ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2021.101.2.120
Annals of Surgical Treatment and Research

Multiple drug-coated balloons can be used effectively for peripheral arterial disease including long femoropopliteal lesions

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Purpose: Drug-coated balloons have shown successful results in treating peripheral arterial occlusive disease. However, using multiple balloons for long femoropopliteal lesions (>15 cm) remains challenging; their safety and efficacy need to be explored. Therefore, we aimed to evaluate the outcomes of multiple drug-coated balloons for long femoropopliteal lesions in terms of the primary patency, freedom from clinically-driven target lesion revascularization, and mortality.
Methods: Between April 2015 and September 2018, 96 patients (117 limbs) who underwent balloon angioplasty using at least 2 drug-coated balloons for femoropopliteal lesions were retrospectively reviewed. Lesions were classified as Trans-Atlantic Inter-Society Consensus (TASC) classification C or D. The outcomes were analyzed using Kaplan-Meyer analysis.
Results: The mean age of 96 enrolled patients was 70.8 ± 9.8 years, and 83 patients were males (86.5%). Critical limb-threatening ischemia was found in 29 cases (24.8%). The mean lesion and drug-coated balloon lengths per limb were 292.3 ± 77.8 mm and 325.0 ± 70.2 mm, respectively. The technical success rate was 99.2%. A total of 82.1% were followed-up for more than 6 months. The primary patency rates at 12 and 24 months were 71.4% and 41.7%, respectively; freedom from clinically-driven target lesion revascularization rates were 96.4% and 71.0% at 12 and 24 months, respectively. The Kaplan-Meier estimate of the 2-year overall cumulative mortality rate was 20.8%. All identified mortalities appeared to be less associated with paclitaxel.
Conclusion: Drug-coated balloons can be effectively used without drug-related mortality, even for long lesions, such as TASC classification C or D femoropopliteal lesions.
[Ann Surg Treat Res 2021;101(2):120-128]

Key Words: Angioplasty, Arterial occlusive diseases, Femoral artery, Mortality, Paclitaxel

INTRODUCTION

Paclitaxel delivery into the vascular wall is a technique that has been developed and improved over the last 20 years. Drug-coated balloon (DCB) angioplasty is known to prevent restenosis by inhibiting neointimal hyperplasia, accomplished by the deposition of paclitaxel in the vascular walls using a paclitaxel-coated balloon [1]. Angioplasty using DCB has proven superiority over standard balloons in numerous studies [2]. Moreover, balloon angioplasty offers various advantages

Received February 18, 2021, **Revised** May 12, 2021,
Accepted June 16, 2021

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over stent insertion, not only freedom from stent-related complications, such as stent fracture and in-stent restenosis (ISR) but also opportunities for reintervention [3].

For the treatment of femoropopliteal artery stenosis, balloon angioplasty has been recognized as the first-line treatment for short femoropopliteal artery segments of <50 mm or simple lesions classified as the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC II) A or B. However, the treatment outcome is poorer for long and complex lesions classified as TASC C or D and inferior to traditional bypass surgery, even to prosthetic graft [4-6]. This is because patients with long femoropopliteal artery stenosis or occlusion often have multiple inflow or outflow lesions; recoiling stenosis due to severe calcification or total chronic occlusion can easily occur in such patients [6,7]. However, with the emergence of DCBs, endovascular treatment outcomes for femoropopliteal lesions have greatly improved [1,4,8,9]. Accordingly, good patency could be expected in such long and complex lesions, with some studies already reporting improved therapeutic outcomes [1,10-14]. Although an increasing number of guidelines recommend using DCB, the level of evidence is still low, and the indications and limitations need to be specified [15]. Moreover, the impact of multiple DCB use on long-term mortality remains controversial, and the accumulation of a more diverse and greater volume of data is needed [16].

The present study was conducted to analyze the safety and durability of treatment using multiple DCBs on long femoropopliteal artery lesions classified as TASC C or D at a single tertiary referral center.

METHODS

Study design

The present study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (No. 05-2019-112) and was conducted as a retrospective study using medical records; the need for obtaining patients' informed consent was, thus, waived by the IRB. The study population comprised patients who underwent surgery for peripheral arterial occlusive disease between April 2015 and September 2018. The patients were categorized as having Rutherford classification 1–5 diseases and underwent balloon angioplasty using at least 2 DCBs on femoropopliteal lesions with lengths of >15 cm.

Procedure

Although best medical therapy was offered to all patients, procedures were offered to patients whom the surgeon thought would benefit from recanalization.

