Drug-coated vs uncoated balloon angioplasty in the treatment of femoropopliteal arterial lesions

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Background
Inspite of immediate technical success, neointimal hyperplasia and restenosis remain the Achilles heel of endovascular interventions. Drug-coated balloons (DCBs) have shown promising outcomes regarding anti-restenotic efficacy in management of femoro-popliteal arterial lesions compared to uncoated balloon.
Objectives
To evaluate the efficacy of the paclitaxel-coated balloon versus uncoated balloon angioplasty in treatment of femoropopliteal lesions regarding primary patency and restenosis at 12 months.
Patients and Methods
Between Sept 2017 and Sept 2019, this prospective randomized study was performed at Menoufia University hospitals. Sixty patients suffering symptomatic lower limb ischemia (Rutherford category 3 to 5) were randomly assigned into group A (30 patients) that were treated by DCB angioplasty, and group B (30 patients) that were treated by uncoated balloon (UCB) angioplasty. The primary patency, mean diameter restenosis, and binary restenosis (≥50% diameter stenosis) of the treated lesions at 12 months were collected and analyzed.
Results
Baseline characteristics were comparable in both groups. The 12-month mean diameter restenosis was significantly lower in DCB group than UCB group (27.8 ±35.2% vs. 44.9±33.8% respectively, $P<0.001$). Furthermore, the binary restenosis rates was significantly lower in DCB patients as compared with the UCB's (27% vs. 46% respectively, $P<0.001$). The primary patency was significantly better in DCB group (70% vs. 48% respectively, $P<0.001$). There were no procedure-related deaths in either study group.
Conclusions
Treatment of symptomatic femoro-popliteal disease with paclitaxel coated balloon angioplasty is associated with superior anti-restenotic efficacy that provides a better primary patency rate compared to uncoated balloon angioplasty at 12 months.

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

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Introduction

Atherosclerotic peripheral artery disease (PAD) affects a large number of patients in the aging Western populations [1]. It is highly associated with cardiovascular mortality and morbidity. Smoking cessation, lifestyle modification, control of risk factors, and medical treatment are well-established treatment regimens [2].

PAD results in decreased quality of life and reduced functional independence, so either surgical or endovascular revascularization often becomes necessary to restore the blood flow to the ischemic limb [3]. Revascularization by means of angioplasty has become the first line of treatment for critical limb ischemia with results similar to surgery in terms of limb salvage and patency; however, restenosis remains a challenge, particularly in the treatment of femoropopliteal lesions [4].

Paclitaxel, as one of antiproliferative agents, delivered into the vessel wall by drug-coated balloons (DCB) or drug-eluting stents inhibits restenosis and improves patency in the infrainguinal arteries compared with uncoated balloon angioplasty alone. DCB and drug-eluting stent strategies are both currently being investigated to optimize interventional treatment of infrainguinal atherosclerotic lesions [5]. The anatomic site of the lesion, its extent, and metabolic factors (e.g. calcification and presence of diabetes) affect outcomes of interventional management and may affect the success of different drug strategies [6].

In many studies of femoropopliteal disease, DCBs were generally used in focal or short lesions, whereas long, complex, or severely calcified lesions were excluded to prevent primary angioplasty failure [7]. Preclinical and initial DCB studies have highlighted the importance of paclitaxel and excipient formulation for rapid drug delivery into the vessel wall during balloon inflation. The TransPax coating of the Ranger Paclitaxel-Coated Balloon Catheter includes a novel citric ester excipient intended to optimize paclitaxel microcrystallinity to increase drug transfer to the arterial wall and sustain therapeutic drug tissue levels [8].

However, it remains a matter of some debate whether the use of DCB for femoropopliteal arterial lesions can lower the risk of reinterventions. Indeed, any such benefit may have considerable implication for the costs associated with PAD and its complications [9].

Patients and methods

A prospective, randomized, controlled study was done between September 2017 and September 2019 at Menoufia University Hospitals on 60 patients with symptomatic lower limb ischemia and superficial femoral artery (SFA) and/or proximal popliteal lesions objectively confirmed by computed tomography (CT) angiography.

