In-Stent Restenosis: Mid-Term Results of Debunking Using Excimer Laser and Drug-Eluting Balloons: Sustained Benefit?

Jos C. van den Berg, MD, PhD1; Milko Pedrotti, MD2; Reto Canevascini, MD2; Sonia Chimchila Chevili, MD2; Luca Giovannacci, MD3; Raffaele Rosso, MD3

ABSTRACT: Background. In-stent restenosis (ISR) after endovascular treatment of stenotic and occlusive disease of the infrapopliteal arteries is still a clinical challenge. The purpose of this study is to evaluate the mid-term follow-up of a combination therapy using laser debunking and drug-eluting balloons for ISR.

Methods. A prospective cohort of 14 patients (10 female, 4 male) with clinically relevant (Rutherford 3-6) ISR who were treated with excimer-laser angioplasty and drug-eluting balloons and a clinical follow-up of at least 9 months was evaluated. Results. Mean age was 78 ± 6.5 years (range, 67-88 years). The mean lesion length treated was 133.2 ± 107.2 mm (range, 10-380 mm). The mean time to occurrence of restenosis after initial treatment was 8.6 ± 4.7 months (range, 2-18 months). Technical success was 100%. Distal embolization occurred in 2 cases, and was treated successfully by endovascular means. No other perioperative major adverse events occurred. All patients were available for clinical follow-up and 12 patients were available with Duplex follow-up. At a mean clinical follow-up of 19.1 ± 8.7 months (range, 9-38 months), 1 target lesion revascularization was seen (at 3 years after the ISR treatment). In the patients with critical limb ischemia (n = 7), no major amputations were needed. Twelve patients had Duplex control (mean follow-up, 19.4 ± 9.4 months; range, 9-38 months). Binary restenosis (>50%) was seen in 1 case at 36 months; it was the same patient who had TLR. A 25%-50% stenosis was seen in 4 patients (mean follow-up, 25 months; range, 19-38 months). No sign of neointimal hyperplasia was demonstrated in 7 patients (mean follow-up, 14.3 months; range, 9-19 months). Conclusion. These mid- to long-term data compare favorably with results obtained with standard balloon angioplasty, cutting-balloon angioplasty, and balloon angioplasty using drug-eluting balloon. Longer follow-up and randomized trials are necessary to further define the role of combined excimer-laser debunking and drug-eluting balloon angioplasty in the treatment of ISR.

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Over the last few years, new techniques and technologies have been developed for the endovascular treatment of arterial occlusive disease affecting the superficial femoral artery (SFA) and infrapopliteal arteries. The favorable outcome of several randomized clinical trials has led to an increased use of self-expandable nitinol stents in the lower limb. Restenosis, and more specifically in-stent restenosis (ISR), remains a problem that significantly affects mid- and long-term outcomes of SFA stenting, with restenosis rates that are approximately 20% and 40% at 1-year and 2-year follow-up, respectively.2,3 The rate of recurrent stenosis in below-the-knee lesions after percutaneous transluminal angioplasty (PTA) and stenting is even higher than after femoropopliteal procedures.4 The results of plain balloon angioplasty in the treatment of ISR of self-expandable stents in the SFA are disappointing, with 6-month restenosis rates that can be as high as 60%-70%.3,6

With the development of drug-eluting balloon (DEB) technology, a potential novel treatment modality for ISR has become available (with or without debunking). This study offers the mid- to long-term results of the application of a combination therapy using laser debunking and DEBs.