All surgical interventions were performed by 2 experienced vascular surgeons with 8–15 years of experience. Low-extremity CT angiography was performed on all patients before surgery; the general treatment goal was to recanalize from the iliac artery to at least 1 below the knee arteries without stenosis of ≥50%. The following surgical procedures were generally performed under a hybrid operating environment and general anesthesia. General anesthesia was performed under the following considerations to maximize the advantages of hybrid operation; close monitoring by anesthesiologists, possibility of prolonging operation time, age, and poor cooperation level of patients with decreased cognition. Also, for the prevention of anesthesia complications and the possibility of acute reocclusion, the intensive care unit monitoring protocol was applied to all patients for 1 day postoperatively.

Stenting was mostly done for aortoiliac lesions. Endarterectomy and patch angioplasty were mostly performed for common femoral artery lesions. For femoropopliteal lesions, predilatation was performed for 10 seconds using a plane balloon after passing a guidewire through the lesion antegradely or retrogradely. Subsequently, IN.PACT Admiral DCB (Medtronic, Dublin, Ireland) was inflated for 2 minutes at 10–14 atm. For some lesions with severe calcification, DCB was inflated after atherectomy using the Jetstream atherectomy device (Boston Scientific, Maple Grove, MN, USA). For cases involving thrombosis, balloon thromboembolectomy was performed using a Fogarty balloon catheter (Edwards Lifesciences AG, Nyon, Switzerland). When multiple DCBs were continuously applied, the general rule was to have each balloon overlap the other by approximately 1 cm. If intimal dissection or a remnant thrombus was present after the balloon procedure or a stenosis of ≥50% persisted, an additional bailout stent procedure was performed. In cases with a stenosis of ≥50% in distal runoff vessels, balloon angioplasty was performed using an uncoated balloon to secure perfusion at the foot level. The ankle-brachial index (ABI) was checked on the first or second postoperative day and during outpatient follow-up visits every 6 months after the surgery. CT angiography was performed annually in patients with good kidney function, considering the coverage of the national health insurance policy.

Variables

Sex, age, smoking, hyperlipidemia, stroke, cardiovascular disease, chronic obstructive pulmonary disease, dialysis, and renal insufficiency were investigated as patient characteristics. Renal insufficiency was defined as an estimated glomerular filtration rate of ≤60 mL/min/1.73 m^2. The length, bilaterality, Rutherford classification, *de novo* lesions, restenosis or ISR, chronic total occlusion, and severity of calcification were investigated as lesion characteristics. The severity of calcification was based on the CT angiography findings on femoropopliteal arterial percentage stenosis due to calcification, with calcification of up to 30% classified as mild, 30%–50% as

moderate, and ≥50% as severe. Thrombosis was defined as a case in which balloon thromboembolectomy was performed with thrombotic findings in radiological examinations.

The number of DCBs used, total length of DCBs, common femoral artery endarterectomy, endovascular atherectomy, bailout stent insertion, balloon thromboembolectomy, retrograde approach, crossover approach, and additional inflow or outflow intervention were assessed as procedure-related factors.

Outcome measures

The primary patency and freedom from clinically-driven target lesion revascularization (CD-TLR) were investigated as outcome factors. The primary patency was defined as restenosis during the follow-up period, while restenosis was defined as a 20% decrease in ABI value relative to that obtained immediately after the surgery, ≥0.15 decrease relative to the baseline, or ≥50% restenosis, or ≥50% ISR on CT angiography. CD-TLR was defined as cases requiring reoperation for the same side femoropopliteal lesions due to findings of restenosis accompanied by symptoms during the follow-up period. Technical success was defined as the successful recanalization without residual stenosis of >50% with endovascular treatment only without requiring femoropopliteal bypass surgery.

Statistical analysis

To quantify the degree of paclitaxel exposure, the product of multiplying the total DCB contents (mg) by the number of exposure days was used as a variable in performing a logistic regression analysis on mortality rate. Electronic medical records were reviewed to investigate mortality and the cause of death.