Patients with symptomatic limb ischemia defined as Rutherford category 3–5 (3=severe claudication, 4=ischemic rest pain, or 5=minor tissue loss), *de novo* or restenotic femoral or proximal popliteal lesion (2–15 cm in length) and have at least one infrapopliteal artery with good run-off (<50% stenosis) to the foot were included in the study, whereas those with previous surgery in the target vessel, major amputation in the target limb, and known hypersensitivity or contraindication to contrast dye (renal insufficiency with serum creatinine >2.0 mg/dl), paclitaxel, or other components of the used medical devices were excluded from the study.

The patients were randomly categorized into two groups: group A (30 patients), which was treated by DCB angioplasty, and group B (30 patients), which was treated by uncoated balloon angioplasty. Written informed consent about the two techniques' benefits, risks, alternative interventions, and possible complications was obtained from all patients to be included in this study. This study was accepted and approved by an Ethical Committee.

All interventions were done in the angio suite (Allura X per FD 20/722028164; Philips, Philips North America Corp, Andover, Boston, USA), C-arm image intensifier with road mapping was used. Patients were placed in supine position. Both groins were prepared using antiseptic solution povidone iodine (7.5%). All interventions were done under local anesthesia (xylocaine 2%). Saline 0.9%/heparin (500 ml saline+5000 IU heparin) was used to flush all the catheters and angioplasty site all through the procedure.

The arterial access was planned after reviewing of the preoperative imaging through either antegrade ipsilateral common femoral artery puncture or contralateral femoral puncture and performing a crossover approach. After gaining access, Terumo 6 Fr×10 cm length sheath was inserted, and free arterial flow is allowed to confirm the right position of the sheath. Sheath insertion is followed by intravenous administration of 5000 IU of unfractionated heparin to maintain activated clotting time greater than or equal to 200 s. Angiography is done to confirm data obtained by preoperative investigations using nonionic low osmolar dye diluted to 50% with normal saline. Crossing the lesion was done by different techniques and equipment individualized to each case, but the standard tools for recanalization of stenosis and occlusions consist of a 0.035 hydrophilic guide wire and an angled-tip catheter (4 or 5 F Bernstein). Once the lesion has been crossed, the catheter should be advanced beyond the lesion, the wire removed, and contrast was injected to ensure that the catheter was within the lumen. Then balloon catheter, selected for appropriate diameter (4–6 mm) and length, was advanced over the wire to the distal extent of the lesion. The balloon was inflated until any waist on the balloon has been abolished.

During balloon inflation, assessment of the roadmap image should confirm that the balloon catheter was appropriately sized. If there was excessive pain or the balloon looks too big, the balloon was exchanged for a smaller diameter balloon. After balloon deflation, the balloon catheter was withdrawn slightly and the balloon catheter should be re-inflated with overlaps until the whole lesion had been covered. The balloon catheter was withdrawn completely, while keeping the guide wire in place across the lesion to allow re-insertion of the DCB.

Angiography to assess the result was performed by injecting contrast medium through the side arm of the sheath. There should be rapid forward flow through

the treated segment, with no residual stenosis greater than 30%. If there was residual stenosis, the balloon catheter should be re-inserted and re-inflated at the site of stenosis.

The IN.PACT over-the-wire balloon paclitaxel-eluting, dilatation catheters (Invatec-Medtronic, Brescia, Italy) were used in patients of group A. The specific balloon catheters were available at a maximum diameter of 7 mm and a maximum length of 150 mm for diameter 5 and 6 mm arteries, whereas the dose of paclitaxel on the balloon's surface was 3 μg/mm^2. Patients in group B (UCB group) underwent angioplasty with a variety of high-pressure balloon catheters brands.

The run-off was assessed at the end of the procedure for the occurrence of distal embolization caused by the PTA. Lastly, PTA of any relevant tibial lesions is performed during the same procedure.

