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Comparison of standard balloon and drug-coated balloon angioplasty in patients with the below-the-knee peripheral artery disease

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SUMMARY

OBJECTIVE: The objective of this study was to compare the interventions of percutaneous transluminal drug-coated balloon angioplasty (DCB PTA) and standard PTA in the treatment of patients with the below-the-knee peripheral artery disease (BTK PAD).

METHODS: Overall, 196 patients (113 males and 83 females; mean age: 63.56±11.94 years; 45–83 years) were treated with PTA for BTK PAD between June 2014 and March 2019.

RESULT: Standard PTA (group 1; 96 patients) and DCB PTA (group 2; 100 patients) results were analyzed and compared retrospectively. No statistically significant difference was found between the mean ages of group 1 and 2 patients (p=0.371, p>0.05). Demographic and clinical data were compared and no any statistically significant differences was found between the two groups. Comparing in terms of the iliac lesion, there was no statistically significant difference between the two groups. However, a statistically significant difference was found between the two groups in terms of frequency of popliteal lesions (p=0.001; p<0.05). There was not a statistically significant difference between the two groups in terms of other lesions. In addition, limb salvage rates were 82.0% (18 amputations) and 65.6% (33 amputations) in the drug-release balloon group and the naked balloon group, at the end of 1 year, respectively. No distal embolism, limb-threatening ischemia, and mortality were observed in any patients.

CONCLUSIONS: Based on this study, patients in the DCB group had significantly higher rates of primary patency as compared with the other patients.

KEYWORDS: Peripheral artery disease. Drug coated balloon. Angioplasty. Stenting. Percutaneous. Transluminal.

INTRODUCTION

Peripheral artery disease (PAD) is usually characterized by intermittent claudication (IC), rest pain, ischemic ulcers, or gangrene. Over a 5-year period, 5–10% of patients with asymptomatic PAD or IC will progress to critical limb ischemia (CLI)[1]. Patients with CLI are at increased risk of amputation and major cardiovascular ischemic events[2]. Therefore, revascularization treatment of these patients must be planned as soon as possible.

Revascularization is an effective treatment modality despite the benefits of pharmacological agents. Selected revascularization treatment of the patient with CLI depends upon the premorbid conditions and the extremity as well as estimating the risk of intervention based on the comorbid conditions and expected patency and durability of the vascular reconstruction[3]. Although surgical revascularization is an effective revascularization method in the treatment of PAD, the existence of the patients with high surgical risk, lack of adequate venous conduit, and poor runoff in the infrapopliteal level and foot led to

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a number of increasing percutaneous transluminal endovascular treatment (EVT) for revascularization. Nowadays, advancements in technique and technology have increased the feasibility and practicality of EVT, which now represents the preferred method of revascularization over surgical procedures in many centers across the world[4]. Unlike the open surgical technique, it can be performed under local anesthesia. Rapid application and rapid response, especially in emergency cases, enables EVT to be preferred method in patients with CLI[5]. On the other hand, the presence of long, calcific, and often occluded lesions in the infrapopliteal PAD negatively affects the patency rate after the EVT[5]. Since the optimal strategy for the management of a patient with CLI must be determined on a case-by-case basis[6]. Furthermore, patients should be informed about revascularization modalities and patients' preference should be questioned before the intervention.

It is known that drug-coated balloon (DCB) angioplasty and standard percutaneous transluminal angioplasty (PTA) (in other names are bare, naked, and old) are among EVT modalities. There is no consensus in the literature regarding the use of DCB or standard PTA in infrapopliteal lesions. This study aimed to compare the endovascular intervention techniques of DCB angioplasty and standard balloon angioplasty (PTA) in the treatment of patients with infrapopliteal PAD.

METHODS

Between June 2014 and March 2019, 196 patients (224 limb intervention) (113 males and 83 females; mean age: 63.56±11.94 years; 45–83 years) with infrapopliteal PAD who underwent endovascular revascularization operation were enrolled in this retrospective single-center study. Standard balloon angioplasty and DCB angioplasty were performed in 96 (group 1 patients' mean ages: 64.27±10.45) and 100 (group 2 patients' mean ages: 62.83±11.94) patients, respectively. Color flow Doppler ultrasound and peripheral digital subtraction or computed tomography angiography were performed after the physical examination in all patients. Control radiological imaging studies were performed during the intervention or after the procedure if needed.

Inclusion criteria were determined as lifestyle-limiting IC or CLI (Rutherford classification stages 3–6). During EVT procedure, ipsilateral or contralateral femoral artery was used for the arterial access. In case of flow-restricting dissection or ≥30% residual stenosis, the inflation time was prolonged (3 min) during the intervention. Exclusion criteria were life expectancy of less than 1 year, contraindication for dual-antiplatelet therapy, known allergy against paclitaxel, and a requirement for extensive amputation during the procedure. Also, patients with infrapopliteal vascular disease were excluded from the study if they were diagnosed with Buerger's disease. Patients received medical treatment postoperatively. Patients were called up at 1, 3, and 6 months after the procedure and followed up with ankle-brachial index (ABI) measurements and Rutherford classification. In the demographic data of patients, 6-month patency and clinical status were compared between the groups.