One vascular surgeon and 1 experienced senior researcher were responsible for data collection and analysis. Kaplan-Meier survival analysis was used to estimate each outcome variable at the 24-month time point. Multivariate Cox proportional-hazards analysis was used to analyze the risk factors. Multivariate analysis was performed with factors with a significance of ≤0.2 in the univariate analysis, and the criteria for entry and removal in stepwise regression analysis were set at 0.05 and 0.1, respectively. We also performed a scatter plot and logistic regression analysis to analyze the relationship between drug exposure and mortality in each patient. In patients who had been treated with DCB more than 2 times, the accumulated paclitaxel content value was applied. The significance level was set at $P \leq 0.05$, and all analyses were performed using the statistical software IBM SPSS Statistics ver. 16.0 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Patient cohort

Data on 101 procedures performed on a total of 117 limbs (96 patients) were collected between April 2015 and September 2018. The mean age of the patients was 70.8 ± 9.8 years, and the patient population included 83 males (86.5%). The other patient characteristics are shown in Table 1.

Table 1. Demographics of patients

Characteristic	Data
No. of patients	96
Age (yr)	70.8 ± 9.80
Male sex	83 (86.5)
Body mass index (kg/m^2)	22.8 ± 3.15
Diabetes mellitus	62 (64.6)
Hypertension	66 (68.8)
Hyperlipidemia	28 (29.2)
Renal insufficiency	38 (39.6)
End-stage renal disease[a)]	13 (13.5)
Smoking history	52 (54.2)
CVA	26 (27.1)
CAD	20 (20.8)
COPD	8 (8.3)

Values are presented as number only, mean ± standard deviation or number (%).
CVA, cerebrovascular accident; CAD, coronary arterial disease; COPD, chronic obstructive pulmonary disease.
[a)]This group refers to patients undergoing dialysis among patients with renal insufficiency.

Table 2. Characteristics of lesions

Characteristic	Data (n = 117)
TASC II classification	
C	93 (79.5)
D	24 (20.5)
Rutherford classification	
0–2	36 (30.8)
3	52 (44.4)
4	16 (13.7)
5	12 (10.3)
Affected vessels	
SFA	45 (38.5)
SFA + popliteal artery	72 (61.5)
Left-sided lesion	60 (51.3)
Bilateral lesion[a)]	57 (48.7)
Mean lesion length (mm)	292.3 ± 77.8
Preoperative ABI	0.57 ± 0.24
Severe calcification	25 (21.4)
Chronic total occlusion	67 (57.3)
Critical limb-threatening ischemia	28 (23.9)

Values are presented as number (%) or mean ± standard deviation.
TASC II, Trans-Atlantic Inter-Society Consensus; SFA, superficial femoral artery; ABI, ankle-brachial index.
[a)]It was based on whether the contralateral side was treated simultaneously or with a staged operation. In this case, TASC A, B lesions were also included.

Pre- and perioperative characteristics

With respect to lesion characteristics, there were 93 TASC C lesions (79.5%) and 24 TASC D lesions (20.5%). The mean lesion length measured by CT was 292.3 ± 77.9 mm. ISR was found in 36 cases (30.8%). Thirty-nine cases (33.3%) had previously undergone 1 or more angioplasties. Among these, 5 cases had previously used DCB. In 45 cases (38.5%), the lesion was confined to the superficial femoral artery; whereas in 72 cases (61.5%), the lesion extended down to the popliteal artery. The mean preoperative ABI was 0.57 ± 0.24 (Table 2). Total chronic occlusion was found in 67 cases (57.3%). Lesions with calcification were found in 82 cases (70.1%), of which 36 cases (30.8%), 22 cases (18.8%), and 25 cases (21.4%) were classified as mild, moderate, and severe calcification, respectively. Critical limb-threatening ischemia was found in 29 cases (24.8%).

The mean number of DCBs used per limb was 2.32 ± 0.50, and the mean balloon length was 325 ± 70.22 mm per limb. A hybrid operation was performed in 37 cases (31.6%), common femoral artery endarterectomy in 26 cases (22.2%), and balloon thromboembolectomy in 11 cases (9.4%). Endovascular atherectomy was performed in 9 cases (7.7%), whereas bailout stenting was performed in 20 cases (17.1%) due to failed revascularization by balloon angioplasty alone (Table 3).

