A prospective, randomized study of drug-coated balloon versus plain old balloon angioplasty in management of femoropopliteal artery disease in diabetic patients: 12-month results

Ahmed K. Gabr[a], Ahmed K. Allam[b]

[a]Department of Vascular Surgery, Ain Shams University, Cairo, [b]Vascular Surgery Unit, Department of General Surgery, Benha University, Banha, Egypt

Correspondence to Ahmed K. Allam, MD, Mohamed Atteiyia Mansour Street, Khairy Allam Building, Kalubeiyia, Benha, 13512, Egypt. Tel: +20 122 338 3639/+20 101 332 6487; e-mail: ahmed.allam01@fmed.bu.edu.eg

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Background/Purposes
Despite enhanced immediate technical success, neointimal hyperplasia and restenosis remain the Achilles' heel of endovascular interventions. Drug-coated balloons (DCBs) have shown promise in improving the outcomes of patients with peripheral arterial disease. Several trials have shown that DCB angioplasty has superior antirestenotic efficacy in the femoropopliteal artery (FPA) disease. This controlled, prospective, multicenter study was designed to establish the efficacy of DCB to improve angiographic outcomes and inhibit restenosis of the FPAs in an exclusive diabetic population in a 12-month follow-up period.
Aim
This controlled, prospective, multicenter study was designed to establish the efficacy of DCB to improve angiographic outcomes and inhibit restenosis of the FPAs in an exclusive diabetic population in a 12-month follow-up period.
Settings and design
A randomized, controlled, prospective, and multicenter study was conducted.
Patients and methods
Between January 2016 and December 2017, 84 consecutive adult patients with type 1 and 2 diabetes with oral euglycemics or insulin injection had been enrolled. Overall, 42 patients were treated with DCB angioplasty and 42 were treated with plain old balloon angioplasty (POBA) in a 1 : 1 randomization pattern. The primary end point of the study was the primary patency, mean diameter restenosis, and binary restenosis of the treated sites at 12 months without reintervention in the interim.
Results
The 12-month mean diameter restenosis was significantly lower in the DCB arm than in the POBA group (27.9±35.1 vs. 44.8±33.9%, P=0.034). Furthermore, analysis showed that the binary (≥50% diameter stenosis) restenosis rates were significantly lower in DCB patients as compared with the POBA patients (28 vs. 47%, P=0.029). The primary patency was significantly better in DCB group (71 vs. 49%, P=0.028). On the contrary, we noted that the rate of clinically driven target lesion revascularization was slightly higher in the POBA patients, though not statistically significant as compared with the paclitaxel-coated balloon group (28 vs. 20%, P=0.13). There were no procedure-related or device-related deaths in either study arm. The 12-month adverse effects, in terms of all-cause death (N_3=7.1% POBA vs. N_2=4.8% DCB), minor amputation (N_5=12% POBA vs. N_4=9.5% DCB), major amputation (0% POBA vs. N_1=2.4% DCB), and myocardial infarction (N_1=2.4% POBA vs. 0% DCB) were equal in both groups (P=713). Causes of mortality included myocardial infarction, cerebral infarction, and sudden death.
Conclusions
The treatment of diabetic peripheral arterial disease of FPA disease with IN.PACT paclitaxel-coated balloon angioplasty is associated with superior antirestenotic efficacy that provides a better primary patency rate compared with POBA at 12 months. However, DCB showed no clinical benefit over POBA at this 12-month follow-up period. The number of major adverse clinical events was comparable between DCB and POBA groups of patients.

Keywords:
angioplasty, drug-coated balloon, femoropopliteal atherosclerosis, paclitaxel, restenosis

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Introduction

Peripheral artery disease (PAD) is estimated to affect more than 200 million people worldwide [1].

Endovascular treatment of symptomatic atherosclerotic PAD has gained a widespread acceptance and is now recommended as the primary revascularization strategy in many clinical and anatomical scenarios [2–4]. Percutaneous transluminal angioplasty (PTA) remains highly effective for reducing symptomatic stenosis acutely, and PTA of the superficial femoral and/or popliteal artery (PA) has a high initial success rate; however, restenosis occurs in up to 60% of cases [5].

However, the success of these revascularization procedures is limited in the acute phase by vessel recoil and flow-limiting dissections. Long-term patency may be compromised by restenosis and reocclusion owing to intimal hyperplasia or progression of atherosclerotic disease, which occurs in more than 60% of patients within 1 year [6]. Bare nitinol self-expanding stents prevent recoil and flow-limiting dissections, although the incidence of in-stent restenosis remains high [7]. Local antimitotic drug delivery technology has been developed with the intention to reduce neointimal proliferation. A recent study suggested sustained safety and effectiveness of paclitaxel-eluting stents for femoropopliteal arterial (FPA) disease [8]. In spite of improved outcomes reported in some trials with stenting, the dynamic stresses applied by the superficial femoral artery and PA may result in-stent fracture [9,10], in-stent stenosis, or thrombosis, which may further compromise clinical outcome [11]. Given the limitations of stenting, there has been considerable interest in identifying approaches that could improve patency without the need for a permanent metallic implant. Drug-coated balloons (DCBs) eliminate the presence of a mechanical scaffold, and thereby remove the technical burden of treating in-stent stenosis and the inherent risk of stent fracture. Given these challenges, an effective 'leave nothing behind' treatment strategy that circumvents the use of metallic implants while preserving future therapeutic options is attractive [10,12,13].

Several prospective multicenter trials have compared plain old balloon angioplasty (POBA) with DCB angioplasty and showed favorable results for the treatment of symptomatic FPA disease [14–17]. However; PAD in patients with diabetes mellitus (DM) is more aggressive than in nondiabetics, with the risk for major amputation that is 5–10-times higher. In addition, atherosclerosis in diabetic patients is characterized by medial calcinosis and a predisposition of occlusive disease to below-knee arteries [18].

The aim of our study is to compare 1 year outcomes between paclitaxel-coated balloon angioplasty (DCB) versus POBA in the treatment of symptomatic diabetic angiopathy in superficial femoral and/or PAs.

