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Phase III randomised trial

Randomized blinded clinical trial of intracoronary brachytherapy with ^{90}Sr/Y beta-radiation for the prevention of restenosis after stent implantation in native coronary arteries in diabetic patients

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Abstract

***Background*: We report a double-blind, randomized clinical trial of intracoronary β-radiation for prevention of restenosis after stent implantation in native coronary de novo lesions in diabetic patients.**

***Methods*: After successful stent implantation in native coronary de novo lesions, 106 lesions in 89 diabetic patients were randomly allocated to treatment with β-radiation with 18 Gy at 1 mm vessel depth ($n=53$) or placebo treatment ($n=53$).**

***Results*: Angiographic analysis at 9 month follow-up revealed a late lumen loss of 0.7 ± 0.9 mm in the radiotherapy group versus 1.2 ± 0.8 mm in the control group at the injured segment ($P=0.006$), 0.9 ± 1.0 versus 1.3 ± 0.7 mm at the radiated segment ($P=0.02$), and 0.9 ± 1.0 versus 1.3 ± 0.7 mm at the target segment ($P=0.04$) (defined as active source length plus 5 mm on proximal and distal sites). Binary restenosis rates were significantly lower in the radiation group in all subsegments (injured segment: 10.9 versus 37.3%, $P=0.003$; radiated segment: 21.7 versus 49.0%, $P=0.005$; target segment: 23.9 versus 49.0%, $P=0.01$). Target lesion revascularization for restenosis was required in nine lesions (17.6%) in the radiotherapy group versus 18 (34.0%) in the placebo group ($P=0.05$). Late thrombosis occurred in four radiated patients (after premature discontinuation of antiplatelet therapy in all), resulting in a major adverse clinical event rate of 37.2% in the brachytherapy group versus 38.6% in the placebo group ($P=$ns).**

***Conclusions*: In diabetic patients with de novo coronary lesions, intracoronary radiation after stent implantation significantly reduced restenosis. However, this clinical benefit was reduced by the frequent occurrence of late thrombosis.**

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Diabetic individuals have a 2–4 fold increased risk for developing vascular disease compared to non-diabetics [1]. Diabetics were shown to have a different composition of the atherosclerotic plaque [2,3], with more severe and more diffuse disease [4,5], with a higher incidence of fissured plaques and increased vulnerability for abrupt closure and resultant acute myocardial infarction. Furthermore, diabetic patients show increased blood viscosity [6] and enhanced platelet aggregation [7]. Because of the hormonal and vascular abnormalities that may accelerate smooth-muscle cell proliferation after vascular injury [8], these patients exhibit an increased incidence of restenosis with restenosis rates up to 63% after successful coronary balloon angioplasty [9,10]. Intracoronary stenting has definitely improved the midterm outcome after percutaneous revascularization, however, restenosis rates up to 55% may still be present in this patient cohort [11,12].

Catheter-based delivery of intracoronary brachytherapy with beta or gamma radiation have been proven effective in reducing restenosis after percutaneous coronary interventions in several randomized clinical trials [13–17]. Retrospective studies have also demonstrated its effectiveness in the treatment of recurrent in-stent restenosis in diabetic patients [18,19]. The purpose of this randomized clinical trial was to assess the efficacy of brachytherapy with ^{90}Sr/^{90}Y beta-radiation for the prevention of restenosis after successful percutaneous intervention with stent implantation in native coronary de novo lesions in diabetic patients.

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Methods

Study population, and procedure

Between April 2001 and January 2004, 89 diabetic patients were prospectively enrolled into the REGARD trial (intracoronary radiation with optional use of GPIIb/IIIa antagonist in diabetic de novo lesions) at the Medical University of Vienna, Austria. During this time interval, all patients undergoing coronary angiography were evaluated for inclusion/exclusion criteria. Major inclusion criteria were: (1) patient's age >19 years, (2) diabetes mellitus requiring medication (IDDM: insulin dependant diabetes mellitus; NIDDM: non-insulin dependant diabetes mellitus), (3) target lesion (angiographic evidence of $>50\%$ diameter stenosis) in a native vessel, (4) treatment of a de novo lesion with successful stent-implantation ($<30\%$ residual stenosis). Major exclusion criteria were: (1) myocardial Infarction within the last 72 h, (2) unprotected left main stenosis, (3) lesions within extremely angulated segments $>90\%$ or vessels with extensive tortuosity of the proximal segment, (4) patients with extensive peripheral vascular disease that precludes safe insertion of at least a seven French introducer sheath, (5) presence of other serious illness (including active or metastatic cancer, significant liver disease, active infection, or any life threatening condition), (6) previous radiation treatment to the chest, (7) acute renal failure, (8) previous diagnosis of auto-immune diseases, (9) significant valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or congenital heart disease, (10) past or present bleeding disorders, (11) hypersensitivity to heparin or aspirin. Exclusion criteria for the administration of a GPIIb/IIIa antagonist were: (1) history of stroke within 30 days before intervention or any history of hemorrhagic stroke, (2) intracranial neoplasm, (3) arteriovenous malformation or aneurysm, (4) development of haematoma at the site of arterial puncture during intervention.