The primary termination variables were freedom from amputation, restenosis, and reintervention. Secondary termination variables were technical success, procedural and postoperative complications, conventional primary patency, secondary restenosis, tissue healing, limb salvage, reintervention, and patient survival. Technical success was defined as an angiographic evaluation <30% residual stenosis after the procedure and direct flow to the target site. Treatment failure was defined as any patient requiring reintervention, with/or without restenosis and/or occlusion and reintervention was performed. Also, these patients had decreasing ABI.

Following the procedure, 300 mg (75 mg×4) clopidogrel loading was given, followed by dual-antiplatelet therapy (75 mg clopidogrel and 100 mg acetylsalicylic acid daily) and cilostazol (200 mg daily) for 12 months. Also, intravenous iloprost (20 µg daily) was routinely given to all patients early postintervention term for 10 days. At the end of 6 months, clopidogrel was stopped, and patients were followed with 100 mg acetylsalicylic acid daily.

Statistical analysis

Statistical analysis was performed using SPSS mac v.20 statistical package program (IBM, Armonk, NY, USA). The suitability of the data for normal distribution was examined by the Kolmogorov-Smirnov test. Variables showing normal distribution were compared with parametric tests (Student's t-test), and mean±standard deviation values were used as descriptive statistics. The variables not normally distributed were compared with nonparametric tests (Mann-Whitney U), and median (lower quarter-upper quarter) values were given as descriptive statistics. Pearson's chi-square and Fisher's exact tests were used for the analysis of categorical data. The $p<0.05$ were considered statistically significant. Major amputation was defined as loss of limb above the metatarsal level, whereas small amputation was defined as trans-metatarsal amputation or amputation of the more distal parts of the lower limb.

RESULTS

There was not any statistically significant difference between the mean age of group 1 and 2 patients ($p=0.371$, $p>0.05$).

Demographic and clinical data were compared and found no statistically significant difference between the two groups (Table 1). Lower limb-threatening ischemia and distal embolism were not seen in any patient who enrolled in this study.

Based on the iliac lesion, there was no statistically significant difference between the two groups but iliac stent application was performed in two patients (2.1%) of group 2 (p=0.239). In all, 52 patients in group 2 and 27 patients in group 1 had popliteal lesions and there was a statistically significant difference between the two groups in terms of frequency of popliteal lesions (p=0.001; p<0.05). There was no statistically significant difference between the two groups in terms of other lesions. Lesion features are provided in detail in Table 2. Rutherford classification and ABI were used in the follow-up of the clinical recovery after the procedure. There was no significant difference between the two groups at the beginning; however, clinical improvement was significantly higher in the DCB balloon group with medication at the end of 6 months. Besides, limb salvage rates were 82.0% (18 amputations) and 65.6% (33 amputations) in the DCB balloon group and the naked balloon group, at the end of 6 months, respectively. There was statistically significant difference between the two groups (p=0.009).

DISCUSSION

The first percutaneous EVT for PAD was described by Dotter and Judkins in the mid-1960s[7]. It was reported that for selected patient population with ischemic diabetic foot and isolated infrapopliteal lesions, a successful EVT led to a high percentage of limb salvage at the long-term follow-up[8]. However, the application of standard PTA is limited due to complications associated with the endovascular procedure

Table 1. Patient demographics.

Number/percentage, n (%)	Group 1 (n=96)	Group 2 (n=100)	p-value
Gender (male/female)	55/41 (57.3/42.7)	58/42 (58.0/42.0)	0.920
Smoker	60 (62.5)	70 (70.0)	0.267
Diabetes mellitus	52 (54.2)	54 (54.0)	0.981
Hypertension (≥130/80 mmHg)	45 (46.9)	55 (55.0)	0.255
Dyslipidemia (LDL ≥200 mg/dL)	58 (60.4)	54 (54.0)	0.364
Coronary artery disease	60 (62.5)	52 (52.0)	0.138
Chronic renal failure Creatinine >2.0 mg/dL	3 (3.1)	5 (5.0)	0.721
Cerebrovascular disease	11 (11.5)	13 (13.0)	0.742

LDL: low-density lipoprotein.

Table 2. Lesion angiographic and procedural features.