What our study adds

The angiographic superiority of DCB versus POBA in diabetic patient population corresponds with the reduction in the risk of target lesion revascularization (TLR), but it was not statistically significant compared with POBA.

Patients and methods

The study was performed at three tertiary referral centers in Saudi Arabia (Security Forces Hospital Program, Al-Noor Specialist Hospital – Makkah, and Almoosa Specialist Hospital, Al-Ahsaa) and two Hospitals in Egypt (Benha University Hospitals and Nile Insurance Hospital). Our institutional review board approved the study protocol. Before enrollment, patients were informed of the risks and benefits of participating in the study and were given informed consent forms for all to sign.

Study design and patient population

Between January 2016 and December 2017, 84 consecutive adult diabetic patients with type 1 and 2 diabetes with oral euglycemics or insulin injection were enrolled. DM was considered to be known if the patient reported the use of antidiabetic medication. De-novo diagnosis of DM was defined according to American Diabetes Association criteria as the first demonstration of a fasting serum concentrationmore than 126 mg/dl ormore than 200 mg/dl after glucose load or a random plasma glucose level of 200 mg/dl or more in a patient with symptoms of hyperglycemia.

Eligibility criteria

The eligibility criteria were patients aged 30 years and older and patients of both sexes, with nonacceptance of healthy volunteers.

Inclusion criteria

The patients must meet all of the following inclusion criteria:

(1) Patients must agree to undergo the 6-month angiographic follow-up as well as the clinical follow-up (at 6 and 12 months after procedure).
(2) Peripheral vascular disease with following Rutherford classes: 3=severe claudication, 4=ischemic pain while at rest, or 5=minor tissue loss.

(3) Lesion criteria included more than or equal to 50% de-novo or restenotic superficial femoral artery (SFA) lesions with a length of up to 15 cm or up to 10 cm occlusion of the SFA, more than or equal to 50% de-novo or restenotic lesions or occlusion of the PA and till the tibioperoneal trunk with a length of up to 10 cm.
(4) If the index lesion is restenotic, the prior PTA must have been more than 30 days before the treatment in our trial.
(5) Reference vessel diameter of at least 4 mm and up to 7 mm.
(6) Only one lesion per limb and per patient can be treated.
(7) At least one patent infrapopliteal run-off artery to the foot of the index limb.
(8) Successful endoluminal guide wire passage through the target lesion.
(9) Life expectancy, in the investigators' opinion, of at least 1 year.
(10) Patient is able to verbally acknowledge and understand the aim of this trial and is willing and able to provide informed consent.

The lesions were diagnosed by computed tomography angiography or conventional arteriography.

Exclusion criteria

The patients must not meet any of the general exclusion criteria:

(1) Previous surgery in the target vessel.
(2) Patients who require a PTA balloon catheter of a diameter size below 4 mm or diameter size above 7 mm.
(3) Major amputation in the same limb as the target lesion.
(4) Acute myocardial infarction (MI) within 30 days before intervention.
(5) Patients requiring different treatment or raising serious safety concerns regarding the procedure or the required medication.
(6) Women of childbearing potential, except women meeting the following criteria:
    (a) Postmenopausal (12-month natural amenorrhea or 6-month amenorrhea with serum follicle-stimulating hormone >40 mIU/ml).
    (b) Using an effective method of birth control for the duration of the study: implants, injectables, combined oral contraceptives, intrauterine device (in place for a period of ≥2 months prior to screening) and with negative serum pregnancy test.
    (c) Sexual abstinence (e.g. a widow).
    (d) Vasectomized husband.
(7) Pregnant and nursing women.
(8) Acute thrombus or aneurysm in the index limb or target vessel (presence of stent in the target lesion).
(9) In-stent restenosis in the target lesion.
(10) Renal insufficiency with a serum creatinine more than 2.0 mg/dl at a baseline biochemical testing.
(11) Platelet count less than 50 000/ml or more than 600 000 at baseline hematological testing.
(12) Known or documented thrombophilia that necessitating long-term anticoagulant therapy.
(13) Known or documented hypersensitivity or contraindication to contrast agent that cannot be adequately premedicated.
(14) Patients with known allergy to paclitaxel.
(15) Patients with intolerance of antiplatelet or thrombolytic medications that would be administered throughout the trial enrolment.
(16) Dialysis or long-term immunosuppressant therapy.
(17) Treatment of in-stent restenosis of target lesion is not allowed, but treatment of in-stent restenosis outside of target lesion in the target vessel is not an exclusion criteria.

Patients were randomized at a ratio of 1 : 1 to DCB study arm (n=42) or POBA study arm (n=42) by a sealed envelope randomization service [19].

Study devices

The IN.PACT over-the-wire balloon paclitaxel-eluting, dilatation catheters (Invatec-Medtronic, Brescia, Italy) were used in patients randomized in the experimental comparator group (PCB group). The balloon's surface was coated with a paclitaxel-eluting formulation using urea as a spacer. This highly hydrophilic combination enables a better contact of the lipophilic paclitaxel with the vascular wall. The specific balloon catheters were available at a maximum diameter of 7 mm and a maximum length of 150 mm for diameters of 5 and 6 mm, whereas the dose of paclitaxel on the balloon's surface was 3 μg/mm^2. The balloon was coated with FreePac is a paclitaxel-eluting formulation that contains hydrophilic urea to optimize transfer of lipophilic paclitaxel to the endothelial cells upon contact with the vessel wall. Paclitaxel is a cytotoxic agent that promotes tubulin polymerization, unlike other anti-microtubule drugs targeting the disassembly of microtubules. Limiting the microtubules' ability to turn back to their prior state interrupts a number of cell processes, including cell division and protein transport. Hence, the cell cycle is arrested in the mitosis phase, inhibiting smooth muscle

cell proliferation and fibromuscular hyperplasia. Patients randomized to the control group (PBA group) underwent angioplasty with a variety of high-pressure balloon catheters brands [Dorado PTA balloon dilatator catheter (Bard Peripheral Vascular, Tempe, Arizona, USA), Mustang PTA (Boston Scientific, Natick, Massachusetts, USA), and Conquest PTA Dilatation Catheter (Bard Peripheral Vascular)].