Patients were randomly assigned to β-radiation or placebo therapy after successful revascularization with stent implantation. Antiplatelet therapy (clopidogrel, 75 mg/day after a loading dose of 300 mg on the day of intervention) was prescribed for 9 month in combination with aspirin (100 mg/day). Clinical follow-up was obtained at 1, 6, and 9 month. Angiographic follow-up was performed after 9 month. The study was approved by the local ethics committee. Written informed consent according to the institutional guidelines for cardiac catheterization and intracoronary radiation were available for all patients.

Randomization

Lesions were randomly allocated to treatment with β-radiation or placebo treatment using randomization envelopes which were opened by the radiotherapist or medical physicist after the patient was found eligible for the study. Thus, only the radiotherapist and the physicist were not blinded to treatment assignment. Since successful revascularization was one of the study entry criteria, randomization was undertaken after angioplasty intervention.

Coronary angiography, intervention and radiation treatment

All patients underwent routine biplane coronary angiography using the Judkins technique. Before angiography 0.1–0.2 mg intracoronary nitroglycerine were applied to achieve maximal vasodilatation. Baseline and follow-up angiograms were recorded digitally. Interventional treatment included stent implantation ($\pm$balloon angioplasty) followed by intracoronary brachytherapy with beta-radioisotopes $^{90}Sr/^{90}Y$ (Novoste Beta-Cath™, Novoste Corp., Norcross, Georgia), or placebo treatment (sham procedure), using active source lengths of 40 and 60 mm. Radiation treatment was performed by a team consisting of interventionist, radiotherapist and medical physicist. Intervention length was determined, by careful estimation of the length of the overall dilated and stented length, in consensus between the interventionist and the radiotherapist. The treatment-planning for the prescription of therapeutical radiation dose included a minimal safety margin of 5 mm at each end beyond the dilated site [20,21]. By definition, the therapeutical radiation dose was confined to the segment receiving $>90\%$ of the prescribed dose at 1 mm vessel wall depth (i.e. active source length minus 2.5 mm at each end) [22,23]. All patients receiving radiation were treated with a radiation dose of 18 Gy at 1 mm vessel wall depth. This was achieved by advancing of the delivery catheter over the guide wire (by injecting sterile water, causing hydraulic pressure to advance the source). In case of placebo treatment, the patients underwent the same treatment with a non-radioactive treatment source. Tandem positioning was performed for injured segments $>$ 45 mm. Coronary intervention was carried out with administration of a GPIIb/IIIa antagonist in all appropriate patients.

Angiographic analysis

A computer-assisted quantitative coronary angiographic edge detection algorithm (ACOMPC, Siemens, Erlangen, Germany) was used for cineangiographic analysis. Both baseline and follow-up angiographic analyses were performed in two identical projections by experienced observers blinded to the treatment mode.

The injured segment was defined as the segment of balloon and stent injury required to treat the primary lesion, the radiated segment as the segment receiving $>90\%$ of the prescribed dose at 1 mm vessel wall depth (i.e. active source length minus 2.5 mm at each end) [22]. Finally, the target segment was defined as active source length plus 5 mm on both proximal and distal sites (Fig. 1). Minimal lumen diameter (MLD), reference diameter, and percent diameter stenosis (%DS) were assessed for each of the above subsegments. Lesion length was measured as the distance from the proximal to the distal shoulder in the projection with the least degree of foreshortening. Acute gain was calculated as post-interventional MLD minus the pre-interventional MLD, late lumen loss (LLL) as MLD at follow-up minus post-interventional MLD, and late loss index as LLL expressed as a percent of acute gain. Binary restenosis (BR) (defined as $\%DS>50\%$) was determined for the follow-up angiography for all three subsegments. Geographical miss at baseline was assumed in case of intimal injury not

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