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Original Article / *Özgün Makale*

Drug-eluting balloon treatment in femoropopliteal in-stent restenosis of different lengths

Farklı uzunluklardaki femoropopliteal stent içi restenozun ilaç salgılayan balon ile tedavisi

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ABSTRACT

Background: In this study, we present one-year results of drug-eluting balloon treatment of femoropopliteal in-stent restenosis.

Methods: A total of 62 patients (48 males, 14 females; mean age 64.2±9.1 years; range, 54 to 81 years) who underwent drug-eluting balloon stenting for femoropopliteal in-stent restenosis between August 2013 and October 2017 were included in the study. The patients were classified into three groups based on the narrowing length of stenosis in the stents. Group/Class 1 (n=17): narrowing <1/2 of the stent length; Group/Class 2 (n=22): narrowing >1/2 of the stent length, not totally occluded; and Group/Class 3 (n=23): totally occluded. In-stent restenosis was treated with drug-eluting balloon treatment.

Results: There was a significant difference among all classes in terms of in-stent restenosis. The length of stenosis was a predictor for in-stent restenosis. The mean stent length was 107.7±24.6 mm in Group 1, 164.6±17.9 mm in Group 2, and 180±19.3 mm in Group 3. For non-occluded in-stent restenosis, restenosis rate at one year after balloon angioplasty was 47.1% in Group 1, 86.4% in Group 2, and 95.7% in Group 3. Femoropopliteal bypass was performed in five patients in whom treatment failed. None of the patients required amputation.

Conclusion: The length of in-stent restenosis in the femoropopliteal arterial stents is an important predictor for recurrent stenosis, when re-flow is achieved with drug-eluting balloons.

Keywords: Drug eluting balloon, in-stent restenosis, peripheral arterial disease.

ÖZ

Amaç: Bu çalışmada femoropopliteal stent içi restenozun ilaç salgılayan balon ile tedavisinin bir yıllık sonuçları sunuldu.

Çalışma planı: Ağustos 2013 - Ekim 2017 tarihleri arasında femoropopliteal stent içi restenoz nedeniyle ilaç salgılayan stentleme yapılan toplam 62 hasta (48 erkek, 14 kadın; ort. yaş 64.2±9.1 yıl; dağılım, 54-81 yıl) çalışmaya alındı. Hastalar stentlerdeki darlığın daralma uzunluğuna göre üç gruba ayrıldı. Grup 1/Sınıf 1 (n=17): stent uzunluğunda <1/2 oranında daralma; Grup 2/Sınıf 2 (n=22): stent uzunluğunda >1/2 oranında daralma, total oklüzyon yok ve Grup 3/Sınıf 3 (n=23): total oklüzyon. Stent içi restenoz, ilaç salgılayan balon tedavisi ile tedavi edildi.

Bulgular: Stent içi restenoz açısından tüm sınıflar arasında anlamlı bir fark vardı. Stenozun uzunluğu stent içi restenozun bir öngördürücüsü idi. Ortalama stent uzunluğu Grup 1'de 107.7±24.6 mm, Grup 2'de 164.6±17.9 mm ve Grup 3'te 180±19.3 mm idi. Tıkanık olmayan stent içi restenoz için balon anjiyoplasti sonrası birinci yılda restenoz oranı Grup 1'de %47.1, Grup 2'de %86.4 ve Grup 3'te %95.7 idi. Tedavinin başarısız olduğu beş femoropopliteal baypas yapıldı. Hiçbir hastaya amputasyon gerekmedi.

Sonuç: Femoropopliteal arteriyel stentlerdeki stent içi restenoz uzunluğu, ilaç salgılayan balon ile yeniden akış sağlandığında, tekrarlayan stenozun önemli bir öngördürücüsüdür.

Anahtar sözcükler: İlaç salınımlı balon, stent içi restenoz, periferik arter hastalığı.

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Femoropopliteal (FP) arterial segment is the most commonly endovascular-treated segment.[1,2] For arterial occlusive disease in FP segment, self-expandable bare metal stents have become standard instruments.[3-5] Despite advances in stent technology, in-stent restenosis (ISR) remains to be a common clinical issue. Following angioplasty and stent placement, the native vasculature reacts with an inflammatory response which precipitates neointimal hyperplasia and tissue ingrowth leading to ISR.[6,7] Previously, it has been documented that the use of drug-eluting balloons (DEBs) for ISR of superficial femoral arteries (SFAs) yields promising results.[8,9] Based on this rationale, we treat FP segment ISR with DEB in our daily practice.