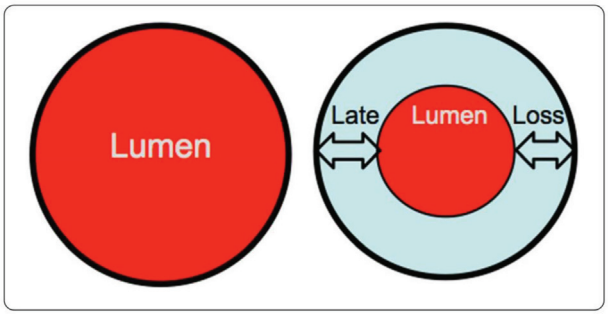
Definitions

Late lumen loss (LLL) as the primary efficacy end point was not designated as a safety issue, and allows researchers to evaluate the efficacy of paclitaxel-coated balloon (DCB) angioplasty as a drug device in inhibiting restenosis and reocclusion of target lesions in the SFA. LLL is defined as the angiographic minimum lumen diameter immediately after PTA minus minimum lumen diameter at angiographic follow-up (Fig. 1). The LLL represents a measure that corresponds to neointimal growth inhibition and predicts TLR occurrence [20]. TLR is defined as a clinically driven repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

Procedure and medical therapy

Endovascular procedures were performed under local infiltration anesthesia (xylocaine 2%: 3–5 mg/kg) percutaneously by antegrade through 6-F sheath or contralateral/cross-over approach through 8-F sheath. In patients receiving metformin treatment, even those who had a glomerular filtration rate greater than or equal to 60 ml/min/1.73 m^2, metformin treatment was stopped 48 h before the intervention and started 48 h after the procedure provided renal function was normal. Unfractionated heparin was recommended during the endovascular procedure (80–100 IU/kg). Patients are only randomized when the most distal lesion was successfully crossed by a guide wire [standard type; (AqWire, ev3) (Terumo Cardiovascular Systems Corp., Ann Arbor, Michigan, USA] for stenosis and stiff type (ZIP Wire; Boston Scientific) for occlusive lesions. The use of other adjuncts for crossing such as atherectomy devices and laser was not allowed. Appropriate balloon size selection was determined on the basis of the diameter of the reference vessel adjacent to the lesion. The DCB study arm-randomized patients were treated with the IN.PACT Admiral DCB. The IN.PACT DCB has a dual mode of action, comprising mechanical dilatation by the angioplasty balloon plus local antiproliferative drug paclitaxel to the arterial wall intended to inhibit restenosis. The IN.PACT DCB coating includes paclitaxel as the antiproliferative agent at a dose of 3.5 μg/mm^2, with urea as the excipient. Available IN.PACT Admiral DCB sizes include 4, 5, 6, and 7-mm diameters and 20, 40, 60, 80, 120 and 150-mm lengths (the 7-mm diameter device was not available in the length of 120–150 mm). Predilatation of the stenotic or occluded lesions with the standard PTA balloon of 1 mm less than that of the reference vessel diameter was mandatory before IN.PACT DCB dilatation. A minimum balloon inflation time of 156 s was required for both POBA and DCB study arms. To avoid geographic miss, DCB length was chosen to exceed the target lesion length by 10 mm at the proximal and distal edges. The IN.PACT DCB is a single-inflation device, and when treatment required multiple balloons, an overlap of 10 mm was applied for contiguous balloon inflations. Postdilation with standard uncoated PTA balloon was allowed at the discretion of the surgeon. In both treatment groups, provisional stenting was allowed when angioplasty was considered suboptimal owing to flow-limiting dissection or residual stenosis more than 30%. A completion angiography had to be invariably performed. Technical success was defined as attainment of up to 30% residual stenosis of the treatment area (Figs 2 and 3).

Figure 1



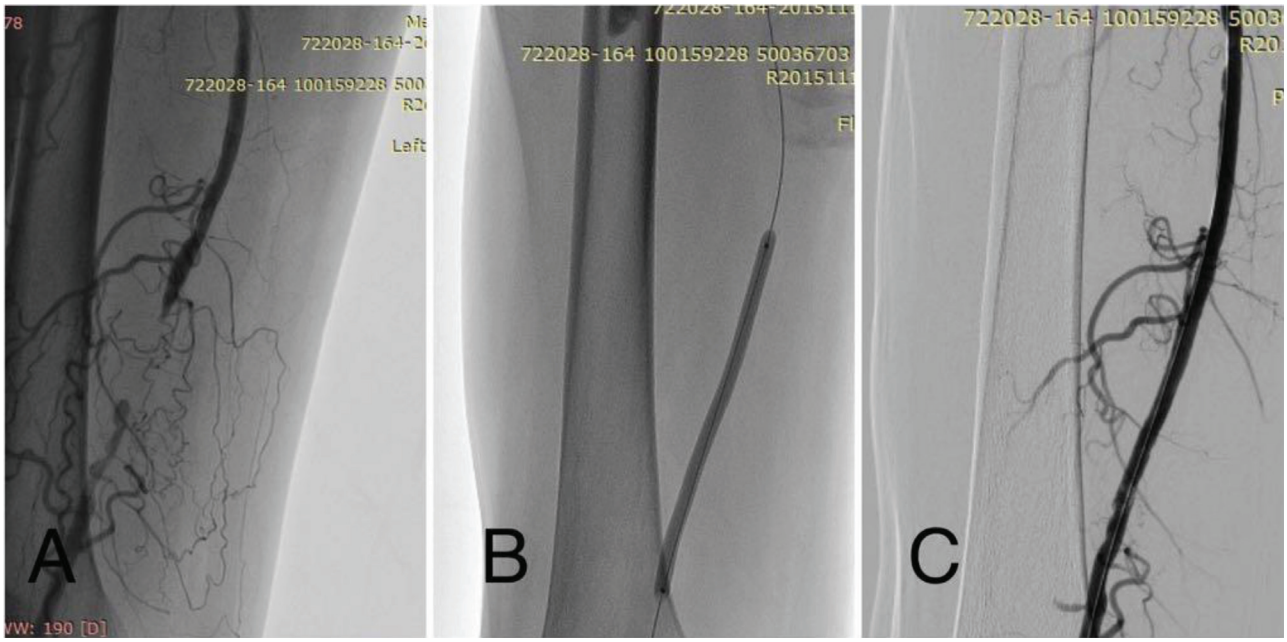
Late lumen loss is defined as angiographic minimum lumen diameter after percutaneous transluminal angioplasty minus minimum lumen diameter at follow-up.