Methods
From March 2010 to June 2012, a consecutive cohort of 14 patients (all-comers) with symptomatic ISR in the infrapopliteal arterial segment was treated with excimer laser atherectomy (Turbo Elite Spectranetics) followed by angioplasty using DEBs (InPact Admiral and InPact Amphirion; Medtronic InVatec). The study was carried out according to the Declaration of Helsinki. All patients gave informed consent prior to inclusion into this observational study. Medical history and comorbidities were recorded. The Rutherford classification was used to describe patient’s clinical statuses. An ipsilateral antegrade approach was used in all patients. After obtaining arterial access, a 4 Fr introducer sheath was placed, and a diagnostic angiography of the entire affected limb was obtained. Stenosis grade and lesion length were determined angiographically. In-stent restenosis was classified by visual estimate as described by T osaka et al:7 class I (focal lesion, ≤50 mm), class II (diffuse lesion, >50 mm in length) or class III (chronic total occlusion of the stent). Both status of the distal run-off vessels and presence of stent fractures were evaluated.
All patients were treated using a standard technique by a single operator. After successful crossing of the lesion with a hydrophilic guidewire, a diagnostic catheter was advanced and contrast was injected distally from the lesion to confirm a proper intraluminal position. In cases of total occlusion, the lesion was crossed with the guidewire “looped” in order to avoid exiting of the wire through the stent struts. The 4 Fr introducer sheath was subsequently exchanged for a 5 Fr or 6 Fr sheath, while maintaining the guidewire in a position with its tip distal to the lesion. Then, the hydrophilic guidewire was exchanged for a 0.014” or 0.018” guidewire. An excimer-laser catheter (diameter range, 1.4-2.0 mm) was subsequently introduced while applying continuous saline flush on both the introducer sheath and through the laser catheter. No distal embolic protection devices were used. The laser catheter was slowly advanced through the lesion under fluoroscopic control (speed <1 mm/s), with the maximum fluence and pulse repetition rate settings (as set by the manufacturer). After removal of the laser catheter, balloon angioplasty (predilation) of the treated segment was performed using standard angioplasty balloons with a diameter 1 mm less than the reference vessel diameter. Control angiography after laser debulking was not routinely performed. This was followed by angioplasty (postdilation) using DEBs with a diameter equal to the reference vessel diameter. Technical success was defined as <30% stenosis at the end of the procedure.

Follow-up was performed with clinical and Duplex examination at regular intervals according to the referring physician’s (angiologist) preference.

At Duplex, the patients were evaluated for the presence of binary restenosis (presence of >50% stenosis at the treatment site; peak systolic velocity ratio >2.4). Target lesion revascularization was defined as any repeat intervention (endovascular or surgical) of the treated lesion. Major amputation was defined as any amputation above the level of the ankle joint.

Results

The mean age of the patients was 78 ± 6.5 years (range, 67-88 years). The majority of patients was female (n = 10; male n = 4). All patients had previously undergone balloon angioplasty and stent placement, with a mean time to recurrence of restenosis of 8.6 ± 4.7 months (range, 2-18 months). Clinical status by Rutherford classification was grade 3 (n = 7), grade 4 (n = 4), grade 5 (n = 2), or grade 6 (n = 1). Dyslipidemia was present in 10/14 patients (71%), 11/14 patients suffered from hypertension (78.6%), 4/14 patients had renal failure (28.6%), and 5/14 patients were diabetic (35.7%). The arterial segments involved were the SFA (n = 5), SFA and popliteal artery (n = 5), popliteal artery (n = 2), SFA/popliteal and crural artery (n = 1), and popliteal and crural artery (n = 1). Eleven of 14 patients (78.6%) presented with a high-grade stenosis (80%, 90%, and 90%, respectively; as measured angiographically, all Tosaka class III; mean lesion length, 161.8 mm), while the remaining 3 presented with a high-grade stenosis (80%, 90%, and 90%, respectively; as measured angiographically, all Tosaka class I, mean lesion length, 28.3 mm). No stent fractures were seen. Mean lesion length of all lesions treated was 133.2 ± 107.2 mm (range, 10-380 mm), mean stent length was 141.1 ± 101 mm (range, 40-380 mm), and mean target vessel diameter was 4.5 mm (range, 3-5 mm). The mean number of run-off vessels was 1.7 per patient. Six patients had a one-vessel run-off, 6 patients had a two-vessel run-off, and 2 patients had a three-vessel run-off.

The following laser catheters were used: 1.4 mm (n = 1), 1.7 mm (n = 4), and 2 mm (n = 9). No Turbo Booster or Turbo Tandem catheters were used. An average of 1.8 DEBs per patient was used: 1 balloon per patient (n = 7); 2 balloons per patient (n = 4); 3 balloons per patient (n = 2); and
5 balloons per patient (n = 1). Hemostasis was obtained in all cases by manual compression.

All procedures were technically successful. No residual stenosis was seen angiographically. There were 2 cases of distal embolization (both in patients with anamnestic acute-on-chronic occlusions). Both could be treated successfully with aspiration embolectomy (n = 2) and local (on-the-table) intra-arterial thrombolysis using a bolus of urokinase of 250,000 U (n = 1). No access-site related complications were seen. The third patient was lost to follow-up (reason unknown) had Duplex follow-up. Mean clinical follow-up was 19.1 ± 8.7 months (range, 9-38 months). Mean Duplex follow-up was 19.4 ± 9.4 months (range, 9-38 months) and 1 of these patients also had an angiographic control (during angioplasty of an ipsilateral superficial femoral artery stenosis; Figure 1). One patient had a binary restenosis and underwent target lesion revascularization (36 months after the laser and DEB procedure). A 25%-50% stenosis was seen in 4 patients (mean follow-up, 25 months; range, 19-38 months). In 7 patients, no signs of neointimal hyperplasia were demonstrated (mean follow-up, 14.3 months; range, 9-19 months). This corresponds to a primary patency rate of 91.7% (11/12) at the mean follow-up (1-year primary patency of 100%). The clinical stage during follow-up improved in all patients (Figure 2; Rutherford 1, n = 15; Rutherford 5, n = 1 (mixed arterial-venous ulcer with untreated crural stenosis and good healing tendency). One patient underwent a (preplanned) amputation of a toe shortly after the revascularization procedure. No major amputations occurred.

