Intracoronary β-radiation for the treatment of patients at very high risk for recurrence of in-stent restenosis: a single center experience

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Coronary stent; Restenosis.

Background. **Intracoronary brachytherapy has significantly reduced the recurrence of in-stent restenosis. The aim of this study was to evaluate the feasibility, safety and efficacy of intracoronary β-radiation in patients at very high risk for recurrence of in-stent restenosis.**

Methods. **We analyzed 42 patients with 50 lesions submitted to catheter-based β-radiation (Beta-Cath System, Novoste Corporation, Norcross, GA, USA) for in-stent restenosis. Thirty-eight lesions were at the second restenosis, 8 at the third, and 4 at the fourth; a diffuse pattern was present in 78%.**

Results. **Balloon angioplasty was performed for 30 lesions (60%) and the cutting balloon technique for 20 (40%). In 12 lesions further 14 stents had to be deployed (28%). The delivery catheter was successfully positioned in 96% of the procedures. The mean dwell time was 179 ± 50 s with a radiation dose ranging from 18.4 to 25.3 Gy, depending on the vessel size. A complete angiographic success without coronary dissection and without any additional stenting after radiation delivery was achieved in 86%. At follow-up (7.2 ± 2.1 months), the overall restenosis rate was 30.4% (14 lesions). A recurrence was detected in 1/11 lesions with initial focal pattern and in 13/39 lesions with initial diffuse pattern. The restenosis rate was higher in patients in whom a geographic miss had occurred ($p < 0.05$ vs lesions without geographic miss) and in those in whom a new stent had been deployed ($p < 0.05$ vs lesions treated without a stent).**

Conclusions. **Brachytherapy reduces the in-stent restenosis rate in patients who are at very high risk of recurrence. The restenosis pattern, geographic miss and new stent deployment seem to be negative prognostic factors for recurrence of restenosis.**

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Introduction

Coronary stenting has significantly reduced restenosis through the inhibition of both the elastic recoil and the late contraction of the vessel. However, neointimal hyperplasia still affects the long-term clinical outcome and is responsible for an overall in-stent restenosis rate of 20 to 35%[1-6].

In spite of treatment with balloon techniques, rotational atherectomy or other devices, the recurrence of restenosis still exceeds 30% and becomes higher in the setting of aggressive and diffuse restenosis[4-14]. Since radiotherapy could be effective in reducing cellular proliferation in hyperplastic diseases such as keloid scars and heterotopic ossification, its use has been proposed as a new technique for the prevention of coronary in-stent restenosis[15-18]. Several studies[19-22] showed a decrease in the restenosis rate after treatment with either β-or γ-radiation[20-27]. Nevertheless, most of available data concern patients at the first recurrence of restenosis. The purpose of this study was to evaluate the early and long-term outcomes of treatment with intracoronary β-radiation in a population at a very high risk of restenosis presenting, at least, with a second in-stent restenosis.

Methods

Study design. All consecutive patients undergoing an angioplasty for at least the second recurrence of in-stent restenosis were treated with β-radiation. The Ethics Committee approved the investigational use of brachytherapy and all scheduled patients signed a written informed consent for coronary irradiation. An angiographic follow-up was initially planned after 6 months. Since a possible role of brachytherapy in delaying rather than suppressing restenosis has been pointed out[28], we decided to ex-

tend the follow-up period up to 9 months. For this reason, the first 5 patients were submitted to angiographic follow-up at 6 months while the others at 9 months.

Population. We analyzed 50 lesions in 42 patients (in 8 patients 2 lesions were treated) presenting with at least the second recurrence of in-stent restenosis: 38 lesions were at the second restenosis, 8 at the third, and 4 at the fourth. All lesions were on the native coronary artery.