In both study arms, postoperative medical therapy included aspirin (minimum 81 mg/day for a minimum of 6 months) and clopidogrel daily for a minimum of 1 month for nonstented patients and 3 months for patients who received stents. Usage of aspirin and antiplatelet drugs did not differ between treatment arms at discharge (97.4%), 30 days (87.5%), 6 months (76.3%), or 12 months (54.6%).

Follow-up

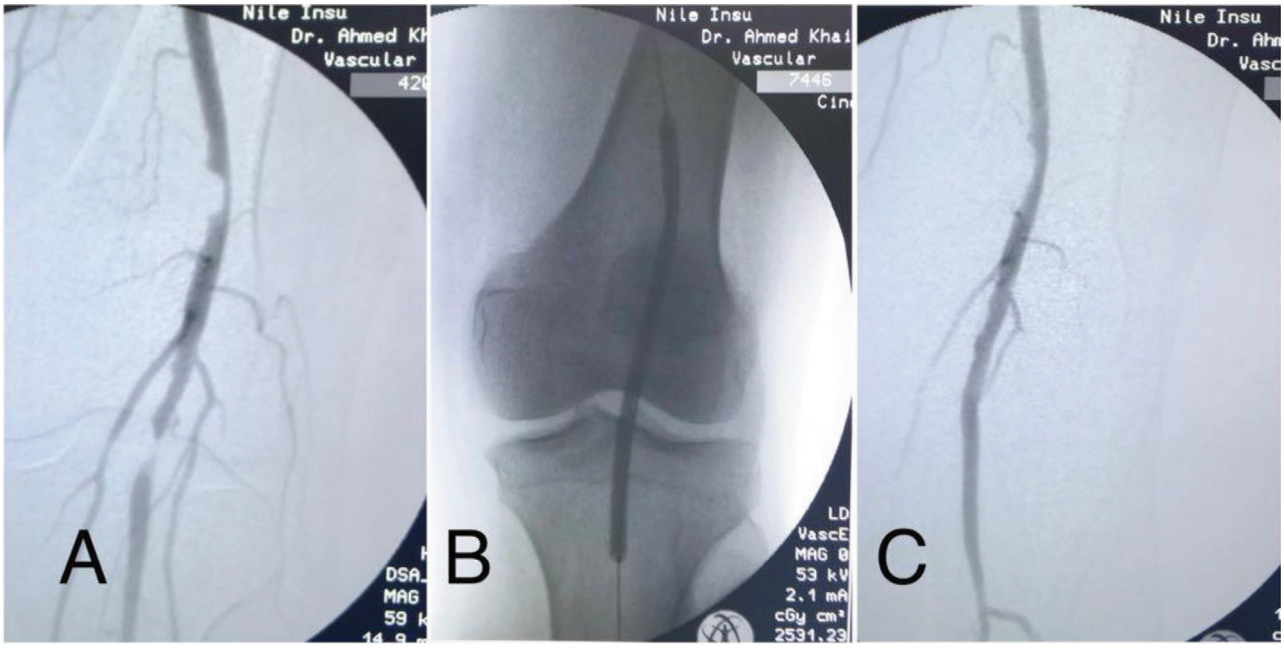
The enrolled patients were clinically evaluated before discharge and at 1, 6, and 12 months after the procedure, and their Rutherford classification was reassessed. The patency of the treated arterial segment was assessed by duplex ultrasonography for the SFA and proximal

Figure 2



Distal SFA segmental occlusion (a), full inflation of IN.PACT Drug coated balloon (b) no residual after angioplasty dissection or stenosis (c).

Figure 3



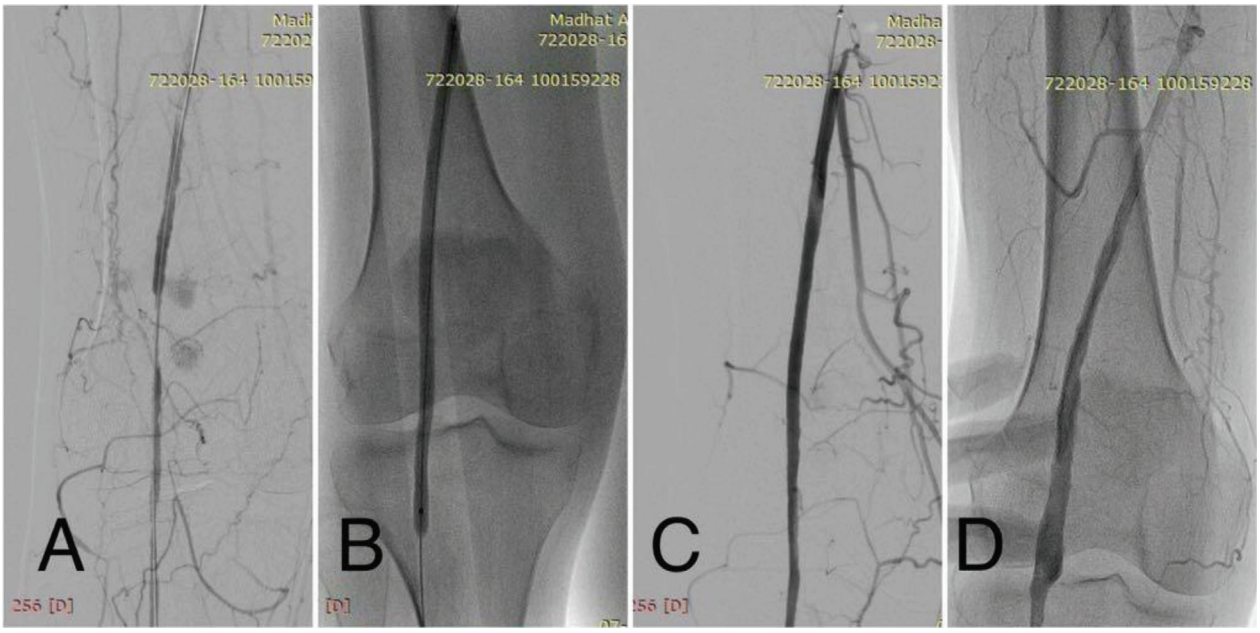
Popliteal artery tight stenosis (a) with inflation of high pressure plain balloon (b) no residual postdilatation stenosis or dissection (c).

popliteal and by computed tomography or conventional angiography for distal PA (Fig. 4).