Postprocedure care

Most patients were discharged on the second day following the procedure after receiving instructions on risk factor control (stop smoking, lipid-lowering agent, and diet) and treatment, including acetylsalicylic acid (Aspirin) 150 mg/day for life, clopidogrel (Plavix) 75 mg/day for 6 months, and atorvastatin (Ator) 40 mg/day. The patients received foot care consisting of wound dressing, minor debridement, limited amputations (up to transmetatarsal amputation), infection control, and appropriate foot wear before discharge.

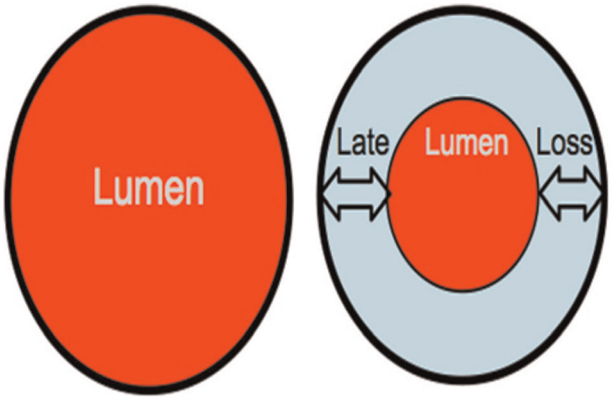
Follow-up

The enrolled patients were clinically evaluated before discharge and then at 1, 6, and 12 months after the procedure, and their ABI and Rutherford classification were reassessed. The patency of the treated arterial segment was assessed by duplex ultrasonography for the SFA and proximal popliteal, and by computed tomography or conventional angiography for distal popliteal artery.

Study end points and definitions

Late lumen loss (LLL) is used 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 target lesion revascularization (TLR) occurrence. TLR is defined as a clinically driven repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

Figure 1



Late lumen loss.

The primary end points of the study were primary patency, mean diameter restenosis, and binary restenosis. Primary patency was defined as the absence of duplex identified restenosis, TLR, or bypass of the target lesion. Binary restenosis was defined as the recurrence of greater than or equal to 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 greater than or equal to 2.5 suggesting a greater than or equal to 50% reduction in luminal diameter. The patency of popliteal artery was assessed by CT or conventional angiography and considered lost if the treated segment appeared occluded or showed a greater than or equal to 50% reduction in the luminal diameter.

The secondary end point was the clinically driven target lesion revascularization (cdTLR) rate at 12 months. A re-intervention was done in case of greater than or equal to 50% diameter stenosis (confirmed by duplex ultrasonography, CT or conventional angiography) within ±5 mm proximal and/or distal to the target lesion after documentation of recurrent clinical symptoms. Clinical success was defined as an improvement of baseline symptoms by at least 1 Rutherford stage that was sustained through follow-up, with no additional intervention, and hemodynamic success was defined as a positive change in ABI of at least 0.1. Major adverse clinical events were defined as death, myocardial infarction (MI), and minor or major amputation.

Statistical analysis and data interpretation

Statistical analysis and data interpretation: Data were fed to the computer and analyzed using IBM SPSS software package version 22.0 (IBM Corp., Armonk, New York, USA). Qualitative data were described using number and percentage. Quantitative data were described using mean and SD for parametric data after testing normality using Kolmogrov–Smirnov test. Significance of the obtained results was judged at the (0.05) level.

Data analysis

Qualitative data

(1) χ^2-test for comparison of two or more groups.
(2) Fischer's exact test was used as correction for χ^2-test when more than 25% of cells have count less than 5 in 2×2 tables.