The mean age of the population was 61.8 ± 8.9 years; 10 patients were female (23.8%). Hypertension was present in 23 (54.7%), diabetes in 12 (28.6%), a history of smoking in 28 (66.6%), a family history of coronary artery disease in 15 (35.7%) and hyperlipidemia in 30 (71.4%). Eighteen (42.9%) patients were admitted for stable angina, 13 (30.9%) for unstable angina, and 11 (26.2%) for silent myocardial ischemia. In 21 (50%) patients a previous history of myocardial infarction was present while 11 (26.2%) patients had previously undergone a coronary artery bypass graft. Seventeen (40.5%) patients had single-vessel disease, 12 (28.6%) two-vessel disease, and 13 (30.9%) three-vessel disease.

The target lesion was on the left main artery in 1 (2%), on the left anterior descending coronary artery or its diagonal branch in 17 (34%), on the left circumflex coronary artery or obtuse marginal branch in 15 (30%), and on the right coronary artery in 17 (34%). The reference vessel diameter was 3.0 ± 0.48 mm and the minimal lumen diameter was 0.55 ± 0.43 mm with a percentage diameter stenosis of 80.7 ± 14.6%. The lesion length was 19.7 ± 14.6 mm.

The restenosis pattern was focal in 11 (22%) lesions and diffuse in 39 (78%) with 9 (18%) total occlusions. The main clinical and angiographic data are summarized in tables I and II.

Table I. Clinical characteristics.

No. patients	42
Age (years)	61.8 ± 8.9
Sex (M/F)	32/10
Stable angina	18 (42.9%)
Unstable angina	13 (30.9%)
Silent myocardial ischemia	11 (26.2%)
Hypertension	23 (54.7%)
Diabetes	12 (28.6%)
Cigarette smoking	28 (66.6%)
Hyperlipidemia	30 (71.4%)
Family history of CAD	15 (35.7%)
Previous myocardial infarction	21 (50%)
Previous CABG	11 (26.2%)
No. diseased coronary arteries	
One vessel	17 (40.5%)
Two vessels	12 (28.6%)
Three vessels	13 (30.9%)

CABG = coronary artery bypass graft; CAD = coronary artery disease.

Table II. Angiographic data.

No. lesions	50
Site of restenosis	
Left main artery	1 (2%)
LAD	17 (34%)
Circumflex coronary artery	15 (30%)
Right coronary artery	17 (34%)
2nd restenosis	38 (76%)
3rd restenosis	8 (16%)
4th restenosis	4 (8%)
Focal restenosis	11 (22%)
Diffuse restenosis	39 (78%)
Intrastent	13 (26%)
Proliferative	17 (34%)
Total occlusion	9 (18%)
Baseline QCA	
Mean lesion length (mm)	19.7 ± 14.6
RVD (mm)	3.0 ± 0.48
MLD (mm)	0.55 ± 0.43
Diameter stenosis (%)	80.7 ± 14.6

LAD = left anterior descending coronary artery; MLD = minimal lumen diameter; QCA = quantitative coronary angiography; RVD = reference vessel diameter.

Procedure. All patients were treated with aspirin 100 mg/day and ticlopidine 250 mg twice daily for at least 2 days before the procedure. A bolus of 10 000 IU of heparin was administered after sheath insertion and additional heparin was given to maintain the activated clotting time > 250 s. The percutaneous intervention was performed according to standard clinical practice. Brachytherapy was performed after achieving an optimal angiographic result. The radiation oncologist and the medical physicist supervised all the procedures.

After the procedure aspirin (100 mg/day) was prescribed indefinitely. Ticlopidine (250 mg twice daily) was associated for 6 months or for 12 months if a new stent was implanted.

Radiation delivery system. The Beta-Cath System (Novoste Corporation, Norcross, GA, USA) consists of three components: 1) the radiation source, 2) the transfer device, and 3) the delivery catheter.

The radiation source train consists of a "train" of several miniature cylindrical sealed sources containing strontium-90, a pure β-emitter. Two gold markers are placed at the edges of the source. A 40 mm source has been used; it allowed us to deliver the full prescribed dose for a length of 35 mm and accounts for the longitudinal dose fall-off at the edges of the radiation source.