Study end points

The primary end points of the study were primary patency (it was defined as the absence of TLR and binary restenosis assessed by doppler ultrasound (DUS) or angiography if DUS was uninformative), mean diameter restenosis, and binary restenosis (was defined as the recurrence of ≥50% diameter stenosis within ±5 mm proximal and/or distal to the target lesion as measured by DUS or angiography at 12 months without re-intervention in the interim). Patency of the SFA was assessed by duplex ultrasonography and considered lost when no flow could be detected at the treated lesion, or an increase in the peak systolic velocity ratio of at least 2.5, suggesting a more than or equal to 50% reduction in luminal diameter. The patency of PA

Figure 4



Popliteal artery tight stenosis (a); full inflation of IN.PACT balloon (b); no residual stenosis or dissection after IN.PACT balloon angioplasty (c); 1 year angioplasty with ectatic popliteal artery (d).

was assessed by computed tomography or conventional angiography (Fig. 4) and considered lost if the treated segment appeared occluded, or likewise showed a more than or equal to 50% reduction in the luminal diameter. The binary restenosis was defined as more than or equal to 50% diameter stenosis at 12-month follow-up.

The secondary end point was the clinically driven target lesion revascularization (cdTLR) rate at 12 months. A reintervention was allowed in case of at least 50% diameter stenosis (confirmed by duplex ultrasonography, computed tomography, or conventional angiography) within ±5 mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms. An improved clinical outcome was defined as an improvement of baseline symptoms by at least 1 Rutherford stage that was sustained through follow-up with no additional intervention.

Major adverse clinical events were defined as death, MI, and minor or major amputation.

Statistical analysis

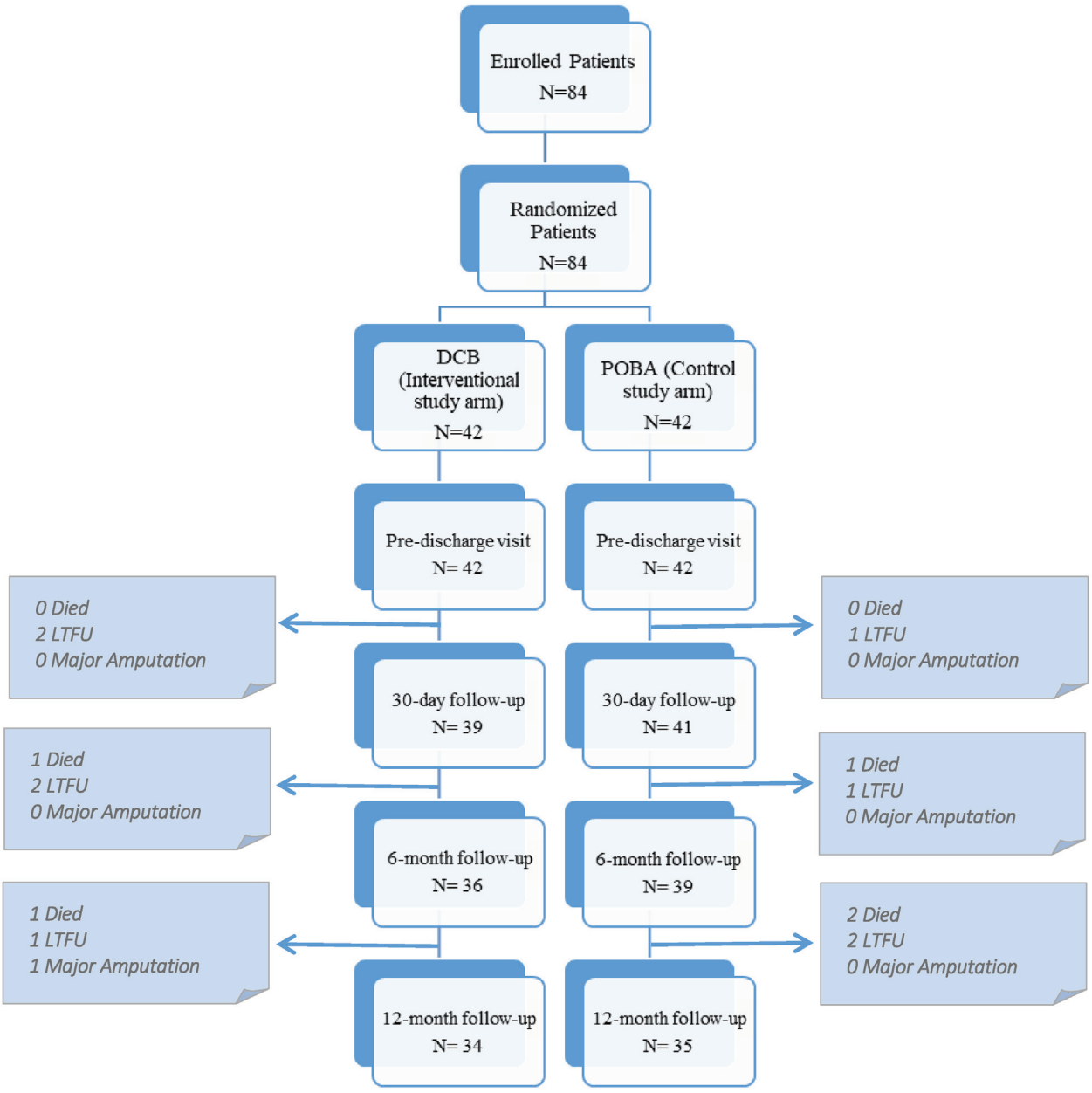
Statistical analysis was performed by using IBM SPSS statistics, version 22 for Windows program package (SPSS Inc., Chicago, Illinois, USA). Distribution of continuous variables is tested for normality by use of the one-sample Kolmogorov–Smirnov test. Continuous variables with normal distribution are expressed as mean ±SD and compared with the independent-samples *t*-test. For Rutherford stage, the change in class number between baseline and follow-up will be calculated for each patient at each office visit. To compare both treatment arms regarding the change, Cochran–Mantel–Haenszel statistics will be applied. Continuous variables with a skewed distribution are expressed as the median and compared with Mann–Whitney *U*-test. Categorical variables are compared with χ^2-test or Fisher's exact test. For all end points, the level of statistical significance was set at *P* value of less than 0.05.