Quantitative data between groups:

Parametric tests

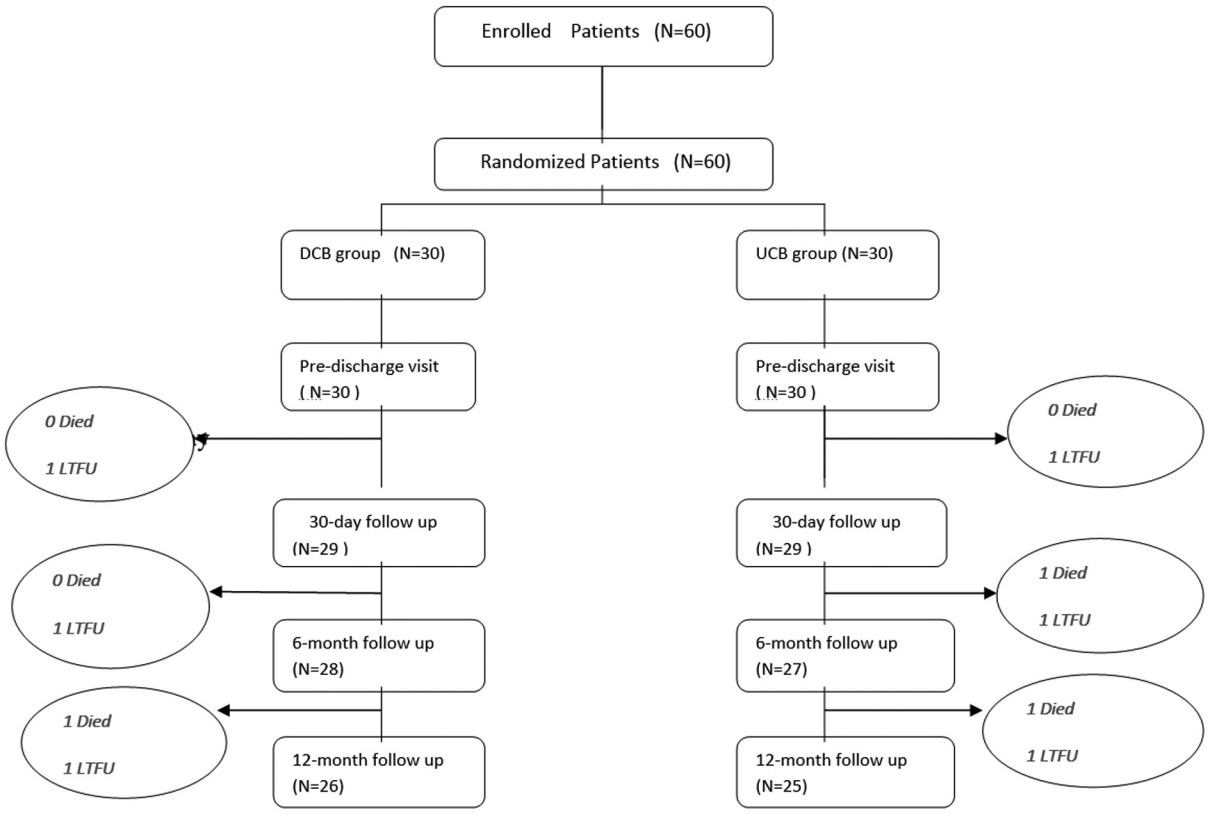
(1) Student's *t*-test was used to compare two independent groups.
(2) Paired *t*-test was used to compare two periods in same group.

Results

Between September 2017 and September 2019, 60 consecutive adult patients underwent treatment for symptomatic lower limb ischemia and were enrolled in the study. Thirty patients were treated with DCB angioplasty (group A) and 30 treated with uncoated balloon angioplasty (UCB) (group B). Patient flow through 12-month follow-up is shown in Fig. 2. The mean age of the patients was 73±10 and 71±10 years for groups A and B, respectively, with no statistically significant difference (*P*=0.75) (Table 1). Male to female ratio was 1.7 : 1 and 2.3 : 1 for groups A and B, respectively, with no statistically significant difference (*P*=0.53) (Table 1). There was no statistically significant difference between both groups regarding risk factors and associated comorbidities except for incidence of cerebrovascular disease (6.5% in group A vs 16.5% in group B; *P*=0.036) (Table 2). Lesion characteristics and procedural data were likewise comparable across both study groups (Tables 3 and 4). The immediate technical success rate was 100% in both groups.

