Endovascular Irradiation in the Therapy of Intimal Hyperplasia

Dieter Liermann, MD, Bernhard Schopohl, MD, Günther Herrmann, MD

Our treatment for the revision of stenoses in stented vascular segments causes injuries to the vascular wall, almost always resulting in intimal hyperplasia, even after stents.1-22 A possible alternative is to combine the methods available for treating intimal hyperplasia. The results obtained in treating keloids by means of irradiation therapy23-34 was the basis for our therapeutic concept for the prophylactic irradiation of hyperproliferative vascular wall reactions. The development of small-caliber probes for afterloading therapy in the biliary tract35 allowed us to use these for therapy in the vascular system. Together with H.D. Böttcher, our considerations were converted into a clinical trial. Before proceeding further, all risks and problems, together with ethical reservations in the context of using afterloading methods for treating arterial occlusive disease in the peripheral vascular system, were discussed in detail when planning the procedure.

MATERIALS AND METHODS

On conclusion of recanalization and PTA of the restenosed, stented vascular segment, a 9 French (F) recanalization catheter was inserted through the positioned 9F sheath via a guidewire, and positioned so that its tip was just below the affected vascular segment. The inner diameter of this catheter permitted insertion of a special catheter having a diameter of 5F. The pointed tip of the catheter means that the measuring rod and special catheter can only be pushed forwards to just before the tip of the recanalization catheter without being able to pass through a catheter opening. This particular feature allowed for exact measurement and calculation of the length of the stented vascular segment and of the insertion length of the afterloading probe under stable, reproducible conditions. The entire treatment was carried out under heparin therapy (100 IU/kg body weight). After stipulation of the distal point of the catheter, the sheath and recanalization catheter were fixed onto the skin to avoid any displacement. The measuring rod whose distal segment marks the lower end of the irradiation field and protrudes 1 cm distally beyond the actual irradiation field, was then exchanged with the 5F special catheter. This catheter was inserted through the 9F catheter as far as possible with its independently-sealed tip, and was again firmly fixed. It later accommodated the iridium probe with its 1.1 mm diameter. This was inserted during the afterloading procedure, after the proximal end of the special catheter had been connected to the outlet valve of the iridium 192 HDR source. We used a Nucletron (Micro) Selectron HDR plan-
nning system version 10.10 for exact calculation, monitoring, and control of the afterloading procedure. Our source was iridium 192 with a strength of 10 Ci. The reference dose was 1200 cGy. After calculation of the exact irradiation dose for the afterloading method, the program controls and monitors the insertion and removal of the iridium probe from the source into the special catheter through to the tip, monitors the irradiation duration. The exposure time depends on the condition of the source and was around 200 sec. During this time, a surface dose of 12 Gy was applied to the vascular wall in one session in the affected region. Subsequently, the catheter material was removed and pressure carefully applied by hand to the puncture point for 10 to 20 minutes. An elastic pressure bandage was then applied for 24 hours and the patient was treated for 72 hours with a dose of heparin 1000 IU/hour via a perfusor. A 6–month course of Marcumar therapy was then initiated.

Follow up. Follow–up examinations were carried out at precisely–defined intervals, consisted of routine ankle–arm indices (AAI) before and during the intervention, after 3 and 6 months, and later at 6 month intervals, together with a study of the case history and examination of the patient. Additionally, magnetic resonance imaging (MRI) examinations were carried out before and after treatment and at 6 month intervals. The examinations were performed in a FLASH gradient, spin echo sequence with a flip angle of 30°, in vertical and coronary sections [1.0 Tesla unit in a cervical coil (300)]. An intravenous digital subtraction angiography (DSA) was also carried out after 6 months or upon MRI evidence of stenotic lesions. The clinical parameters were stipulated according to the Fontaine classification.

Indications. Indications for endovascular after–loading therapy were restricted to clinically–relevant stenoses or recurrent occlusions in the stented vascular segment occurring within less than 8 months after preceding, repeated PTA treatment. All patients must have had a long history of arterial occlusive disease, with recurrent vascular occlusions following PTA treatment in a vascular segment of the superficial femoral artery prior to stent implantation. In the event of restenosis or occlusion in the stented vascular segment, at least one successful treatment of the recurrence must have been carried out by conventional PTA or by using the Nd:YAG laser with matted sapphire tip. Prior to repetition of the PTA in the stented segment with subsequent irradiation therapy, an angiogram control must have been performed, together with diagnostic atherectomy by means of the Simpson catheter to obtain histological material. In order to minimize the somatic tumor risk as a consequence of the radiation therapy, only elder patients were admitted for such treatment. Contraindications to heparin and Marcumar therapy were not to be present following stent implantation and irradiation therapy.

Patient Data. To date a total of 30 patients (10 women, 20 men) have been treated with endovascular afterloading. All patients suffered from clinically–relevant reocclusion or restenosis in stented vascular segments of the superficial femoral artery following successful laser or PTA treatment, within 6 to 8 months after the last therapy. The patients were aged from 54 to 84 years (mean, 68.4 years). All patients had generalized arterial occlusive disease. Fifteen patients had concurrent diabetes mellitus, 21 had high blood pressure, and 22 abused nicotine over a period of more than 20 years. According to the Fontaine classification, before the repeated PTA treatment (28 cases) or laser therapy (two cases), 10 of the patients were in clinical stage IIb and 20 patients were in stage III. The histological analysis indicated intimal hyperplasia as the cause for restenosis in all 30 patients. The case histories for all patients revealed several PTAs as a treatment for reocclusion in the superficial femoral artery prior to implantation of one or more stents. The length of stented vascular segments ranged from 4.5 to 14 cm (mean, 6.7 cm), with the stent diameter ranging from 6 to 7 mm.