The transfer device houses the sources in a quartz chamber and contains a switching system and a gate. The switch allows the physician to either transfer the sources to the end of the catheter or to return them back to the transfer device.

The triple lumen, over-the-wire delivery catheter, is a 5F, closed-ended, flexible coronary catheter. The first lumen is for the hydraulic delivery of the train of radiation sources, the second lumen allows the reversal of

the fluid flow, and the third one is for the passage over a 0.014" guidewire. Correct positioning of the catheter is facilitated by the presence of two radio-opaque markers placed at the edges of the source.

Radiation procedure. The dose to be delivered was planned according to the vessel diameter, measured by means of quantitative coronary angiography: 18.4 Gy at 2 mm from the source line were delivered in 2.5-3.5 mm diameter vessels, 23 Gy in 3.5-4 mm diameter vessels, and 25.3 Gy in vessels > 4 mm. After successful angioplasty the radiation catheter, connected to the transfer device, was advanced over the guidewire until the marker bands encompassed the angioplasty site. The gate of the transfer device was then opened and the source train was hydraulically delivered down the catheter. A continuous, minimal hydraulic pressure was required to maintain the source train at the distal end of the catheter lumen.

Since the full prescribed dose covered lesions ≤ 35 mm in length, a two-step radiation treatment with manual pullback was performed to cover all the injured area in longer lesions.

After radiation therapy, the source train was stepped back to the transfer device by reversing the switching system.

Quantitative coronary angiography. Quantitative coronary angiography was performed, after intracoronary administration of nitrates, in at least two orthogonal views. The projection showing the smallest lumen diameter was selected for measurements. The reference lumen diameter was considered as the average of the apparently normal proximal and distal diameters. In case of total occlusion, the post-procedural diameters were used and the lesion length was measured with manual calipers using information obtainable from the ipsilateral or contralateral collateral penetration. Cineangiograms with contrast injection were obtained to document the site of balloon inflation and the position of the source train. The presence of injured segments not receiving a full dose of radiation was defined as geographic miss[29,30]. The reference vessel diameter, the percentage diameter stenosis and the minimal lumen diameter were measured before and after the treatment, and at follow-up. Restenosis was defined as a > 50% narrowing of the diameter of the irradiated segment. It was classified as "target lesion restenosis" when it was a recurrence at the target in-stent restenosis, as "edge restenosis" if it appeared at one of the edges of the irradiated segment, and as "new stent restenosis" if it was detected at the site of implantation of the new stent.

Statistical analysis. Data are presented as average ± SD or as percentages. Binary variables were compared by means of the χ^2 test. A p value of < 0.05 was considered statistically significant.

Results

Procedural results. In 34 patients a single lesion was treated, 6 had a two-vessel treatment, 1 had two lesions treated on the same vessel, and 1 was treated on a bifurcation. Balloon angioplasty was performed on 30 lesions (60%) and the cutting balloon technique followed by further balloon dilation on 20 (40%). Fourteen additional stents were deployed on 12 lesions (in 2 lesions two stents were required). Ten stents (20%) were implanted before brachytherapy to improve the angiographic result and/or to cover dissections, mainly at the edge of the original stent. Four (8%) stents had to be deployed after brachytherapy: two of them owing to the presence of dissections already present before catheter insertion, the other two owing to the presence of dissections detected after catheter withdrawal. In one patient the dissection was associated with a transient occlusion of the vessel. However, in all patients a final TIMI 3 flow was achieved without myocardial necrosis.

The post-procedural mean minimal lumen diameter was 2.83 ± 0.55 mm with an acute gain of 2.28 ± 0.12 mm. The delivery catheter was successfully placed in 48/50 (96%) lesions: in one patient it was not possible to advance the catheter through a small and calcified vessel; in the other patient, owing to the small diameter of the vessel, it was not possible to reach the distal part of the target segment. The mean dwell time was 179 ± 50 s (range 150 to 240 s) with a radiation dose ranging from 18.4 to 25.3 Gy.