Results

Patient, lesion, and procedural characteristics

Between January 2016 through December 2017, 84 consecutive adult diabetic patients with type 1 and 2 DM (42 in the DCB group and 42 in the POBA group) were enrolled at three centers in Saudi Arabia and two centers in Egypt. Patient flow through 12-month follow-up is shown in Fig. 5. The patient's characteristics, medical history, and medical intake are detailed in Table 1 and reflect a very sick patient population. Most characteristics were well matched between both study arms, except for incidence of cerebrovascular disease (17% POBA vs. 7% DCB, *P*=0.037). There were no significant differences in terms of lesion characteristics as shown in Table 2 between two study arms, neither did we note a difference in arterial calcification (62% for the POBA and 55% for the DCB group). Procedural data (Table 3) were likewise comparable across the two study arms, with the exception of a longer inflation time of the standard balloon in the POBA group (3.0

Figure 5



Patient consort diagram. DCB, drug-coated balloons; LTFU, lost to follow-up; POBA, plain old balloon angioplasty.

vs. 2.6 min, P=0.043). The technical success rate was 100% in both groups.

Safety and efficacy outcomes

There were no procedure-related or device-related deaths in either study arm. The 12-month adverse effects, in terms of all-cause death (N_3=7.1% POBA vs. N_2=4.8% DCB), minor amputation (N_5=12% POBA vs. N_4=9.5% DCB), major amputation (0% POBA vs. N_1=2.4% DCB), and MI (N_1=2.4% POBA vs. 0% DCB), were equal in both groups (P=713). Causes of mortality included MI, cerebral infarction, and sudden death.

Twelve-month duplex and angiographic follow-ups for the primary end points were available for 37 (88.1%) patients in the POBA study arm and 35 (83.3%) patients in the DCB study arm. The 12-month mean diameter restenosis was significantly lower in the DCB arm than in the POBA group (27.9±35.1 vs. 44.8±33.9%, P=0.034). Furthermore, analysis showed that the binary (≥50% diameter stenosis) restenosis rates were significantly lower in DCB patients as compared with the POBA (28 vs. 47%, P=0.029). The primary patency was significantly better in the paclitaxel-coated balloon group (71 vs. 49%, P=0.028) (Fig. 6). On the contrary, we noted that the rate of cdTLR was slightly higher in the POBA patients, though not statistically significant as compared with the paclitaxel-coated balloon group (28 vs. 20%, P=0.13). Figures 7 and 8 demonstrate the

Table 1 Patient characteristics

	POBA (*N*=42)	DBC (*N*=42)	*P* value
Age (years)	71±10	73±10	0.754
Male	27 (64)	29 (69)	0.537
Diabetes			0.371
Oral	21 (50)	20 (49)	
Insulin	19 (45)	22 (51)	
Juvenile	2 (5)	0	
Hypertension	37 (88)	38 (90)	0.921
Dyslipidemia	29 (69)	34 (81)	0.593
Smoking (h and c)	25 (59.5)	24 (57)	0.949
CAD	20 (47.6)	24 (57)	0.852
CVD	7 (17)	3 (7)	0.037*
CKD	15 (36%)	19 (45%)	0.258
BMI	22±4	28±4	0.781
Rutherford stage			0.836
3=Severe claudication	21 (50)	23 (55)	
4=Ischemic rest pain	2 (5)	3 (7)	
5=Minor tissue loss	19 (45)	16 (38)	
Medication intake			0.371
Antipl	37 (88.1)	36 (85.7)	
Antipl+oral AC	2 (4.8)	4 (9.5)	
Oral AC	3 (7.1)	2 (4.8)	

Values are expressed as mean±SD or *n* (%). AC, anticoagulants due to atrial fibrillation and rheumatic valvular heart disease; Antipl, antiplatelet; c, current; CAD, coronary artery diseases; CKD, chronic kidney disease (creatinine levels >1.5 and <2 mg/dl); CVD, cerebrovascular diseases; DCB, drug-coated balloon; h, history; POBA, plain old balloon angioplasty. *Statistically significant values.

Table 2 Lesion characteristics

	POBA (*N*=42)	DBC (*N*=42)	*P* value
De-novo lesions	38 (90.5)	36 (85.7)	0.899
Restenosis	4 (9.5)	6 (14.3)	
Arteries			0.798
SFA	31 (74)	29 (69)	0.783
PA	11 (26)	13 (31)	0.779
Average lesion length (cm)	7.6±5.2	7.7±5.8	0.90
Average vessel diameter (mm)	4.1±3.1	4.3±2.8	0.399
Lesion calcification			0.906
None	3 (7)	4 (9.5)	
Mild	13 (31)	15 (36)	
Moderate	11 (26)	10 (24)	
Severe	15 (36)	13 (31)	
Diameter stenosis (%)	88.4	89.6	0.699
Occlusions	13 (31)	10 (24)	0.296
Patent BTK arteries			0.893
1	11 (26)	14 (33)	
2	16 (38)	18 (43)	
3	15 (36)	10 (24)	

Values are expressed as mean±SD or *n* (%). BTK, below the knee; DCB, drug-coated balloon; PA, popliteal artery; POBA, plain old balloon angioplasty; SFA, superficial femoral artery.

distribution of the Rutherford stage before the angioplasty procedure and after 12-month follow-up. The clinical success rate was not different between both the groups (*P*=0.82).

