Endovascular beta-irradiation with a liquid 188 Re-filled balloon to reduce restenosis after coronary angioplasty.


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ABSTRACT
Introduction: Ionizing radiation reduces neo-intimal proliferation after coronary angioplasty (PTCA). Rhenium-188 is widely available from a generator system. We present our preliminary results as part of a multicenter trial organized by the I.A.E.A.

Objectives: To assess the usefulness of the liquid-filled balloons with rhenium-188 to reduce restenosis post-PTCA.

Material and Methods: We included 25 coronary heart disease patients. We followed the standard PTCA procedure. A new catheter balloon located in the target lesion was used to deliver the dose of 18 Gy at 1.0 mm depth from the surface of the balloon.

Results: Before discharge of the hospital, one patient with balloon PTCA had unstable angina with electric ST-T changes and there was a myocardial infarction at three months. The balloon PTCA cases had the worst follow-up. Late loss index was of 0.24±0.20 for stent patients; 0.67±0.48 for balloon patients; and 0.34±0.37 for in-stent restenosis cases. The restenosis found at six months was of 59±45% for balloon PTCA; 24±16% for stent PTCA and 29±35% for in-stent restenosis.

Discussion: In the group of "de novo" lesions treated with stent previous irradiation, although there is a reported evidence of a significant occurrence of late thrombosis, we only found one case with a myocardial infarction distal to the treated lesion. Hoher et al demonstrated that rhenium-188 brachytherapy was effective with and without stenting, and they consider that stents are not longer associated with increased late thrombosis after prolonging antiplatelet therapy. We had an edge-effect in two patients. In both cases the rhenium-filled balloons were only two millimeters longer than the stenosed segment.

Conclusions: Coronary irradiation for in-stent restenosis with a 188Re-filled balloon is technically feasible and safe. These results are preliminary and a complete follow-up is needed, with a higher number of patients and controls, to adequately assess the results of the treatment.

INTRODUCTION
Restenosis after successful percutaneous transluminal coronary angioplasty (PTCA) is the major shortcoming to long-term success of this procedure. Ionizing radiation have demonstrated significantly reduced neo-intimal proliferation [1,2]. Gamma or beta-emitting solid sources [3-6], radioactive stents and liquid-filled balloons with beta-emitting radioisotopes, mainly rhenium-188 [7-10], have been used. Rhenium-188 has the following advantages: it is a liquid beta-emitter with preservation of the environment of the target; it does not have the problem of the centering issue; it is widely available from a generator system in a cost-effective way and dosimetric data have been estimated for endovascular radiation as well as for intravenous administration. Thus, implementation of endovascular irradiation in coronary angioplasty and set up of the proper procedure using the standard angioplasty balloon filled with rhenium-188, can constitute a very important and cost-effective step for coronary heart disease evolving approach. We present our preliminary results as part of a multicenter trial organized by the International Atomic Energy Agency (I.A.E.A.).

OBJECTIVES
To assess the usefulness of the liquid-filled balloons with rhenium-188 to reduce restenosis post-PTCA.

MATERIAL AND METHODS
Population
Twenty-five patients with coronary heart disease diagnosis were included: 11 (44%) with stent in "de novo"
lesions, 5 (20%) with balloon PTCA in "de novo” lesions and the other 9 (36%) with in-stent restenosis.

Procedure
We followed the standard PTCA procedure, considering that a PTCA was successful when a residual diameter stenosis < 30% was achieved without major complications. A new catheter balloon located in the target lesion was used to deliver the dose of 18 Gy at 1.0 mm depth from the surface of the balloon into the vessel wall, using a rhenium-perrenenate solution without contrast media. A standard heparinization was administered during the procedure.

All patients received 600 mg of oral potassium perchlorate half an hour before the procedure, as well as 325 mg of aspirin daily. Clopidogrel was administered in the following way: 300 mg for loading and 75 mg once a day.

During the procedure, routine x-ray protective measures were used, and radiation exposure at various distances and positions was measured continuously. To exclude potential undetected minor balloon leaks (without noticeable pressure loss), two 5 ml syringes of blood were obtained drawn (one before and one after intracoronary irradiation) and monitored for radioactive contamination.

STATISTICAL ANALYSIS
Continous variables were expressed as mean ± standard deviation (SD). Discrete variables were expressed as counts and percentages. A p<0.05 was considered significant.

RESULTS
Clinical Data
The baseline clinical characteristics are shown in table 1. There were more men than women and 50% of the women were postmenopausal. There was a previous myocardial infarction in 28% of patients.

Regarding the cardiovascular risk factors, the more frequent were high blood pressure and smoking habit (table 1).

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Characteristics and Cardiovascular Risk Factors</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<tr>
<td>Sex (Men/Women)</td>
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<tr>
<td>Postmenopausal Women</td>
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<tr>
<td>Mean age (years)</td>
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<tr>
<td>Previous MI</td>
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<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Active Smokers</td>
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<tr>
<td>High Blood Pressure</td>
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<td>Diabetes Mellitus</td>
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MI: myocardial infarction

Figure 1 shows the target coronary vessel. There was the same number of cases with left anterior descending coronary artery and right coronary artery as the target vessel.

Figure 1. Target Coronary Vessel

LAD: left anterior descending coronary artery
LCx: left circumflex coronary artery
RCA: right coronary artery
No left ventricular dysfunction at rest was found among our patients (left ventricular ejection fraction of 77±7%).