In one patient, ventricular fibrillation occurred during irradiation and the prescribed dose was delivered in two steps. In 15 lesions (30%) manual pullback of the catheter was necessary to cover very long segments, with minimal overlapping of the irradiated segments. A geographic miss occurred in 23/100 edges (23%). It was mainly due 1) to the slipping of the balloon during the procedure, resulting in an injured segment > 35 mm but not so long as to justify a pullback with irradiation of a too large segment; 2) to avoid irradiation of left main or of its bifurcations; 3) to improve the angiographic result with further balloon inflation or stenting after catheter removal. A geographic miss occurred at the proximal edge in 7 lesions, at the distal edge in 10, and at both edges in 3.

Hence, overall, an event-free procedure was performed in 43/50 (86%) lesions.

Follow-up results. Angiographic follow-up was available for 46/48 (95.8%) lesions after 7.2 ± 2.1 months. The mean length of follow-up was strongly influenced by those patients with a worse outcome who needed a very early control. Nevertheless, although the first 5 patients had a 6-month angiographic follow-up, in the majority of the cases the angiographic follow-up was obtained at 9 months.

One patient refused the angiographic control and one died suddenly 5 months after the procedure. Seven

patients complained of angina, and 3 patients had a myocardial infarction. In one of these patients brachytherapy has been performed on a bifurcation. This patient was admitted 30 days after the procedure with thrombosis of one of the two branches and recurrent restenosis of the other. The other 2 patients had a late occlusion of the target lesion. In one of them this event occurred following the withdrawal of antiplatelet therapy because of gastric bleeding.

The restenosis rate was 30.4% (14 lesions in 13 patients). With regard to the lesions in which a recurrence occurred, the initial restenosis pattern was focal in one lesion (9%), diffuse in 10 (33.3%) and a total occlusion in 3 (33.3%). The site of the recurrence was at the target lesion in 5 lesions (10%), at the proximal edge in 5 (8%), at the distal edges in 1 (2%), and at the site of implantation of the new stent in 4 (8%). As for the lesions treated with a new stent, a restenosis occurred in 6 (50%) ($p < 0.05$ vs patients not receiving a new stent). In 5 of these lesions (83.3%), the stent has been implanted before brachytherapy and in 4 (66.6%) lesions restenosis was detected in the new stent implanted.

A geographic miss occurred more frequently in lesions with restenosis (9/14; $p < 0.05$ vs patients without geographic miss). Besides, in 6 of these lesions (66.6%) a new stent had also been implanted. In patients without restenosis, the mean lumen diameter was 2.37 ± 0.81 mm (post-procedural mean lumen diameter 2.84 ± 0.57, p = NS) (Fig. 1) with a stenosis diameter of 22.78 ± 14.94%.

Discussion

In the present study we report our experience with the use of the Beta-Cath System (Novoste) for intracoronary β-irradiation in patients at very high risk for recurrence of in-stent restenosis. The system used was specifically designed for coronary applications with the goal of creating a catheter-based device similar to a balloon catheter that could deliver high-activity β-radiation to different segments of the coronary artery tree. β-irradiation was preferred because of the limited depth of penetration of the source activity and in view of the very short dwell time. Moreover, physicians are not required to leave the patient's bedside during the procedure[31,32].