Table 3 Procedural data

	POBA (*N*=42)	DBC (*N*=42)	*P* value
Ipsilateral approach	39 (93)	37 (88)	0.819
Cross-over approach	3 (7)	5 (12)	
Balloon size (mm)	5±3	5±3	0.762
Balloon length (mm)	74±43	86±33	0.146
Inflation pressure (atm.)	9±3	9±2	0.061
Inflation time (min)	3.0±1	2.6±1	0.043
Provisional stenting	9 (22)	7 (17)	0.191
Residual stenosis (%)	17±22	13±19	0.594
Fluoroscopy time (min)	7±2	8±3	0.684
Contrast volume (ml)	51±25	51±24	0.738
Closure			0.427
Manual	33 (78.6)	34 (83.3)	
Device	9 (21.4)	7 (16.7)	
Technical success	42 (100)	42 (100)	

Values are expressed as mean±SD or *n* (%). DCB, drug-coated balloon; POBA, plain old balloon angioplasty. provisional stenting was owing to either residual stenosis more than 30% or flow-limiting dissection.

Discussion

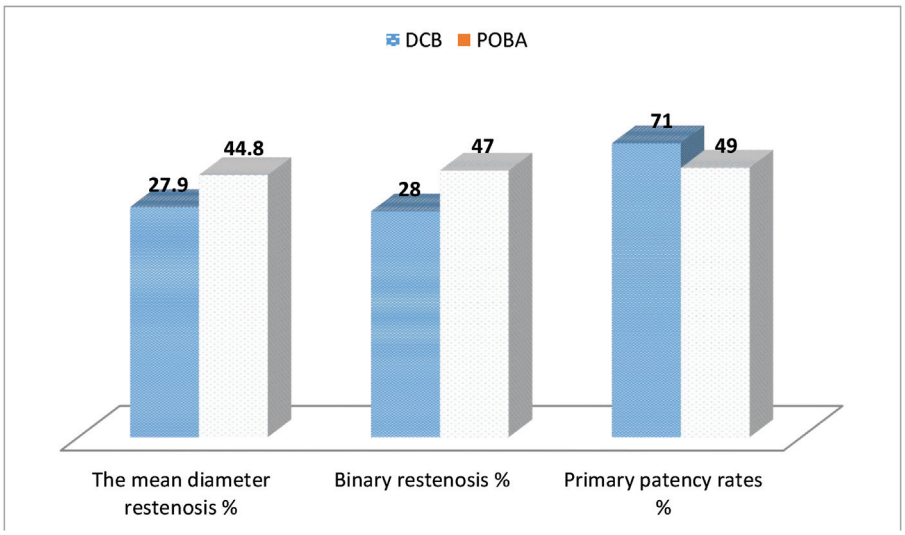
In our study, we evaluated the efficacy and safety of IN. PACT paclitaxel-coated balloon angioplasty versus POBA of symptomatic diabetic PAD of FPA segment. The salient findings were as follows:

(1) The primary patency and angiographic outcome of the target lesion at 12-month following treatment with DCB was significantly better compared with POBA.
(2) The rate of cdTLR was slightly higher in the POBA patients, though not statistically significant as compared with the paclitaxel-coated balloon group.
(3) The use of DCB was safe and did not increase the major adverse clinical events (death, MI, and minor or major amputation) when compared with those seen with the use of the uncoated balloons.

Early randomized trials showed favorable short-term, mid-term, and longer-term results with DCB angioplasty compared with POBA for symptomatic FPA disease [14–17]. The present study may be considered important for several reasons. First, this is one of the few trials up to date that focused on diabetic patients exclusively; none of those prior studies enrolled exclusively the diabetic patients and demonstrated an improved efficacy of paclitaxel in this particular patients' population. The DEBATE-ISR trial also studied diabetic patients but with femoropopliteal in-stent restenosis and concluded that DCB treatment led to a significant reduction of recurrent restenosis [21].

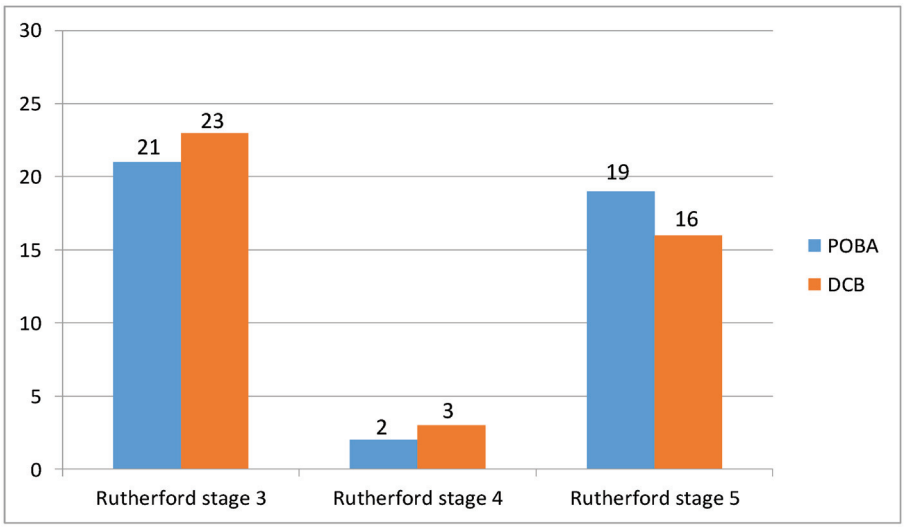
Second, in our study, we did not find a significant difference between both study arms in the cdTLR at

Figure 6



The mean diameter restenosis, the binary restenosis and the primary patency rates between the DCB and POBA study arm at 12 months. DCB, drug-coated balloons; POBA, plain old balloon angioplasty.