Twelve-month duplex and angiographic follow-up for the primary end points were available for 26 (86.7%)

Figure 2



Patient flow diagram. DCB, drug-coated balloon; UCB, uncoated balloon angioplasty; LTFU, lost to follow-up.

Table 1 Patients' demographic data

	Group A: DCB (*no*=30)	Group B: UCB (*n*=30)	*P* value
Age (years)	73.4±6.8	72.89±4.5	0.77
Sex			
Females	11 (37)	9 (30)	χ^2=0.30
Males	19 (63)	21 (70)	*P*=0.58

Values are mean±SD or in *n* (%). DCB, drug-coated balloon; UCB, uncoated balloon angioplasty.

Table 2 Risk factors and co-morbidities of the studied patients

	Group A: DCB	Group B: UCB	*P* value
Diabetes	12 (40)	10 (33.5)	χ^2=0.28, *P*=0.59
Hypertension	27 (90)	26 (86.5)	FET, *P*=1.0
Hyperlipidemia	24 (80)	20 (66.5)	χ^2=1.36, *P*=0.24
Smoking (h and c)	17 (56.5)	18 (60)	χ^2=0.07, *P*=0.79
CAD	17 (56.5)	14 (46.5)	χ^2=0.60, *P*=0.44

Values are represented in *n* (%). c, current; CAD, coronary artery diseases; DCB, drug-coated balloon; FET, Fischer's exact test; h, history; UCB, uncoated balloon angioplasty.

Table 3 Lesion characteristics

	Group A: DCB	Group B: UCB	*P* value
De-novo lesions	25 (83.3)	27 (90)	χ^2=0.57, *P*=0.45
Restenosis	5 (16.7)	3 (10)	
SFA	21 (70)	22 (73.3)	χ^2=0.08, *P*=0.77
PA	9 (30)	8 (26.7)	
Average lesion length (cm)	7.7±5.8	7.6±5.2	*t*=0.07, *P*=0.94
Average diameter (mm)	4.3±2.8	4.1±3.1	*t*=0.26, *P*=0.79
TASC II classification			
A	20 (67)	19 (63.5)	χ^2=0.07, *P*=0.79
B	6 (20)	7 (23.5)	χ^2=0.09, *P*=0.75
C	4 (13)	4 (13)	FET, *P*=1.0
Diameter stenosis (mean±SD)	89.6±10.2	86.3±9.7	*t*=3.3, *P*=0.20
Occlusions	7 (23.3)	9 (30)	χ^2=0.34, *P*=0.56
Patent BTK arteries			
1	10 (33.3)	8 (26.6)	χ^2=0.32, *P*=0.57
2	13 (43.3)	11 (36.7)	χ^2=0.28, *P*=0.59
3	7 (23.4)	11 (36.7)	χ^2=1.27, *P*=0.26

Values are represented in *n* (%). BTK, below the knee; DCB, drug-coated balloon; FET, Fischer's exact test; PA, popliteal artery; SFA, superficial femoral artery; UCB, uncoated balloon angioplasty.