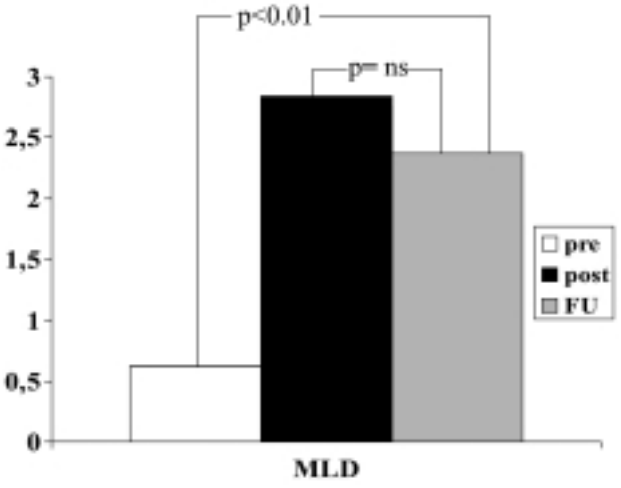

Figure 1. *Baseline, post-procedural and follow-up (FU) minimal lumen diameter (MLD) in patients without recurrence of restenosis.*

From our experience we can confirm that the Beta-Cath System can be successfully used for the majority of procedures. The flexibility and maneuverability of the device allowed us to reach the distal part of almost all vessels, in spite of the catheter size. However, after catheter positioning, coronary dissections might occur and an optimization of the angiographic result with further stents may be required. It is well known that in the treatment of in-stent restenosis the deployment of "new stents" is necessary in up to 36% of the interventions[33,34]. Using this device, the need of further stenting in our population could be related both to the lesion length as well as to the small ratio between the catheter and vessel diameters. The development of longer and thinner catheters is expected to overcome this problem and probably will limit the need of further stenting.

At follow-up, the restenosis rate was less than the 30-80% reported in previous studies for such lesions[35]. However, available data refer to patients at the first treatment of in-stent restenosis[35]; our population, at the second, third and fourth recurrence, should be considered at higher risk for further restenosis and a worse outcome should have been expected, independently of the device used or the technique performed. However, the initial pattern of restenosis still remains a negative prognostic factor on the rate of recurrence.

The worse outcome has been observed mainly in patients receiving new stents at the time of brachytherapy. The need of further stenting was mainly required in aggressive and diffuse restenosis. The adverse outcome related to new stent deployment could be partially explained by both the late stent malapposition as well as by late thrombosis due to delayed re-endothelialization[36]. In previous clinical trials with irradiation followed by a double antiplatelet therapy for less than 2 months, the late thrombosis rate ranged from 6 to 14%[37-41], occurring mainly when adjunctive stents were deployed at the time of brachytherapy[37,38]. After prolonging ticlopidine and aspirin administration, the late thrombosis rate has been reduced even in patients receiving new stents, though a warning 1.8-3% persists. Therefore, it is advisable to avoid brachytherapy in patients with any kind of intolerance to a full antiplatelet regimen. The reason for the occurrence of an exaggerated restenosis in stents implanted at the time of brachytherapy is still uncertain. In recent studies the placement of new stents influenced restenosis mainly at the site in which a geographic miss had also occurred[42]. It is now common opinion that irradiation of

at least 7 mm of a "not injured" vessel at both edges of the target lesion, may be considered a safe approach for the prevention of edge restenosis. For this reason in case of long lesions we performed a pullback thus achieving a very low rate of geographic miss, when compared with previous experiences[42]. Nevertheless, in our population a geographic miss occurred mainly in those patients who were also submitted to new stent deployment. As a result, the higher restenosis rate observed in the group of patients with geographic miss might be related more to the new stent deployed than to the geographic miss itself. Thus, further studies including a broader population of patients are needed to confirm this hypothesis.

In conclusion, in our experience the Beta-Cath System has not increased the periprocedural risk and has reduced the rate of restenosis even in case of lesions at a very high risk of recurrence. Despite these promising results, a further improvement in the acute and long-term results is expected with the use of longer and thinner delivery catheters.

Besides, as long as the association between new stent deployment and recurrence of restenosis is not fully clarified, the implantation of a new stent at the time of brachytherapy should be discouraged, in view of the worse outcome observed in these patients.

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