Figure 7

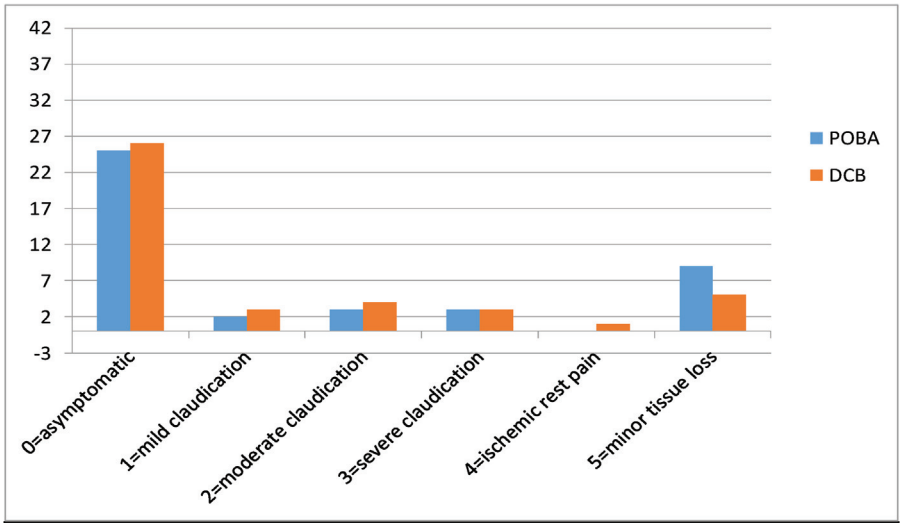


Distribution of Rutherford stage between the both study arms before angioplasty. DCB, drug-coated balloons; POBA, plain old balloon angioplasty.

12-month follow-up. This is in contrast to the results of other DCB trials in which TLR rates were significantly lower in the paclitaxel balloon arms [14,22].

The findings of a better primary patency but no difference in cdTLR can be explained by several contributing factors. First, the sample size was small, but we noted the trend toward a lower cdTLR rate in the DCB than POBA (28 vs. 20%, P=0.13) but might have been statistically significant if more patients have been enrolled. Second, the healing response after arterial injury begins immediately after the angioplasty and may last for weeks or months, after that the cytotoxic drug paclitaxel has accomplished its action in the wall of the targeted artery. Third, diabetic foot wounds are notoriously intractable to heal, and patency loss may be only one of different contributing factors: infection and neuropathy may lead to the loss of protective sensation, in addition to the degeneration of sympathetic innervation of arteriovenous shunts, bone or tendon exposure, and persistent pressure or friction; this is another critical factor that may hinder wound healing and significantly affect the incidence of lesions and major amputations in diabetic patients. The correlation between nonhealing and patency loss therefore may be weaker than in the nondiabetic population (that present with fewer neuropathy and

Figure 8



Distribution of Rutherford stage between the both study arms at 12-month follow-up. DCB, drug-coated balloons; POBA, plain old balloon angioplasty.

infection). Finally, the outflow of BTK-arteries (occlusive disease in the pedal arteries) was not assessed in our study. Our results are also consistent with the LEVANT II trial – a single-blind, randomized trial of 476 patients compared that Lutonix DCB-angioplasty (Bard Peripheral Vascular) with POBA-angioplasty for PAD – which also failed to demonstrate a significant difference in the clinically improvement end points of TLR at 12 months [14].

Our study demonstrated that the IN.PACT DCB is superior to POBA in terms of primary patency in diabetic patients with PAD Rutherford stage 3, 4, and 5 with short (>10 cm) SFA occlusions or less than 15 cm stenotic lesions of the SFA and PA. We did not include longer occlusive lesions as it is difficult to control the loss of the drug from the balloon while observing the balloon reaching the target lesion and inflating there; in addition, while treating long lesions, inadequacies relating to carriers may make the drug level in the vessel wall at a subtherapeutic level, which is why DEB may not attain their expected primary patency rates [23,24].

The concept of DCB technology is based on the combination of conventional angioplasty and local drug delivery in the vessel wall, designed to inhibit neointimal formation. All currently available DCBs carried paclitaxel as a cytotoxic agent. The difference between the balloons lies in the dose of paclitaxel drug delivery ranging from 2 to 3.5 $\mu g/mm^2$ and in the coating technology. The carrier or excipient is a hydrophilic spacer capable of delivering the lipophilic (hydrophobic) molecules of paclitaxel into the vessel wall. Various coating technologies are currently available including iopromide, urea, polisorbate, shellac, and butyryl trihexyl citrate.

The results of our study are promising but do not provide definitive guidelines in managing diabetic PAD. We do agree that the studied patients' group was relatively small. Several trials have shown that after balloon angioplasty, restenosis occurs in ~50% of cases within the first 6 months. The justification for this is that during this period the paclitaxel has to do its job (to inhibit the endothelial cell cycle in the M phase of the mitotic cycle). The IN.PACT SFA [14], the LEVANT [17], and the debate-ISR [21] trials have shown that the benefit of paclitaxel occurs during the first months after angioplasty. The Kaplan–Meier curves showed significant better results at 6-month follow-up; after this period, the curves of DCB and POBA are approximately parallel. Furthermore, we studied a very sick diabetic patient population exclusively with high incidence of chronic kidney disease. Longer and repeatedly angiographic follow-up would be hazardous for worsening of the grade of the diabetic nephropathy. DCB randomized trials of diabetic patients with inclusion of the below the knee arteries with larger sample size and with a longer follow-up period are necessary to (dis)prove our results.

Limitations of the study

The study was limited by a small sample size, and the trial protocol did not provide uniform guidelines for amputation or tools for wound care. Another limitation of our study is that not all patients had follow-up angiography.

Conclusion

DCBs can be safely used in the treatment of diabetic patients with FPA disease. Moreover, treatment with IN.PACT paclitaxel-coated balloon angioplasty provides a better primary patency rate compared with POBA at 12 months. DCB showed no clinical benefit over POBA at this 12-month follow-up period. The number of major adverse clinical events was comparable between DCB and POBA groups of patients.

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Conflicts of interest

There are no conflicts of interest.

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