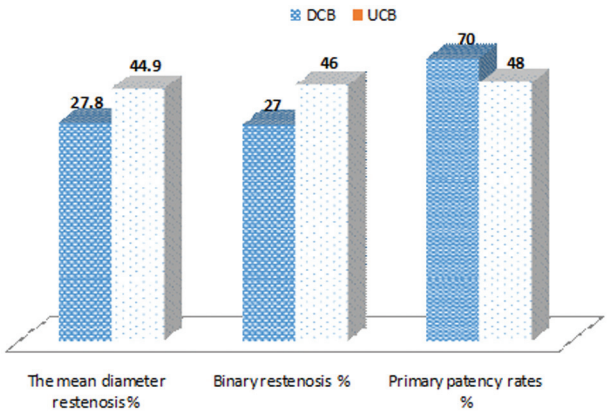
Table 4 Procedural data

	Group A (DCB)	Group B (UCB)	*P* value
Ipsilateral approach	26 (86.7)	28 (93.3)	FET, *P*=0.67
Crossover approach	4 (13.3)	2 (6.7)	
Balloon size (mm)	5.34±3.1	5.44±2.99	*t*=0.13, *P*=0.89
Balloon length (mm)	86±33	74±43	*t*=1.21, *P*=0.23
Inflation pressure (atm)	9.1±2.04	9.3±3.1	*t*=0.29, *P*=0.77
Residual stenosis	13±4.2	17±2.2	*t*=4.62, *P*=0.001*
Fluoroscopy time (min)	8±3	7±2	*t*=1.52, *P*=0.13
Contrast volume (ml)	51±24	51±25	*t*=0.0, *P*=1.0
Technical success	30 (100)	30 (100)	–

DCB, drug-coated balloon; FET, Fischer's exact test; UCB, uncoated balloon angioplasty. *Statistically significant (if $P<0.05$).

patients in group A and 25 (83.3%) patients in group B. The 12-month mean diameter restenosis was significantly lower in group A compared with group B (27.8±35.2 vs 44.9±33.8%, respectively; $P<0.001$). Furthermore, analysis showed that the binary restenosis rates (≥50% diameter stenosis) was significantly lower in group A compared with group B (27 vs 46%, respectively; $P<0.001$) (Fig. 3). The

Figure 3



The mean diameter restenosis, the binary restenosis, and the primary patency rates between the drug-coated balloon and uncoated balloon angioplasty study arm at 12 months.

Table 5 Primary patency, mean diameter stenosis, and clinically driven target lesion revascularization of both groups

	DCB group	UCB group	Tests of significance
Mean diameter restenosis	27.8±3.2	44.9±3.8	t=18.85 P<0.001*
The primary patency	70±5.7	48±3.6	t=17.87 P<0.001*
Clinically driven TLR	6 (20)	8 (27)	χ^2=0.37 P=0.54

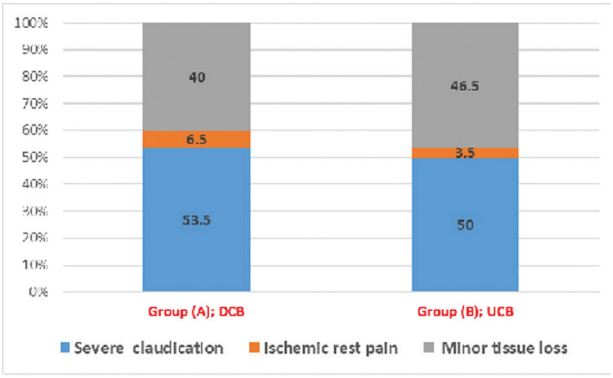
DCB, DCB, drug-coated balloon; FET, Fischer's exact test; TLR, target lesion revascularization; UCB, uncoated balloon angioplasty. *Statistically significant (if P<0.05).

12-month primary patency was significantly better in group A than group B (70 vs 48%, respectively; P<0.001). On the contrary, we noted that the rate of cdTLR was slightly higher in group B patients; however, not statistically significant as compared with group A (27 vs 20%, respectively; P=0.54) (Table 5 and Fig. 3).

After 12 months, a significant improvement in distribution across Rutherford categories was observed in both Ranger DCB and control groups (P<0.001 for each group). For the DCB group, most participants presented with no or mild symptoms at 12-month follow-up (60% had symptoms classified as Rutherford category 0 and 6.5% were classified as category 1). The difference between the groups was not statistically significant (P=0.635) (Figs 4 and 5).

