Late Acute Thrombotic Occlusion After Endovascular Brachytherapy and Stenting of Femoropopliteal Arteries

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OBJECTIVES

The aim of this article is to underline the importance of this complication after endovascular brachytherapy (EVBT) and intravascular stenting of the femoropopliteal arteries occurring in a running randomized trial.

BACKGROUND

Endovascular brachytherapy has been proposed as a promising treatment modality to reduce restenosis after angioplasty. However, the phenomenon of late acute thrombotic occlusion (LATO) in patients receiving EVBT after stenting is of major concern.

METHODS

In an ongoing prospective multicenter trial, patients were randomized to undergo EVBT (iridium 192; 14 Gy at a depth of the radius of the vessel +2 mm) after percutaneous recanalization of femoropopliteal obstructions. Of the 204 patients who completed the six months follow-up, 94 were randomized to EVBT.

RESULTS

Late acute thrombotic occlusion occurred exclusively in 6 of 22 patients (27%) receiving EVBT after intravascular stenting and always in concomitance with reduction of antithrombotic drug prevention (clopidogrel). Conversely, none of the 13 patients with stents and without EVBT (0%; p < 0.05) and none of the 72 patients (0%; p < 0.01) undergoing EVBT after simple balloon angioplasty presented LATO.

CONCLUSIONS

Late thrombotic occlusion occurs not only in patients undergoing EVBT after percutaneous coronary recanalization but also after stenting of the femoropopliteal arteries and may compromise the benefits of endovascular radiation. The fact that all our cases with LATO occurred concomitantly with stopping clopidogrel may indicate a possible rebound mechanism. An intensive and prolonged antithrombotic prevention is probably indicated in these patients. (J Am Coll Cardiol 2003;41:409–12) © 2003 by the American College of Cardiology Foundation

The phenomenon of restenosis after angioplasty was anticipated by Grünzig and Hopff (1) 30 years ago at the time they first applied balloon angioplasty for lower limb arteries. Further large clinical series after angioplasty of the lower limb arteries, and numerous reports during the last two decades involving patients undergoing percutaneous transluminal coronary angioplasty (PTCA), have confirmed the clinical and economical impact of restenosis. The magnitude of restenosis after PTCA and after angioplasty of the lower limb arteries varies according to the diagnostic methods used (clinical, quantitative angiography, intravascular ultrasound) and has been reported in a range between 15% and 50% (2–6). Through introduction of coronary stents, the incidence of restenosis after PTCA has only been moderately reduced to 20% to 30% (7). The use of intravascular stenting at the femoropopliteal level to prevent restenosis remains controversial (8–11).

In animal studies and in patients, one of the most promising modalities to reduce restenosis seems to be the application of endovascular brachytherapy (EVBT) (12,13). Although EVBT was also first applied after angioplasty of the lower limb arteries in the early 1990s (12), few prospective studies have been published on the efficacy of brachytherapy after angioplasty of the femoropopliteal arteries as a strategy to prevent restenosis. In a recently published randomized trial on EVBT after angioplasty of very long obstructions of the femoropopliteal arteries, the incidence of restenosis at six months follow-up could be significantly reduced from 53% to 28% in the group of patients receiving endovascular gamma-irradiation (14). The phenomenon of late acute thrombotic occlusion (LATO) has been reported in larger PTCA trials with an incidence of 6% to 9% (15,16), and in one single nonrandomized pilot study of patients undergoing EVBT after femoral stenting (17).

We decided to report on LATO in femoropopliteal arteries in relation to EVBT and stenting based on the results of the preliminary analysis of our ongoing, randomized, four-arm, multicenter trial, because of the high relevance of this phenomenon which may challenge the benefit of vascular radiation.

METHODS

The aim of our ongoing multicenter trial is to evaluate the effect of a combined prevention strategy (physical and
Abbreviations and Acronyms

EVBT = endovascular brachytherapy  
IL = interventional length  
LATO = late acute thrombotic occlusion  
PTCA = percutaneous transluminal coronary angioplasty

chemical on restenosis after percutaneous recanalization of the femoropopliteal arteries. The protocol includes a randomized, unblinded comparison of the efficacy of EVBT (iridium 192) performed immediately after angioplasty and a blinded comparison of a medical prevention using probucol randomized versus placebo (18).