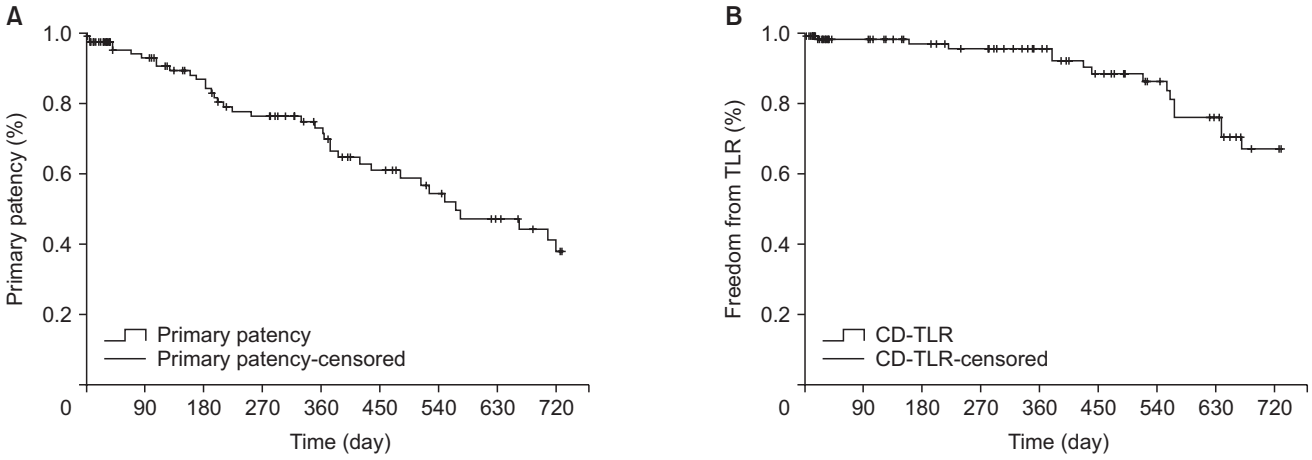
Postoperative outcomes

The mean ABI immediately after the procedure was 0.88 ± 0.18. Of the 101 cases, only 1 case was performed femoropopliteal bypass due to recanalization failure with endovascular treatment alone. Among 96 patients (101 procedures), 3 of 101 (2.9%) died within 30 days postoperatively from pulmonary complications (n = 2) and myocardial infarction (n = 1). Of the 117 cases, 105 (89.7%) were followed up as outpatients at least once; of these 105 cases, 84 (80.0%) were evaluated through ABI or CT. In some patients, follow-up tests were limited due to renal insufficiency, economic burden,

Table 3. Characteristics of procedures

Characteristic	Data (n = 117)
No. of drug-coated balloons	
2	82 (70.1)
3	33 (28.2)
4	2 (1.7)
No. of balloons	2.32 ± 0.50
Balloon length (mm)	325.0 ± 70.22
Hybrid operation	37 (31.6)
Balloon thrombectomy	11 (9.4)
Endarterectomy	26 (22.2)
Inflow bypass	4 (3.4)
Endovascular atherectomy	9 (7.7)
Stent implantation	20 (17.1)
Inflow intervention	36 (30.8)
Outflow intervention	50/116[a] (43.1)
Cut-down approach	68 (57.6)
Crossover approach	31 (26.3)
Retrograde approach	10 (8.5)
Conversion to femoropopliteal bypass	1 (0.8)

Values are presented as number (%) or mean ± standard deviation.
[a]A patient who had already undergone amputation was excluded.



Days	0	90	180	270	360	450	540	630	720
No. at risk	116	82	68	57	44	33	24	18	13
Primary patency (%)	99.1	92.9	86.8	76.4	73.1	61.0	54.4	47.3	41.2

Days	0	90	180	270	360	450	540	630	720
No. at risk	117	87	77	72	57	47	36	28	19
Primary patency (%)	100	98.2	96.9	95.6	95.6	88.5	86.3	76.1	67.1

Fig. 1. Estimated cumulative primary patency (A) and freedom from clinically-driven (CD) target lesion revascularization (TLR) rate (B) by Kaplan-Meier analysis.

and below knee amputated state; therefore, only physical examinations were conducted. The median follow-up duration was 351 days. The rate of freedom from restenosis (primary patency rate) calculated by Kaplan-Meier survival analysis was 71.8% and 41.7% in the first and second years, respectively; freedom from CD-TLR rate was 95.6% and 71.0% in the first and second years, respectively (Fig. 1). There were 15 cases of all-cause 2-year mortality, and the 2-year survival rate by Kaplan-Meyer analysis was 79.2%; the causes of death are shown in Table 4.

Risk factor analysis

The results of the Cox proportional-hazards analysis of risk factors for restenosis are shown in Table 5. The factors that had a significant influence on restenosis were sex, Buerger's disease, hyperlipidemia, and thrombosis.

Paclitaxel exposure and mortality analysis

We found no significant relationship between the 2 factors (odds ratio, 0.623; 95% confidence interval, 0.344–1.128; P = 0.120) (Fig. 2).