Discussion

In-stent restenosis after endovascular procedures is still a major problem in all vascular territories in the long-term follow-up, but especially in the SFA and below-the-knee arteries. Given the increasing number of stents being used in the SFA and popliteal segments, and to a lesser extent in the tibial arteries, the number of patients presenting with ISR will increase. In the future, stenting will still be needed even when the use of DEB technology becomes more accepted. At this moment, the prevention of ISR is still a utopian ideal.

Percutaneous transluminal angioplasty alone in cases of ISR or occlusion of self-expandable stents in the SFA does not work. This can be explained by two factors. First, self-expanding stents reach their nominal size quickly after implantation, not allowing further luminal gain by further expansion of the stent, as is the case in balloon-expandable stents. The second contributing factor is the sponge-like behavior of neointimal hyperplasia. Two mechanisms contribute to the formation of in-stent intimal lesions after stent implantation: smooth muscle cell replication and accumulation of extracellular matrix. The extracellular matrix is composed of various collagen subtypes and proteoglycans and over time constitutes the major component of the mature restenotic plaque, accounting for over 50% of the neointimal volume. The extracellular matrix is not susceptible to angioplasty and therefore debulking of the high lesion burden is essential. Relatively little is published on the outcome of balloon angioplasty as stand-alone treatment for ISR. Early
studies indicate a 12-month patency in recurrent lesions of 33% using balloon angioplasty. In a randomized study that compared conventional balloon angioplasty with peripheral cutting-balloon angioplasty in patients with ISR with lesion lengths up to 20 cm (mean lesion length, 80 mm), it was found that restenosis rates at 6 months were 65% after cutting-balloon angioplasty and even worse within conventional PTA (73% restenosis). No statistically significant difference between the two techniques was seen, and the overall patency for both treatment modalities was disappointing.

More recent data (that use the same classification of ISR as this paper) similarly demonstrate poor outcomes of plain balloon angioplasty: at 1-year follow-up, ISR was 27.5% in class I, 34.4% in class II, and 77.3% in class III. Patency rates further reduced at 2-year follow-up: 50.1% in class I, 46.7% in class II, and 15.2% in class III. Likewise, another recently published study (that also included several patients treated with a variety of debulking techniques) showed that repeat restenosis and occlusion remain common: repeat stenosis occurred after 2 years in 39% for class I, 67% for class II, and 72% for class III, while stent occlusion rates were 8%, 11%, and 52% for class I, class II, and class III, respectively.

Our results, which had a slightly shorter follow-up but a similar lesion length, compare favorably to the outcomes data from Armstrong et al12 (28.3 mm for class I and 161.8 mm for class III vs 32 mm and 26 mm for class I and 178 mm and 197 mm for class III, respectively).

The results of DEB angioplasty in de novo lesions appear to be very promising: both the FemPac pilot trial and the THUNDER trial demonstrated a reduction of angiographic late lumen loss, a lower incidence of restenosis at 6 months, and a significant reduction in target lesion revascularization at 6, 12, and 24 months. It can therefore be hypothesized that the use of DEBs as stand-alone treatment can be beneficial in the treatment of ISR. Results of two studies in patients with coronary ISR have demonstrated the efficacy of a balloon that is coated with a paclitaxel-ipromide mixture. The process of ISR (contrary to primary lesions) in coronary and peripheral muscular arteries is considered to be similar, and therefore results can probably be extrapolated. Two-year follow-up data of a randomized trial comparing uncoated balloons with paclitaxel-coated balloons in patients with coronary ISR demonstrated a statistically significant reduction of target lesion revascularization. In this study, in-segment late lumen loss after 6 months was 0.81 ± 0.79 mm in the uncoated balloon group vs 0.11 ± 0.45 mm (P < .001) in the drug-coated balloon group. This resulted in a binary restenosis rate of 25/49 (uncoated) vs 3/47 (coated; P < .001). At 12 months post procedure, 20 patients in the uncoated balloon group vs 2 patients in the coated balloon group required target lesion revascularization (P = .001). The Journal of Invasive Cardiology

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One study evaluated the use of DEBs for the treatment of SFA-ISR and demonstrated a 92.1% primary patency rate at 1-year follow-up in a patient cohort with a mean lesion length of 82.9 ± 78.9 mm. In this study, the number of class III lesions was 20.5%, which is low compared to the 78.6% in our series. In this study, laser debulking was also used (in 4/34 patients), but it is not specified which lesion types underwent laser debulking. Therefore, as stated by the authors, “the use of laser in a few cases complicates the analysis.”