All patients >50 years, with chronic claudication (Fontaine II A and B), and with arterial stenosis >50% or total occlusion at the femoropopliteal level, who are referred to our four vascular centers were eligible for the trial. Utilization of stenting during the angioplasty procedure because of unstable dissection or unsatisfactory results after balloon dilation is left to the discretion of the interventionist.

Following the initial notification of the Food and Drug Administration in 1998 of cases with LATO in patients undergoing intracoronary stenting and brachytherapy (19), our protocol mandates that patients receiving stenting and EVBT are treated with a double antiplatelet regimen (aspirin 100 mg and clopidogrel 75 mg/day) for an unlimited time after the procedure. The appropriate institutional review boards approved the protocol, and all patients gave written informed consent.

High-dose rate EVBT was performed using gamma-irradiation with a 192Ir-source. A 5F closed-tip, noncentered applicator catheter (Nucletron, Veenendaal, The Netherlands) was advanced through the 6F sheath and placed in the balloon-treated lesion so that the tip of the catheter reaches 1.5 cm distal to the distal end of the interventional length (IL). The active source length corresponded to the IL plus 1.5 cm on the distal and proximal end. The dose distribution was calculated by means of a computer-assisted planning system (Plato-BPS, version 13.2, Nucletron) with a 2.5-mm stepping source. The reference dose of 14 Gy was applied in a depth from the source given by the radius from the center of the dilated segment plus 2 mm. Marks on the dummy wire defined the IL and the length of the irradiated segment. After its appearance of claudication and was documented by angiography. The primary end point of the trial is to quantify the incidence of >50% restenosis at six months follow-up. Late acute thrombotic occlusion is defined as an acute occlusion of the dilated vascular segment occurring beyond the three months follow-up in a patient without any evidence of progression or restenosis at the preceding duplex scanning. Statistical comparison between the occurrence of LATO in the different subgroups was calculated by the Student t test.

RESULTS

A total of 204 patients have reached the predefined six months follow-up period and are available for an interim analysis of the unblinded part of the protocol (EVBT vs. no EVBT). Of the 204 patients, 94 underwent EVBT immediately after angioplasty. Of these 94 patients, 22 patients with EVBT needed stenting. The LATO of the dilated segment occurred in 6 of the 22 patients (27%). Conversely, none of the 13 patients (0%; p < 0.05) undergoing stents without EVBT presented LATO. Furthermore, none of the 72 patients (0%; p < 0.01) undergoing EVBT after only balloon angioplasty and none of the 97 patients (0%; p < 0.01) without EVBT presented LATO. Late acute thrombotic occlusion was not seen in any of the patients taking clopidogrel and undergoing EVBT after stenting.

Figure 1 shows the restenosis rate at six months and the corresponding proportion of LATO in the two groups of patients undergoing stenting with and without EVBT. The restenosis rate in patients undergoing stenting with and without EVBT was similar (41% and 43%, respectively). Late acute thrombotic occlusion occurred exclusively in patients receiving EVBT after stenting (Fig. 1, black area), with major impact on the rate of restenosis in this group of patients. If LATO could have been avoided in these patients with stent and with EVBT, given the absence of an underlying restenotic process after thrombus extraction and/or lysis, as indicated in the following text, the restenosis rate would have decreased from 40% to 12% (Fig. 1).

Late acute thrombotic occlusion occurred at 16, 17, 18, and 23 weeks after stenting and EVBT. In a further case, LATO occurred 68 weeks after percutaneous recanalization. All cases of acute occlusion occurred concomitantly with the reduction of the antithrombotic drug prevention, because of gastric side effects (three patients) or noncompliance (three patients). Clopidogrel was stopped between two and six weeks before the sudden occlusion of the stented segment. Late acute thrombotic occlusion was associated with reappearance of claudication and was documented by angiography and in one case by duplex ultrasound. Four patients underwent thrombolysis with urokinase infusion overnight; another patient was treated with thrombus extraction followed by glycoprotein IIb/IIIa infusion. All five patients

an Acuson Sequoia 256 (Mountain View, California) unit, and measuring the ratio between the peak systolic Doppler velocities of the dilated segment and at 1 to 2 cm proximal to the lesion.