DISCUSSION

Endovascular treatment of long occlusive arterial lesions remains complicated and requires further research and development [1,10,12,17]. The popularization of DCB has led to significant improvement in treatment outcomes for femoropopliteal artery lesions [2,4,8,9]. However, more favorable long-term patency after bypass surgery is reported for long and complex vascular lesions classified as TASC II C or D [5,7,10,18]. Considering the underlying diseases of patients with TASC II C or D lesions, the pre-and postoperative risks, limited availability of vessels for harvesting autogenous grafts, and rapid advances in techniques and equipment for endovascular treatment, it is clear that there is an increasing preference for endovascular treatment among these patients [18]; however, there is a lack of solid evidence to support this treatment approach [19].

Table 4. Causes of mortality during the follow-up period

Cause	Data
Pneumonia	4
Postoperative pulmonary edema	3
Myocardial infarction	1
Congestive heart failure	1
Biliary sepsis	1
Ischemic colitis	1
Sepsis due to recurrent wound infection	2
Sepsis due to urinary tract infection	1
Metastatic bladder cancer	1
Total 2-year mortality[a]	15 (20.8)[a]
30-Day mortality[b]	3 (2.9)[b]

Values are presented as number only or number (%).
[a]Mortality was calculated by Kaplan-Meier survival analysis. [b]The number of deaths was divided by the total number of operations.

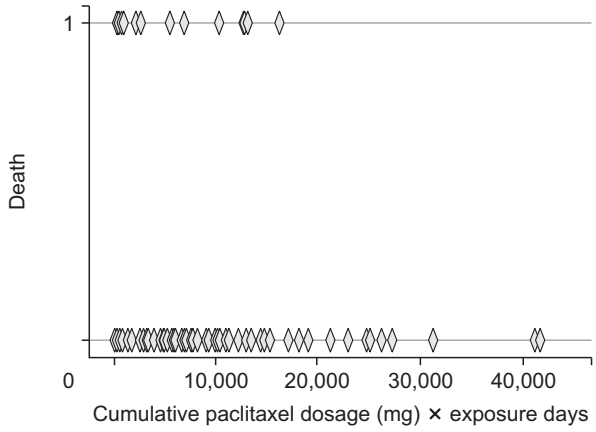


Fig. 2. Scatter plot on the relationship between death and paclitaxel exposures. For paclitaxel dosage, refer to the manufacturer's instruction for use for each balloon.

Table 5. Risk factors for restenosis as assessed by the Cox proportional-hazards model

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex	3.10 (1.49–6.47)	0.003	3.67 (1.58–8.54)	0.003
Hyperlipidemia	2.02 (1.06–3.83)	0.032	2.38 (1.15–4.91)	0.019
Smoking history	0.49 (0.27–0.89)	0.019		
Outflow disease	1.72 (0.95–3.09)	0.073		
Thrombosis	2.55 (1.06–6.12)	0.036	3.40 (1.35–8.57)	0.010
Preoperative ABI[a]	0.21 (0.05–0.95)	0.043		
Buerger's disease	5.44 (1.65–17.9)	0.005	9.93 (2.78–35.42)	<0.001

HR, hazard ratio; CI, confidence interval; ABI, ankle-brachial index.
[a]This value was small and was thus corrected by multiplying by 100 for use in the statistical analysis.

In the present study, the primary patency rates of long femoropopliteal artery occlusive lesions were 71.4% and 41.7% in the first and second years, respectively. Other studies on long and complex occlusive lesions reported a first-year patency rate of 60%–85%, which was relatively excellent, but the second-year patency rate decreased to 46%–65.3%, showing a pattern similar to that in the present study. In the case of CD-TLR rate, it was 95.6% in the first year and decreased slightly to 71% in the second year in our study. This pattern is also similar to that reported in other studies, which showed a CD-TLR rate of 79%–93% in the first year and 67%–87.1% in the second year (Table 6) [1,5,11-14,17,19-22].

Restenosis after the endovascular treatment is known to occur mostly within 6 months after a non-DCB procedure and within 1 year after a self-expanding stent insertion [23,24]. Moreover, the restenosis rate increases with increasing lesion length or increasing disease severity in the runoff vessel [7]. In the current study, however, the primary patency curve (Fig. 1) showed a value of 86.8% at 6 months, and although there was a consistent decrease over time, the result is much superior to the 43% reported in a study on angioplasty published by Schillinger et al. [23]. Moreover, as shown in Fig. 1, the TLR rate remained low for up to 1 year but began to increase at 18 months. Based on these findings, it can be concluded that treatment using DCB had the distinct effect of delaying the time point of restenosis and TLR in cases involving long lesions classified as TASC II C or D. This demonstrates the clinical usefulness of DCB angioplasty for TASC II C and D lesions compared to a plane balloon or stent.