In this study, we present our one-year results of DEB for the treatment of FP arterial segment ISR in patients with peripheral arterial disease.

PATIENTS AND METHODS

In this two-center study, 62 patients (48 males, 14 females; mean age 64.2±9.1 years; range, 54 to 81 years) who underwent DEB stenting for FP arterial segment ISR were included between August 2013 and October 2017. Patients with confirmed iliac artery stenosis or infra-popliteal lesions by diagnostic angiography were excluded. In all patients, the Supera™ (Abbott Vascular Inc., CA, USA) self-expandable stents were implanted previously. For ISR, DEBs were used (Legflow® Paclitaxel-Eluting Balloon, Cardionovum Sp.z.o.o, Warsaw, Poland). A written informed consent was obtained from each patient. The study protocol was approved by the Pamukkale University, Faculty of Medicine Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Interventions

The patients who were not using acetylsalicylic acid and/or clopidogrel prior to study enrollment received loading doses of acetylsalicylic acid (300 mg, p.o.) and clopidogrel (300 mg p.o.) 12 hours before the procedure. To define the anatomy, diagnostic arteriography was performed routinely before the intervention. Restenosis was defined as ≥50% stenosis as assessed by angiography. An undetectable signal in stented segments by the Duplex scan was accepted as a complete occlusion. In terms of ISR, the patients were divided into three groups based on the ISR classification by Tosaka et al.[10] as follows: *(i)* Group/Class 1 (n=17): narrowing <1/2 of the stent length; *(ii)* Group/Class 2 (n=22): narrowing >1/2 of the stent length, not totally occluded; *(iii)* Group/Class 3 (n=23): totally occluded. Based on angiographic results, most suitable location for the intervention was planned.

An antegrade or retrograde access site was selected to guarantee the best accessibility of the lesion, and each approach employed various sizes of introducer sheaths ranging from 5 to 7 F (Pinnacle®; Terumo Medical Corp., NJ, USA). The patients received 5,000 IU heparin bolus after the introducer sheath insertion. The lesion was crossed using a 0.018- or 0.035-inch hydrophilic guidewire (Terumo Europe, Leuven, Belgium). After crossing the lesion, angioplasty was performed by inserting a DEB (Legflow® Paclitaxel-Eluting Balloon, Cardionovum Sp.z.o.o, Warsaw, Poland) at an appropriate size and length (Figures 1-3). The target lesion was dilated to approximately up to 10 mm beyond both of its ends using a DEB with a vessel/balloon ratio of 1:1 (based on visual estimation) and an inflation time of 3 min at 4 to 12 atm. Control arteriography was performed at the end of the procedure to assess the procedural success and potential complications such as dissection, vasospasm, thrombosis, or distal embolism (Figure 3).

Following the procedure, all patients were prescribed daily acetylsalicylic acid (100 mg, p.o.) indefinitely

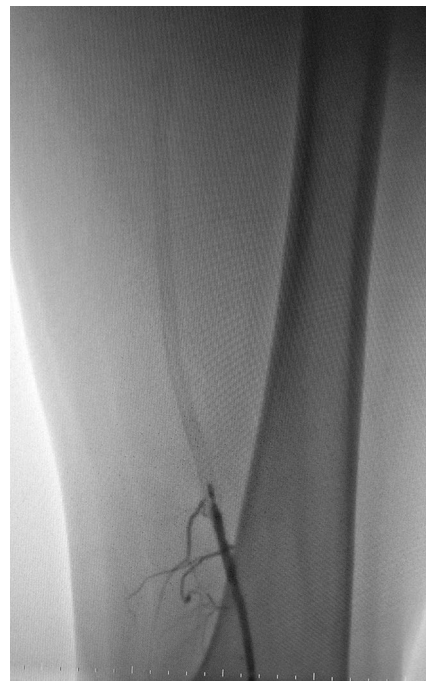

Figure 1. A totally occluded long stent in superficial femoral artery.