Duplex scanning, a well validated method to measure significant vascular obstructions at the femoropopliteal level, is performed according to the criteria of Jäger et al. (20) by the same operator in each of the four vascular centers, using
had a final result of complete patency with no evidence of restenosis and no need of re-angioplasty. The sixth patient with minor symptoms was treated medically.

All six patients with LATO had three patent run-off vessels, compared with a mean value of two patent run-off vessels for the whole trial. The baseline severity and length of the obstruction varied between 75% and 100% and from 4.0 to 6.5 cm, respectively, and were comparable to that in the overall study population.

DISCUSSION

The preliminary analysis of our randomized, multicenter trial shows that the benefit of EVBT may be challenged by the occurrence of LATO, which in our series was observed exclusively in patients treated by stenting and EVBT. To our knowledge, this is the first report that demonstrates in a large randomized trial the impact of LATO on the long-term follow-up after EVBT in patients undergoing stents of the lower limb arteries.

There is limited experience with intravascular stenting after angioplasty of the femoropopliteal arteries, with controversial results (8–11), in contrast to the positive experience for coronary stenting, which moderately reduces the restenosis rate compared with simple balloon PTCA (7).

Endovascular brachytherapy may be a promising treatment modality to reduce restenosis after angioplasty, as recently reported in some randomized coronary trials (13) and in one randomized trial on peripheral percutaneous transluminal angioplasty (14).

An unusual rate of LATO after brachytherapy was first reported in 1998 in the interim analysis of the first trials of patients undergoing EVBT after intracoronary stenting (15,16), and was recently reported in a pilot study at the femoropopliteal level (17). The pathogenesis of LATO after stenting and EVBT is probably related to the same mechanism of action intended to reduce restenosis (i.e., reduction of neointimal proliferation). The same mechanism prevents endothelial regeneration to cover the stent struts, which usually occurs within two to three weeks after stenting without irradiation. The fact that five of our patients with a LATO could be treated by either thrombolysis or thrombus aspiration confirms the hypothesis that these occlusions may be attributed to thrombosis. This hypothesis is supported by the fact that all these patients with LATO presented normal patent run-off vessels.

To avoid this vascular complication after brachytherapy, the interventionist may limit the application of EVBT to nonstented arteries. Alternatively, a more intensive and prolonged antithrombotic prevention should be prescribed, as recently proposed for coronary revascularization (16–22). In fact, if LATO could have been avoided in our group of patients undergoing brachytherapy after stenting, the restenosis rate would have fell from 40% to 12% (Fig. 1). Because stenting was usually used in patients with suboptimal results after balloon angioplasty, we cannot exclude that these patients were prone to LATO due to the complication of the intervention. This consideration may be applicable also to the unusually high rate of restenosis found in the subgroup of patients with intravascular stenting without EVBT.

All our cases of LATO occurred concomitantly with a reduction of the antithrombotic drug prevention and may indicate that platelet recruitment and thrombus formation which occur in non-re-endothelialized irradiated stents are not prevented sufficiently (23). Our finding of a case with acute occlusion immediately after stopping clopidogrel 68 weeks after intravascular stenting and EVBT leaves open the question of the necessity of a double antithrombotic prevention beyond the six-month threshold after EVBT (22). Further randomized studies are needed to clarify this problem. Patient compliance and side effects of this long-term secondary prevention may be limiting factors, as observed in our cases.

Our findings of a high incidence of LATO after stent and
EVBT may have clinically relevant implications; therefore, interventionists should be aware of this important complication which occurs also in the peripheral circulation, especially when a long-term double antiplatelet prevention with aspirin and clopidogrel is not assured.

The crucial answer to the question whether our combined physical and chemical prevention strategy will have a relevant impact on restenosis will be available only at the time of complete inclusion and follow-up of our randomized trial.

Acknowledgments
We thank Dr. Vitali Verin for the review of the manuscript and Dr. L. Cozzi for the statistical analysis.

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APPENDIX

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