Furthermore, the femoropopliteal bypass conversion rate was 0.9% (1 of 117), indicating a high technical success rate of endovascular treatment alone. An endovascular approach using DCB, performed by an experienced surgeon, has the potential to be used alone for TASC II C or D lesions. Of course, the retrograde approaches from the ankle level may be required frequently. This favorable success rate from the endovascular treatment of occlusive lesions was also found in other studies [1,11,13,14,17,20-22].

Neointimal hyperplasia is considered one of the main mechanisms involved in restenosis. Balloon angioplasty provides short-term expansion of the vessel lumen, but, at the same time, it causes mechanical injury to the vessel walls, which can result in intimal hyperplasia [25]. Therefore, balloon angioplasty would be more effective for TASC A or B lesions, i.e., localized lesions for which vascular wall injury and intimal hyperplasia could be minimized by local balloon angioplasty. However, DCB angioplasty has a significant value as a treatment option for older patients with long and complex peripheral arterial occlusive disease. This is primarily because these patients have limited availability of autogenous graft and high intra- and postoperative risks due to underlying diseases, making bypass surgery an unacceptable option, and the surgical risks often outweigh the expected benefits of recanalization. For these patients, the emergence and advancement of DCBs that can exceed the therapeutic effects of uncoated balloons are advantageous. Second, various treatment methods incorporating DCBs are being developed. For example, other new instruments, including drug-eluting stents, interwoven nitinol stents, stent-grafts, and plaque modification devices, are being used competitively or complementarily with DCB to improve treatment outcomes [4,24,26].

In the present study, most of the cases were severe and had relatively long lesions with a mean length of 29.2 cm, and the inflow and/or outflow vessels were being treated

Table 6. Results of other trials on drug-coated balloons in long and complex femoropopliteal lesions

Study	Study design	Lesion length (mm)	1-Year primary patency	2-Year primary patency	1-Year TLR	2-Year TLR
Du et al. [11]	DCB for long diabetic FP	153.3 ± 15.5	72	50	93	85
Tepe et al. [1]	DCB for CTO cohort	228.3 ± 97.6	85.3			
Schmidt et al. [17]	DCB for complex FP lesion cohort	240 ± 102	79.2	53.7	85.4	68.6
Lai et al. [20]	DCB for long occlusive FP	186 ± 86.3	78.8		91.4	
Micari et al. [8]	DCB for IC and resting pain cohort	251 ± 71		70.4		84.7
Roh et al. [13]	DCB for complex FP	222 ± 116	85.2	65.3	93	87.1
Teymen et al. [21]	DCB for complex FP	140.6	79.2			
Jia et al. [14]	DCB for FP	150	77.5			
Phillips et al. [22]	DES for long FP lesion	242 ± 113	60	46	79	67
Xu et al. [12]	DCB for severe FP lesion	147 ± 110		64.6		86.5
Shin et al. [5]	Bypass for TASC C		91.7	73.3	91.7	73.3
Shin et al. [5]	Bypass for TASC D		77.1	66.6	80.2	73.3
Present study	DCB for TASC C,D	292.3 ± 77.8	71.4	41.7	96.4	71

TLR, target lesion revascularization; DCB, drug-coated balloon; FP, femoropopliteal artery; CTO, chronic total occlusion; IC, intermittent claudication; DES, drug-eluting stent; TASC, Trans-Atlantic Inter-Society Consensus.

concurrently in approximately 74 of 117 cases (63.2%). We used DCB angioplasty to treat patients with long and severe femoropopliteal and multilevel lesions with an acceptable outcome. The durability of this treatment is definitely not as excellent as the bypass surgery, but it is considered sufficiently acceptable considering the life expectancy and risk/benefit balance of these patients and has been approaching results that could only have been obtained by bypass. We support that endovascular treatment using DCB has the potential to be a tried-and-tested treatment option for patients with TASC C and D femoropopliteal lesions.

To summarize, endovascular treatment with DCB for short femoropopliteal lesions has already been established as an essential treatment by replacing the plane balloon. Endovascular treatment using DCB in patients with TASC II C or D lesions had a significant value since it not only reduced intra- and postoperative risks in patients with a short life expectancy but also preserved the option for future treatments, such as reballooning, stent insertion, and bypass surgery for restenosis in patients with a long-life expectancy. Therefore, all physicians and surgeons treating peripheral vascular diseases should become familiar with paclitaxel-coated balloon and help patients easily receive this new modality treatment.