Our data show lower restenosis rates when using a combination therapy of laser debulking and DEB as compared to the treatment of coronary and SFA-ISR with DEB angioplasty as a stand-alone treatment (at 6 months and 12 months, respectively). This can probably be attributed to the additional use of debulking. It is likely unnecessary to achieve a complete debulking prior to application of DEBs (in our series, no Turbo Tandem catheters, which are designed for large-vessel debulking, were used). The fact that good patency can still be achieved without maximal debulking is probably related to the cytotoxic effect of paclitaxel, which leads to apoptosis. This so-called positive remodeling effect has already been demonstrated in the treatment of primary SFA lesions with DEBs: in one study, a mean late lumen loss of -0.01 mm (indicating slight enlargement of the lumen) was seen at 6-month angiography (as compared to +0.65 mm late lumen loss in the uncoated balloon group).

Our results show that the formation of neointimal hyperplasia is not completely abolished, but its occurrence is significantly postponed.

Our results remain satisfactory even when not considering the patients lost to follow-up; excluding these patients would lead to a cohort of 11 patients with 1 TLR/binary restenosis, and thus a TLR rate of 9.9% and a primary patency rate of 90.1% at a mean follow-up of 20 ± 9.6 months (range, 10-38 months).

As in the study by Armstrong et al, distal embolization occurred using laser atherectomy (almost 15% of the cohort in our study) that could be attributed in both cases to the presence of an acute-on-chronic stent occlusion, and could be treated successfully with thrombolysis and/or thromboaspiration. This emphasizes the importance of carefully reviewing the clinical history, and pretreating with local thrombolytic therapy if there is suspicion of fresh thrombus.

No further distal embolization was seen in subsequent cases in this cohort. Any acute-on-chronic occlusions in subsequent patients were pretreated with local thrombolysis. All
cases performed subsequently (even in the absence of acute-on-chronic occlusion) were also treated using a modified laser technique that involved a first passage at low-energy settings (which reduces the size of the “vapor bubble,” but is efficient for ablating areas of less organized thrombus and thus decreasing the embolic risk) and a second passage at higher-energy settings (which is more effective at removing neointimal hyperplasia and extracellular matrix). Several factors are correlated with a higher incidence of restenosis after endovascular procedures of the SFA, and include female gender, small target vessel diameter, long lesion length, and poor distal run-off.20-23 These factors were also present in the patients in this cohort (strong female preponderance with corresponding small-diameter arteries and poor distal outflow), and explain the short time to recurrence of stenosis. All studies mentioned above had a better distal outflow score, absence of female preponderance, and larger mean target vessel diameter. The presence of restenosis in an early stage (mean time to recurrence, 8.6 months) and multiple factors that negatively influence the occurrence of restenosis, as well as the high number of class III lesions, underline the fact that this cohort represents a group of patients that tend to do worse with any kind of therapy. Therefore, the results are very promising, although the number of patients treated is limited, and the study is non-randomized (lacking a control group) and observational. No direct comparison with previous experience using laser debulking combined with standard balloon angioplasty from our center is available. Therefore, the results of this study should be considered a proof of concept, and generate a hypothesis that needs to be evaluated in larger randomized trials. In the treatment of ISR, debulking is probably key, as is indicated in this small case series and in a recently published paper that used a similar approach (directional atherectomy and DEB) in the treatment of restenotic femoropopliteal arteries. The latter study included both native restenotic vessels and ISR and is thus not completely comparable to our study population, but demonstrated a clear benefit of adding drug-eluting therapy to debulking (estimated freedom from restenosis was 43.8% in the angioplasty group and 84.7% in the patients treated with additional drug-eluting therapy).11

Conclusion

In our series of 14 patients with ISR, the mid- to long-term data are very promising and compare favorably to results described in the literature that were obtained with standard balloon angioplasty, cutting-balloon angioplasty, or DEB angioplasty. Long-term follow-up and randomized studies are warranted to further define the role of combined excimer laser and DEB angioplasty in the treatment of ISR.

References