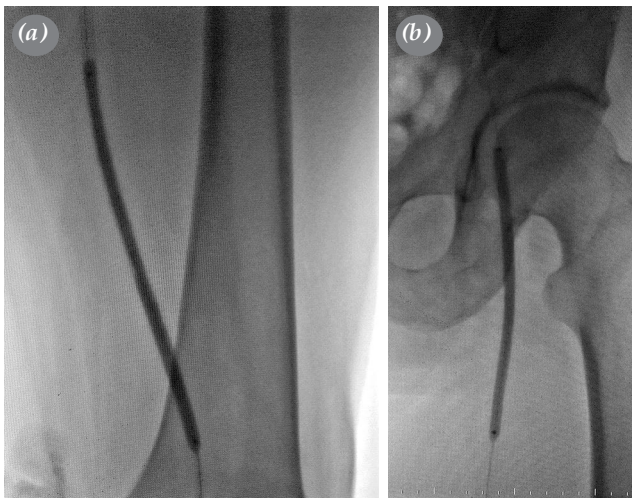

Figure 2. (a) Re-opening distal part of the stent with a drug-eluting balloon. **(b)** Re-opening the proximal part of the stent with a drug-eluting balloon.

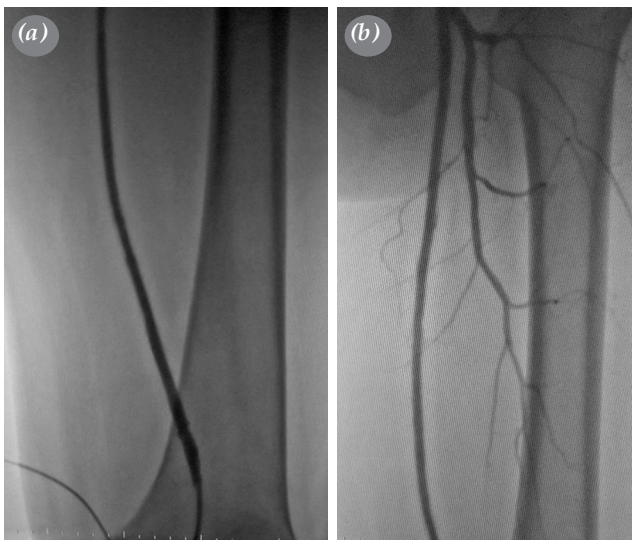

Figure 3. (a) An angiographic view of treated distal part of the stent. **(b)** An angiographic view of treated proximal part of the stent.

combined with daily clopidogrel (75 mg, p.o.) for a total of 12 weeks.

All patients were followed postoperatively at the vascular clinic. The patients were encouraged to return for scheduled follow-up visits at four weeks and 2, 4, 6, 8, 10, and 12 months after the procedure or anytime if symptoms recurred. The Rutherford classification and ankle-brachial index (ABI) were also assessed during follow-up visits. Duplex sonography and quantitative angiography, if necessary, were performed. Patient risk modifications including smoking cessation and antiplatelet and hypercholesterolemia control (target low-density lipoprotein [LDL] cholesterol: <75 mg/dL) were emphasized during follow-up visits.

Statistical analysis

Statistical analysis was performed using the PASW version 18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were expressed in number and percentage for categorical variables and in mean ± standard deviation (SD) or median (25^{th} percentiles [Q1]- 75^{th} percentiles [Q3], and min-max) continuous variables. For categorical variables, the chi-square test was used for the comparison of two independent groups and multiple comparisons, while the Fisher exact test was used for the comparison of independent groups, when the conditions for the chi-square test were not met. The Student's t-test was used for inter-group comparisons of normally distributed numerical variables, while the Mann-Whitney U test was used for comparisons of skewed numerical variables. The Wilcoxon signed-rank test was used to compare skewed numerical variables in the independent groups. A p value of <0.05 was considered statistically significant.

RESULTS

The length of stent lesions (ISR length) ranged from 80 to 220 mm. The mean ISR length was 107.7±24.6 mm in Group 1, 164.6±17.9 mm in Group 2, and 180±19.3 mm in Group 3. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

For DEB treatment of FP ISR, retrograde approach from the popliteal artery was preferred in 47 patients (75.8%). All patients were treated with DEBs, except for five in whom total clearance could not be achieved and FP bypass was performed. None of the patients in the study required amputation.

The Rutherford classification and ABI results of the patients prior to and following DEB treatment for FP segment ISR are shown in Tables 2 and 3, respectively. Except for two patients in Class 3, ABI improved, indicating a technical success rate of 96.8% (n=60).