Moreover, sex, Buerger's disease, hyperlipidemia, and thrombosis were identified as risk factors of restenosis. Particularly, when thrombosis was involved, the risk of restenosis was 3.3 times higher than that of typical atherosclerotic lesions (Table 5). Considering the mechanism of arterial thrombosis, including von Willebrand factor and platelet aggregation following plaque rupture in atherosclerotic vessels, paclitaxel, which inhibits neointimal hyperplasia by inhibiting the migration, and proliferation of smooth muscle cells, may not be critical for preventing re-thrombosis. Therefore, it is suggested that a stent procedure, such as the interwoven stent, drug-eluting stent, or stent graft, should be considered to cover any prothrombogenic surface that may remain after a thrombectomy. Moreover, there is a greater need to develop and upgrade drugs that can target vWF [27].

In the present study, the causes of death during the follow-up period included infection, cardiovascular disease, and malignancy, which were mostly associated with aging. However, complications believed to be associated with paclitaxel (i.e., drug-related, allergic, or idiopathic reactions) were not noted (Table 4). Further, the logistic regression analysis showed no causal relationship between exposure to paclitaxel and mortality. Although the mechanism by which paclitaxel causes death is not clear, likewise, no evidence of obvious drug-related side effects has been found. Moreover, it is known that the peak systemic blood levels of paclitaxel are insignificantly minimal [28]. Thus, considering the abovementioned data, DCB can currently be considered safe for at least 2 years.

The limitations of the present study included the single-center retrospective design. Additionally, the study included a mixture of patients with multilevel arterial disease with varying severity and mixed treatments. The number of cases and follow-up period were limited. Further, the present investigation was a single-arm study, and it did not present data on direct comparisons with a drug-eluting stent, interwoven nitinol stent, or bypass procedure. In the future, it is necessary to collect, stratify, and analyze larger amounts of prospective data through multicenter studies led by our vascular societies.

In conclusion, DCB angioplasty showed favorable patency and inhibitory effect on restenosis and reintervention rate even in long femoropopliteal arterial occlusive lesions. Furthermore, evidence of paclitaxel-related deaths was not noted in the 2-year follow-up period. Therefore, in patients for whom a bypass procedure may not be a viable option, DCB angioplasty could be considered as the first-line treatment.