RESULTS

In all 30 patients it was possible to perform re–PTA treatment without remaining residual stenosis in the stented region. Subsequent irradiation therapy with the 192 iridium HDR afterloading method was successfully performed. In all cases, the dose was 12 Gy in the plane of the vascular wall; the exposure time was approximately 200 sec. The additional time required in comparison to a sole PTA procedure was approximately 45 minutes, with most of this time consisting of transport between the treatment room and afterloading room. After conclusion of the treatment, there was no bleeding from the puncture sites. The follow–up period for the 30 patients ranged from 4 to 68 months. According to the Fontaine classification, it was
possible to improve the clinical stage for 11 patients from stage IIb to stage I, and for 12 patients from stage III to stage I. It was only possible to improve two patients from stage II to stage IIa, and 4 patients from stage III to stage IIa. In these cases, contralateral occlusion was present as a limiting factor. In a fourth case, it had been possible to improve the clinical stage from III to IIa, but after approximately 2 years this patient suffered from an occlusion which became manifest in the exit region of the superior femoral artery, resulting in a bypass.

During the follow-up examinations, there was no deterioration of the clinical stage and no recurrent stenosis for 22 patients. One patient suffered from an acute thrombosis approximately 3 months after stent implantation, without a cause being found. Histological examination using the atherectomy catheter revealed fresh thrombotic material, as expected. Following local lysis therapy, the thrombosis was entirely eliminated. We suspect that was due to an underdose of Marcumar in an otherwise physically active patient. One other patient had a stenosis 3 cm above the stented vascular segment 12 months after irradiation treatment. During treatment to eliminate the severe stenosis, angioscopic and angiogram controls revealed no evidence of constrictions or intimal hyperplasia in the stented and irradiated region. The restenosis above the stent was successfully eliminated. In a third case, approximately 10 months after the combined therapy, restenosis occurred in a vascular segment approximately 8 cm long which had not been included in the irradiation treatment. It occurred between two treated sections in the superficial femoral artery, and was successfully removed by PTA treatment. In this case also, there was no intimal restenosis in the vascular segment previously treated by stent implantation, PTA, and irradiation. In three cases we had a reocclusion. Follow-up examinations have revealed no evidence of nerve lesions following irradiation therapy. The tissue surrounding the artery showed no recordable change following irradiation therapy, either in the CT, color-coded Doppler, endovascular ultrasonic scan, or MRI. No complaints of discomfort were reported during or after irradiation. With the exception of the changes described above, and the one acute thrombosis likely caused by an underdose of Marcumar, there was no evidence of any complications.
exception of the somatic risk during irradiation therapy described above, we saw no other relevant short or long-term complications. Potential short-term effects possibly include an increased thrombosis risk following an edema or inflammatory reaction to irradiation, although such effects were not detected.\textsuperscript{38, 39} Cicatization with corresponding lumen constriction of the iliac artery is a feared long-term effect of high-dose radiation therapy.\textsuperscript{40-44} Various analyses about the effect of irradiation show that cicatization in the vascular system only occurs following high doses with complete tissue necrosis. Cicatization is not anticipated following endovascular application of low doses of 12 Gy. The dose we have used in our therapy only causes a significant reduction of mitosis in the most exposed cells with only isolated cell necrosis.\textsuperscript{39, 43, 45-53} This effect, combined with reduction in myofibroblast migration velocity, is possibly responsible for the lack of restenosis in our patient population.\textsuperscript{54} It should be noted that recurrences have also been observed in our patients. Zeitler and colleagues, who also use our procedure, have indicated a higher recurrence rate than our group using a single dose of 10 Gy applied to vascular wall. Our application of 12 Gy also gives rise to doubts whether the dose is always homogeneously distributed in the vascular wall, achieving the same antiproliferative effect all over, or whether certain adjacent areas may be differentially exposed resulting from the decentral position of the probe. In order to minimize this effect, I have developed a catheter which can accommodate the probe system with an inner lumen of just 6 Fr, but which has an outer diameter of approximately 8 Fr with balloons for centering the catheter in the lumen during dose application. Preliminary experimental tests have already been successfully completed here. In comparison to alternative methods for the treatment of intimal hyperplasia, endovascular afterloading irradiation is the only method which is used locally in the stented region with success under clinical conditions. Some models use heparin, Marcumar, aspirin, low-molecular weight heparin, corticoids, or other substances to influence intimal hyperplasia, but therapeutically effective doses all have systematic side effects.\textsuperscript{55-70} Knowledge about the mediators responsible for prolifer growth after any kind of damage to the vascular wall led to the development of substances aimed at interrupting or reducing this process. Unfortunately, such processes are always only aimed at one or two growth factors, while leaving others largely unaffected.\textsuperscript{19, 56, 59, 69, 71, 72}

Another model favors the genetic influence on the vascular wall.\textsuperscript{73-76} A few animal experiments have been carried out with rather discouraging results following implantation of so-called “coated stents”. Hyperproliferation has been observed at the transition zones between stent end and vascular wall.\textsuperscript{77, 78} Finally there are a few initial models in which the stent is prepared with heparin or other chemotherapeutic substances to reduce intimal hyperproliferation following implantation.\textsuperscript{56, 79} And finally it is worth mentioning the development of so-called biocompatible stents which have been tested in animal experiments.\textsuperscript{79, 80} Most of these models are still only in the experimental stage, so that it is necessary to wait for further developments.

REFERENCES

Endovascular Irradiation in the Therapy of Intimal Hyperplasia


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