioactive stents can stimulate rather than inhibit intimal hyperplasia, as demonstrated by Carter at al[12] in the porcine model of restenosis, in which the 1.0-μCi stents had a significantly greater neointimal formation and luminal narrowing than the control nonradioactive stents. Other animal studies[28,34] have analyzed the effect of radiation delivery by a stent on the extracellular matrix deposition. In the rabbit model, Hehrlein[28] demonstrated by immunocytochemical analysis an increase in the expression of collagen type I after radioactive stent implantation, whereas production of collagen type III and IV was unchanged. We do not have data regarding the composition of the plaque in the lesions with edge restenosis. However, we observed that the plaques at the sites of restenosis had a low echo density by IVUS and were easily treated with balloon inflations at low pressure, suggesting that these plaques probably consisted mostly of extracellular matrix. Finally, a study by Carter et al[35] in cholesterol-fed pigs demonstrated stimulation of intimal hyperplasia when radioactive stents were implanted 1 month after angioplasty, possibly because the plaque was still in the healing phase. These results support our hypothesis that the mechanism of edge restenosis is the consequence of a combination of 2 factors: (1) a low dose of radiation at the stent margins and (2) the fact that an aggressive approach to stenting, as indicated by a high balloon-to-artery ratio, creates an injury in the reference segments, and these segments are possibly still in the healing phase after 1 month.

Study Limitations

Angiographic follow-up was obtained in 70 of 82 patients (85%). However, at 6-month clinical follow-up in the 12 patients without angiographic follow-up, 2 underwent bypass surgery shortly after stenting because of a multivessel CAD and persistent angina, 2 had atypical chest pain, and 8 were asymptomatic. IVUS imaging was not performed in all the lesions because of technical problems (after stenting), the inability of the operator to cross the lesions with the IVUS catheter, or the decision of the operator not to cross a tight restenotic lesion for the patient's safety (at follow-up).

Future Directions

We are continuing this dose-finding study (12 to 20 μCi) to determine whether a further increase in the overall stent radioactivity level combined with a different approach to radioactive stent implantation will solve the problem of edge restenosis. The stent implantation technique we are currently using is more conservative, selecting a small balloon to predilate the lesion and deploying the stent on a balloon with a diameter that closely matches the angiographic reference diameter inflated at the nominal pressure of 8 atm. In addition, postdilation is done with a shorter balloon whose ends do not extend outside the stent struts, so as not to mechanically damage the proximal and distal reference segments, with a 1:1 balloon-to-artery ratio.

Conclusions

Implantation of ^{32}P radioactive β-emitting stents in patients with CAD is feasible. At 6-month follow-up, there had been no deaths, and only 1 patient had stent thrombosis with a Q-wave MI associated with discontinuation of both aspirin and ticlopidine. Radioactive β-emitting stents with an initial activity level between 0.75 and 12.0 μCi reduce intrastent neointimal hyperplasia in a dose-related manner. However, intralesion restenosis was higher because of a high late lumen loss in the reference segments at the stent edges, possibly resulting from a low activity level of radiation at the edges of the stent in combination with an aggressive approach to stenting, as indicated by a high balloon-to-artery ratio.

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