ACKNOWLEDGEMENTS

Fund/Grant Support

This study was supported by Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Tepe G, Micari A, Keirse K, Zeller T, Scheinert D, Li P, et al. Drug-coated balloon treatment for femoropopliteal artery disease: the chronic total occlusion cohort in the IN.PACT Global Study. JACC Cardiovasc Interv 2019;12:484-93.
2. Laird JR, Schneider PA, Tepe G, Brodmann M, Zeller T, Metzger C, et al. Durability of treatment effect using a drug-coated balloon for femoropopliteal lesions: 24-month results of IN.PACT SFA. J Am Coll Cardiol 2015;66:2329-38.
3. Laird JR, Yeo KK. The treatment of femoropopliteal in-stent restenosis: back to the future. J Am Coll Cardiol 2012;59:24-5.
4. Torii S, Kolodgie FD, Virmani R, Finn AV. IN.PACT™ Admiral™ drug-coated balloons in peripheral artery disease: current perspectives. Med Devices (Auckl) 2019;12:53-64.
5. Shin SH, Kwon SH, Cho JH, Ahn HJ, Oh JH, Park HC. Outcomes of bypass surgery versus endovascular therapy for TASC II C and D femoro-popliteal lesions in patients with chronic limb ischemia. Korean J Vasc Endovasc Surg 2010;26:90-7.
6. Baril DT, Chaer RA, Rhee RY, Makaroun MS, Marone LK. Endovascular interventions for TASC II D femoropopliteal lesions. J Vasc Surg 2010;51:1406-12.
7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45 Suppl S:S5-67.
8. Micari A, Nerla R, Vadalà G, Castriota F, Grattoni C, Liso A, et al. 2-Year results of paclitaxel-coated balloons for long femoropopliteal artery disease: evidence from the SFA-long study. JACC Cardiovasc Interv 2017;10:728-34.
9. Jaff MR, Rosenfield K, Scheinert D, Rocha-Singh K, Benenati J, Nehler M, et al. Drug-coated balloons to improve femoropopliteal artery patency: rationale and design of the LEVANT 2 trial. Am Heart J 2015;169:479-85.
10. Zeller T, Rastan A, Macharzina R, Tepe G, Kaspar M, Chavarria J, et al. Drug-coated balloons vs. drug-eluting stents for treatment of long femoropopliteal lesions. J Endovasc Ther 2014;21:359-68.
11. Du X, Wang F, Wu DM, Zhang MH, Jia X, Zhang JW, et al. Comparison between paclitaxel-coated balloon and standard uncoated balloon in the treatment of femoropopliteal long lesions in diabetics. Medicine (Baltimore) 2019;98:e14840.
12. Xu Y, Jia X, Zhang J, Zhuang B, Fu W, Wu D, et al. Drug-coated balloon angioplasty compared with uncoated balloons in the treatment of 200 Chinese patients with severe femoropopliteal lesions: 24-month results of AcoArt I. JACC Cardiovasc Interv 2018;11:2347-53.
13. Roh JW, Ko YG, Ahn CM, Hong SJ, Shin DH, Kim JS, et al. Risk factors for restenosis after drug-coated balloon angioplasty for complex femoropopliteal arterial occlusive disease. Ann Vasc Surg 2019;55:45-54.
14. Jia X, Zhang J, Zhuang B, Fu W, Wu D, Wang F, et al. Acotec drug-coated balloon catheter: randomized, multicenter, controlled clinical study in femoropopliteal arteries: evidence from the AcoArt I trial. JACC Cardiovasc Interv 2016;9:1941-9.
15. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg 2019;69(6S):3S-125S.
16. Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the leg: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc 2018;7:e011245.
17. Schmidt A, Piorkowski M, Görner H, Steiner S, Bausback Y, Scheinert S, et al. Drug-coated balloons for complex femoropopliteal lesions: 2-year results of a Real-World Registry. JACC Cardiovasc Interv 2016;9:715-24.
18. TASC Steering Committee; Jaff MR, White CJ, Hiatt WR, Fowkes GR, Dormandy J, et al. An update on methods for revascularization and expansion of the TASC lesion classification to include below-the-knee arteries: a supplement to the inter-society consensus for the management of peripheral arterial disease (TASC II). Vasc Med 2015;20:465-78.
19. Micari A, Brodmann M, Keirse K, Peeters P, Tepe G, Frost M, et al. Drug-coated balloon treatment of femoropopliteal lesions for patients with intermittent claudication and ischemic rest pain: 2-year results from the IN.PACT Global Study. JACC Cardiovasc Interv 2018;11:945-53.
20. Lai Z, Zhang X, Shao J, Li K, Fang L, Xu L, et al. One-year results of drug-coated balloons for long and occlusive femoropopliteal artery disease: a single-arm trial. BMC Cardiovasc Disord 2020;20:65.
21. Teymen B, Akturk S, Akturk U, Tdjani M. Comparison of drug-eluting balloon angioplasty with self-expanding interwoven nitinol stent deployment in patients with complex femoropopliteal lesions. Vascular 2018;26:54-61.
22. Phillips JA, Falls A, Kolluri R, Whipp A, Collins C, Mohir-Sadaai S, et al. Full drug-eluting stent jacket: two-year results of a single-center experience with Zilver PTX stenting for long lesions in the femoropopliteal arteries. J Endovasc Ther 2018;25:295-301.
23. Schillinger M, Sabeti S, Loewe C, Dick P, Amighi J, Mlekusch W, et al. Balloon angioplasty versus implantation of nitinol stents in the superficial femoral artery. N Engl J Med 2006;354:1879-88.
24. Schneider PA. Evolution and current use of technology for superficial femoral and popliteal artery interventions for claudication. J Vasc Surg 2017;66:916-23.
25. Ueda M, Becker AE, Tsukada T, Numano F, Fujimoto T. Fibrocellular tissue response after percutaneous transluminal coronary

angioplasty: an immunocytochemical analysis of the cellular composition. Circulation 1991;83:1327-32.
26. Kim MS, Joo YS, Park KH. Results of simultaneous hybrid operation in multi-level arterial occlusive disease. J Korean Surg Soc 2010;79:386-92.
27. Kim D, Bresette C, Liu Z, Ku DN. Occlusive thrombosis in arteries. APL Bioeng 2019;3:041502.
28. Swaminathan RV, Jones WS, Patel MR. Is paclitaxel causing mortality during lower-extremity revascularization? J Am Heart Assoc 2019;8:e012523.