**Procedural Data**
A 1.5 - 2ml of 188Re solution with a specific volume of 5256±2371 MBq/ml was used. Irradiation was done with catheter balloons whose mean balloon diameter was 2.99±0.37 mm; the mean balloon catheter diameter was 0.86±0.05 mm. In all patients, the prescribed dose of 18 Gy was delivered. The mean irradiation time was 466±195 seconds. The dose was fractionated in 80% of the cases (mean: 3±2 fractions).

In table 2 are presented the angiographic measurements before coronary angioplasty: a mean minimal lumen diameter of 0.68±0.19 mm, a diameter stenosis of 73±4% and a mean lesion length of 9.34±4.94 mm.

<table>
<thead>
<tr>
<th>Measurements before coronary angioplasty</th>
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<tr>
<td>Reference diameter (mm)</td>
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<tr>
<td>Minimal lumen diameter (mm)</td>
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<tr>
<td>Diameter stenosis (%)</td>
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<td>Lesion length (mm)</td>
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The postangioplasty stenosis diameter was of 3±7%.

There was no radiation leakage within a patient.

**Follow-Up Data**
Regarding clinical data, up to date we have done the follow-up until twelve months in 17 patients, as well as the angiographic follow-up at six months in 19 of the 25 irradiated patients. Specifically in the case of in-stent restenosis, we have five irradiated patients with clinical and angiographic follow-up, and 4 irradiated patients with three months clinical follow-up.

Before discharge of the hospital, one irradiated patient with balloon PTCA had unstable angina with electric ST-T changes. At one month, four patients (16%) had experienced chest pain (one of them had an unstable angina at one month -PTCA with stent- and two had atypical pains), and one case had dyspnea at rest (table 3). At three months three patients with balloon PTCA and two with stent PTCA experienced angina (one of the last ones had an anterior acute myocardial infarction); while one irradiated patient with stent PTCA suffered from dyspnea at stress (see table 3 for the general data). The clinical behavior at six and twelve months is also presented in table 3.

In table 4 we present the angiographic results at six months divided into three different groups: "de novo" lesions with stent PTCA, "de novo" lesions with balloon PTCA, and in-stent restenosis. The balloon PTCA cases had the worst follow-up, with two patients with a complete occluded RCA and other with a very severe atherosclerotic disease who had a 74% restenosis, a target vessel revascularization with stent and later an in-stent restenosis in the same place. Among the cases with stent PTCA there were one progression of the lesion in the case with an AMI at three months and one edge-effect; while among the first five in-stent restenosis cases there were a 90% restenosis in a patient who did not continue the treatment with clopidogrel after the first month, and one edge-effect. Considering only the in-lesion restenosis in the in-stent restenosis patients, there was a 20% of cases (figure 3).
The restenosis (percent of reduction of the coronary lumen) found at six months was of 59±45% for balloon PTCA cases; 24±16% for stent PTCA and 29±35% for in-stent restenosis patients.

**DISCUSSION**

This clinical safety and feasibility study shows our preliminary results regarding the usefulness of intracoronary irradiation with 188-rhenium in the reduction of restenosis in "in-stent" lesions and in "de novo" lesions with stent PTCA, but not in balloon PTCA. We have not found any specific reference about a negative effect of radiation after balloon PTCA. Nevertheless, in our case the results in this subset of patients precluded its use in the rest of the trial.

In the group of "de novo" lesions treated with stent previous irradiation, although there is a reported evidence of a significant occurrence of late thrombosis [11,12], we only found one case with an anterior myocardial infarction distal to the treated lesion at three months of the procedure. According to this, Hoher et al [10], in a randomized study where they included "de novo" and restenotic lesions, demonstrated that rhenium-188 brachytherapy was effective in the subgroups with and without stenting, and they consider that stents are not longer associated with increased late thrombosis after prolonging antiplatelet therapy (6 months at least). They found a 6.3% of cases of restenosis at the target lesion in "de novo" lesions, which corresponds with our 11% of cases in this type of patients.

It is also important to point out the problem of the "geographic miss" and the edge-effect. Edge restenosis has been an important issue associated with radiation therapy, especially with radioactive stents [13]. The pathophysiology of the edge-effect may be the result of vessel wall injury concomitant with low-dose radiation at the edges of the irradiated area ("geographic miss") [14]. Among our cases we had an edge-effect in two patients. In both cases the rhenium-filled balloons were only two millimeters longer than the stenosed segment. The radiation balloon should be sufficiently longer than the injured segment to avoid geographic miss ("the longer, the better").

Regarding the "in-stent" restenosis patients, there was an occlusion in a patient who decided not to take more clopidogrel after the first month of treatment, as well as one edge-effect.

It has been shown that the radiation dose immediately adjacent to an air bubble can be 30% lower than that for a completely filled balloon [15]. Although according to Park et al. [8] the dose fractionation might increase the chance of air inclusion in the balloon, we did not find a significant correlation between the presence of restenosis and the dose fractionation.

A conventional PTCA balloon filled with a 188-rhenium solution results in a self centering radiation source independent from bending of the artery, cardiac motion, or stenosis morphology, providing a homogeneous dose delivery. Beta-radiation compared with gamma-radiation requires less radiation protection and shorter
CONCLUSIONS

Coronary irradiation for in-stent restenosis with a 188Re-filled balloon is technically feasible and safe. These results are preliminary and a complete follow-up is needed, with a higher number of patients and controls, to adequately assess the results of the treatment.

REFERENCES