At one-year follow-up, 49 patients (79%) had restenosis. Eight of 17 patients (47.1%) in Group 1, 19 of 22 patients (86.4%) in Group 2, and 22 of 23 patients (95.7%) in Group 3 developed restenosis. Restenosis was statistically significantly higher in Group 3 (total occlusion) compared to Groups 1 and 2 (non-occluded stenosis) (p<0.05). Restenosis

Table 1. Baseline demographic and angiographic characteristics of patients

	Stenosis				Occlusion					
	Total (n=62)		Class 1 (n=17)		Class 2 (n=22)		Class 3 (n=23)		Among 3 classes	Stenosis vs. occlusion
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	*p*	*p*
Age (year)		64.2±9.1		64.7±7.9		63.3±8.8		64.7±10.5	0.975	0.763
Sex									0.091	0.168
Male	48		10		18		20			
Female	14		7		4		3			
Hypertension									0.684	0.661
Yes	37		10		14		13			
No	25		7		8		10			
Hyperlipidemia									0.684	0.661
Yes	21		5		9		7			
No	41		12		13		16			
CLI									0.003	0.001
Yes	13		2		1		10			
No	49		15		21		13			
CAD									0.972	0.852
Yes	18		5		6		7			
No	44		12		16		16			
Cerebrovascular accident									0.355	0.173
Yes	3		1		2		0			
No	59		16		20		23			
Smoking									0.501	0.245
Yes	46		12		15		19			
No	16		5		7		4			

SD: Standard deviation; CLI: Critical limb ischemia; CAD: Coronary artery disease.

rates between Groups 1 and 2 were comparable. The patency rates at time intervals are shown in Table 4 and Figure 4.

Multivariate analysis revealed that the lesion length at the time of DEB treatment was an independent factor for restenosis (p=0.031).

There was no change at post-ISR evaluation period of Class 1 patients. Among post-ISR Class 2 patients, two with the Rutherford Class 3 and an ABI of 0.5 shifted to the Rutherford Class 4 and an ABI of 0.4 at 10 and 12 months. Two patients in the post-ISR Class 3 with the Rutherford Class 2 and an ABI of 0.6 shifted to the Rutherford Class 3 and an ABI of 0.4 at post-ISR

Table 2. Rutherford classes before and after in-stent restenosis treatment

	Pre-treatment			Post-treatment		
Rutherford classes	Class 1	Class 2	Class 3	Class 1	Class 2	Class 3
2	0	0	0	10	8	12
3	5	2	2	7	11	8
4	5	8	8	0	2	1
5	7	12	13	0	1	2
Total	17	22	23	17	22	23

Table 3. ABI before and after in-stent restenosis treatment

	Pre-tretment ABI			Post-treatment ABI		
Index	Class 1	Class 2	Class 3	Class 1	Class 2	Class 3
0.3	4	3	2	0	0	2
0.4	3	6	6	0	2	0
0.5	7	7	11	1	2	2
0.6	3	4	4	3	7	3
0.7	0	2	0	12	8	14
0.8	0	0	0	1	3	1
0.9	0	0	0	0	0	1

ABI: Ankle-brachial index.

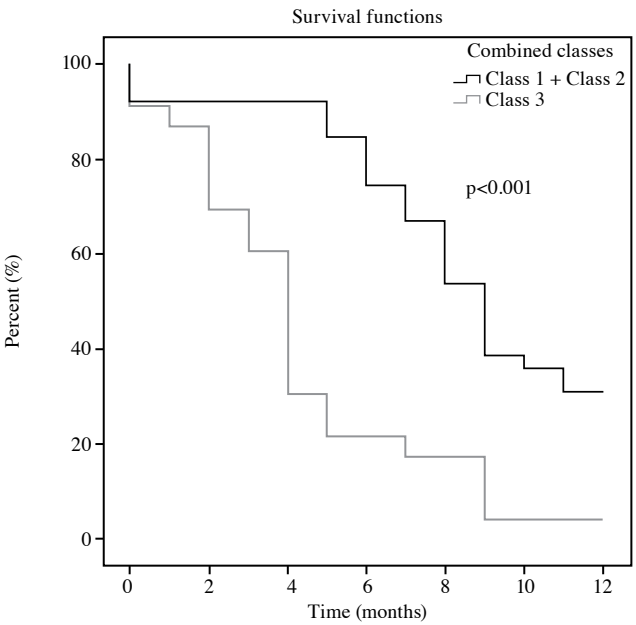

Figure 4. Recurrent in-stent restenosis rates of patient groups.

Table 4. Restenosis rate between classes

	Restenosis at 12 months	
Classes	n	%
Class 1	8	47.1
Class 2	19	86.4
Class 3	22	95.7

six and 10 months. Another two patients in the same class shifted from the Rutherford Class 3 with an ABI of 0.5 to the Rutherford Class 4 and an ABI of 0.3 at four and six months. One patient in post-ISR Class 3 group with the Rutherford Class 5 and an ABI of 0.3 underwent open surgery at the second control.