	Group 2	Group 1	p-values
Lesion length, cm	12.3±7.60	13.7±8.76	0.0019
Angiography lesion length, cm	7.89±4.17	7.97±7.46	0.060
Restenotic lesions	6.7 (24/359)	3.7 (7/189)	0.176
% Diameter stenosis (before procedure)	91.2±9.8	90.71±9.29	0.065
% Diameter stenosis (after procedure)	19.8±10.1	20.2±11.7	0.068
Maximum inflation pressure, atm	6.9±3.4	11.2±4.8	0.015
Procedure complications*	9.7 (23/238)	3.4 (4/119)	0.035
Distal embolization	2.8 (9/319)	0.6 (1/169)	0.176

*Vessel rupture, vessel dissections, peripheral emboli, and hematoma.

and a relatively high restenosis rate. PTA treatment may result in residual stenosis, early elastic recoil, and flow-limiting dissection[9].

Lack of desired results caused by high restenosis with the bare metal stent and standard balloon applications in infrainguinal lesions led to the technological innovation of locally administered DCB and drug-coated stents[10]. Drug-coated stents were developed in 1999 to provide local administration of an agent without systemic side effects, which have capable of inhibiting intimal hyperplasia caused by an inflammatory reaction following stent implantation or balloon expansion[11]. In this way, the cellular mechanisms responsible for atherosclerosis and neointimal hyperplasia are inhibited.

Ipema et al. reported in their meta-analysis that no significant differences were found between DCB angioplasty and standard PTA angioplasty in patients with infrapopliteal PAD[12]. On the other hand, Schmidt et al. reported that the early restenosis rate of long-segment infrapopliteal disease is significantly lower after treatment with DCBs compared with historical data using uncoated balloons[13]. Also, Roh et al.[14] reported that treatment of the complex femoropopliteal arterial occlusive disease with DCBs showed excellent primary patency and target lesion revascularization-free survival at 1 year after the procedure. In this study, similar results were obtained in parallel with the literature.

When the disease affects infrapopliteal level, frequency of lesion increases in other parts of the limb. In this study, the incidence of superficial femoral artery lesion was 45.8 and 47% in patients with bare balloon PTA and DCB, respectively. In both groups, when the lesions complicated, this has a negative effect especially on the success of the long-term results of angioplasty.

Fernandez et al.[15] reported that tibial artery endovascular intervention is an effective treatment for CLI with acceptable limb salvage and wound healing rates, but endovascular intervention requires a high rate of reintervention. Gür et al.[5] reported that DCBs are found superior to naked balloons at 12-month patency rates and clinical follow-up. The authors also pointed out that DCB application gives successful results in the long term and have positive contributions to limb salvage in cases with BTK lesions[5]. In this study, the clinical results of the DCB group were superior to the bare balloon group in the 6-month follow-up. Also, Liistro et al.[16] reported in their study on drug-eluting balloon in peripheral intervention for below-the-knee angioplasty evaluation trial that DCBs compared with PTA strikingly reduce 1-year restenosis, target lesion revascularization, and target vessel occlusion in the treatment of BTK lesions in the diabetic patients with CLI. Similarly, lower lumen loss was detected at 6 months in the DCB group compared with standard balloon angioplasty group (0.4±1.2 mm versus 1.7±1.8 mm; p<0.001) in THUNDER trial[17].

We can conclude that increased clinical healing, walking distance, and wound healing and low amputation rates are seen after the DCB angioplasty. Accordingly, ABI rates and Rutherford levels of the patients are also improved compared with pretreatment. In this study, the improvement of the patients' status was better in current situations in the DCB group.

Interestingly, Katsanos et al.[18] reported that there seems to be an increased long-term risk of death beyond the first year after the intervention of femoropopliteal application of paclitaxel-coated balloons and stents in the lower limbs. They also mentioned that actual causes for this serious late side effect remain unknown, and further investigations with longer term follow-up are urgently warranted. On the other hand, Zeller et al.[19] reported that paclitaxel exposure was not related to increased risk for amputation or all-cause mortality at 5-year follow-up. Similarly, any patient did not develop such a complication in this study (increased death associated with paclitaxel).

There is another limitation in the literature. A long (>3 min) inflation period during balloon dilatation may prove effective as an initial angioplasty strategy to prevent severe dissection in femoropopliteal lesions[20]. Although longer inflation time did not improve primary patency within 1 year, it might result in better immediate angioplasty success[20]. Moreover, Rockley et al.[21] reported that both coronary and peripheral vascular evidence are in agreement that prolonged angioplasty balloon inflation greater than 60 seconds appears to be associated with improved immediate postinflation results. This shows that prolonged inflation time improves patency rates in DCB compared with PTA. Similarly, the inflation time was 3 min in this study.

CONCLUSIONS

In conclusion, DCB group had significantly higher rates of primary patency as compared with the PTA group, although there was no statistically significant difference between the two groups in terms of limb recovery, survival, and restenosis rates between DCB angioplasty and standard PTA. We think that it should be supported by high population, differently designed devices, and studies.

AUTHORS' CONTRIBUTIONS

MAK: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **ÜH:** Formal analysis, Software, Supervision, Writing – review & editing.

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