DISCUSSION

In the present study, we evaluated the characteristics of FP-ISR stents and report our one-year results of DEB after re-intervention.

The use of stents in vascular surgery has rapidly evolved to leave nothing behind concept. Stents are designed to improve the technical success rate and maintain arterial patency. The stents prevent from obstructive plaque dissection by fixation of the artery plaque to the arterial wall, but this may tend to decrease in-lumen opening which may result in restenosis or occlusion. On the other hand, stents in the SFA and popliteal arteries are subject to external forces such as twisting, bending, elongation, and external compression.[4] In-stent restenosis refers to the loss of luminal volume from an ingrowth of cells, extracellular matrix, and thrombus within the walls of the stented artery and 5-mm margins proximal and distal to the stent. Previous studies reported that the use of nitinol stents improved the durability in SFA[8,11-13] with a restenosis rate of only 7.7% at six months.[12] For the treatment of ISR following SFA stents, DEBs showed promising results in terms of clinical benefit and primary patency over one year.[9] The promising results with DEBs in SFA ISR led us to prefer primary use of a DEB to treat FP segment ISR and we studied the one-year results in this study.

For endovascular treatment of FP segmental ISR, cutting or scoring balloon angioplasty, cryoplasty and catheter-based atherectomy are options with different success rates. Nevertheless, no standard treatment exists for the treatment and limited data exist on the risk factors for FP segment ISR.[14] The Femoral Artery In-Stent Restenosis (FAIR) trial showed that DEB for FP artery-ISR was associated with less recurrent restenosis and DEB had better results than standard balloon.[15] Likewise, Siablis et al.[16] demonstrated

improved patency utilizing DEBs versus percutaneous transluminal angioplasty in a single-center trial (predominately short lesions) improved patency in the DEB arm compared to standard balloon angioplasty. Another study for the treatment of FP-ISR with DEBs was Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis (DEBATE-ISR) which was designed to treat symptomatic diabetic patients and compared their 12-month restenosis rate with that of a historical control group of 42 diabetic patients treated with conventional balloon angioplasty.[17] The authors concluded that the DEB use for the treatment of FP-ISR led to a significant reduction in recurrent restenosis and TLR at one-year follow-up compared to historical controls. In our study, we only documented one-year results, and we did not compare the results with any other group of patients. Different from those studies, we divided the patients into three groups based on the classification system by Tosaka et al.[10] according to stenosis length. We found that the ISR length was an independent predictor for restenosis after DEB treatment. The rate of restenosis significantly increased in Group 3 patients who had total occlusion compared to Groups 1 and 2. This can be attributed to continuation of neointimal hyperplasia in native vessel by inducing inflammatory response as a result of continuum between stent and native vessel. Thus, we also showed that risk for occlusion increased by increased length of the stent. Tosaka et al.[10] also concluded that restenotic patterns after FP stenting are important predictors of recurrent ISR and occlusion.

A previous study reported that the Trans-Atlantic Inter-Society Consensus II (TASC II) C and D lesions, hemodialysis, stent fracture, and cilostazol administration were independent predictors of primary patency.[18,19] However, we did not use TASC II classification systems in our study.

The balloon we used in the present study is different in some terms compared to other studies. The DEB used in our study required a short inflation time of 45 sec, and the resulting limited exposure to paclitaxel might reduce aneurysm formation in the treated segment. Additionally, shellac is used to ensure an equally distributed tissue concentration of paclitaxel and to achieve an optimal dose over a short inflation period, thus reducing both neointimal growth and restenosis risk. As each DEB is unique (different manufacturer, drug dose, balloon type), the brand preferred may alter clinical effects.

The main limitation of our study is the small number of patients, but the patient groups had similar demographic characteristics which makes our study reliable. The second limitation is that stent-in-stent implantation was performed in 37 patients, as the maximum length of the stent we used in our study was 150 mm. However, we believe that this does not affect the results of the study, as the intra-stent intersecting areas were quite too short. Also, despite the fact that lesion length was found to be an independent predictor for patency, variable mean lengths in three groups may have limited certain conclusions to be made.

In conclusion, our study results show acceptable our-year patency rates of drug-eluting balloon and the lesion length is an independent risk factor for recurrent in-stent restenosis. These findings indicate that restenotic pattern is a strong predictor of recurrent restenosis.

Declaration of conflicting interests

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