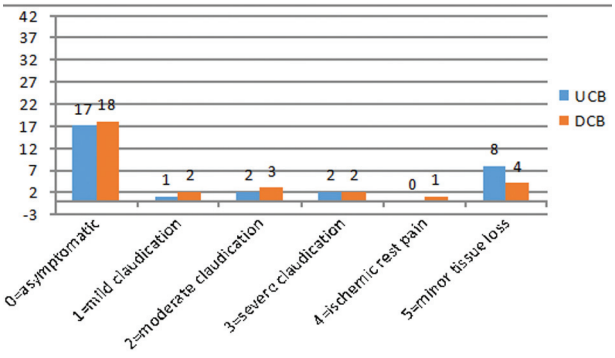
The preintervention mean ABI was 0.34±0.16 and 0.25 ±0.17 for group A and group B, respectively. ABI measurements were improved significantly over baseline in both groups at 12 months (P<0.001 for each group), but the difference between both groups was not statistically significant (ABI was 0.95±0.15 and 0.94±0.21 for groups A and B, respectively; paired

Figure 4



Distribution of Rutherford stage between both study groups before angioplasty.

Figure 5



Distribution of Rutherford stage between both study groups at 12-month follow-up.

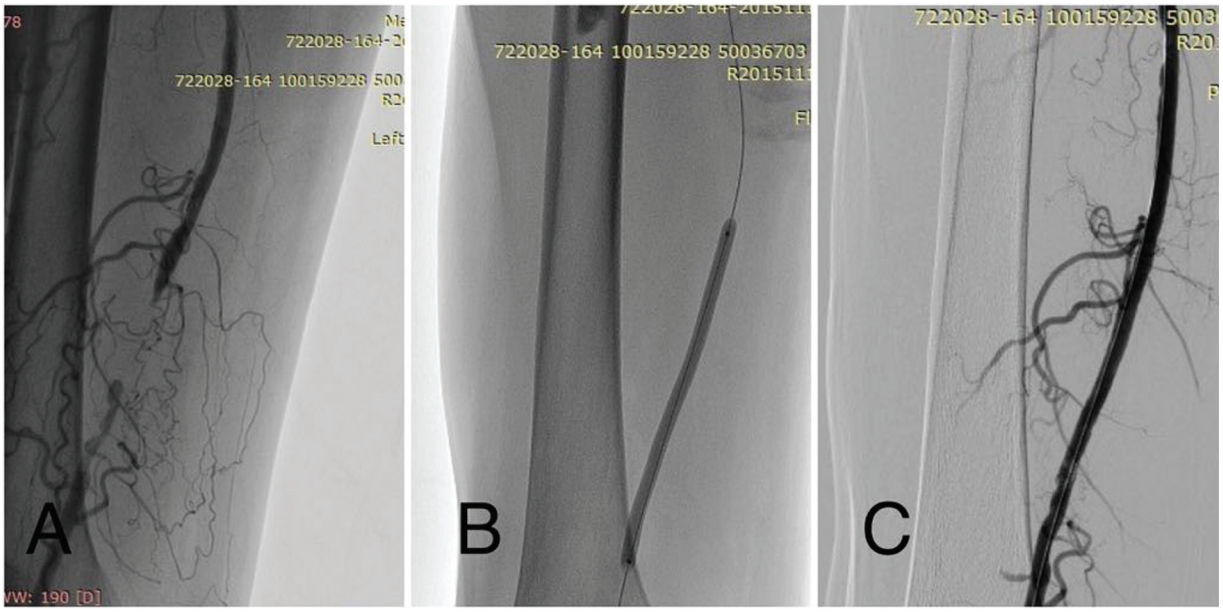
t-test=0.21, P=0.83). There were no procedure-related or device-related deaths in either study group. The 12-month adverse effects were as follows: death occurred in one (3.3%) patient in group A vs two (6.7%) patients in group B, minor amputation occurred in three (10%) patients in group A vs four (13.3%) patients in group B, and MI occurred in only one patient in group B (Figs 6–8).

Discussion

Lower extremity PAD affects 5–18% of the population in the USA, with expected increase in the prevalence as atherosclerotic risk factors become more prevalent and the treatments for chronic diseases become more sophisticated [1]. Atherosclerotic stenosis and occlusion of the SFA are common patterns of arterial disease in patients with claudication and limb-threatening ischemia [10].

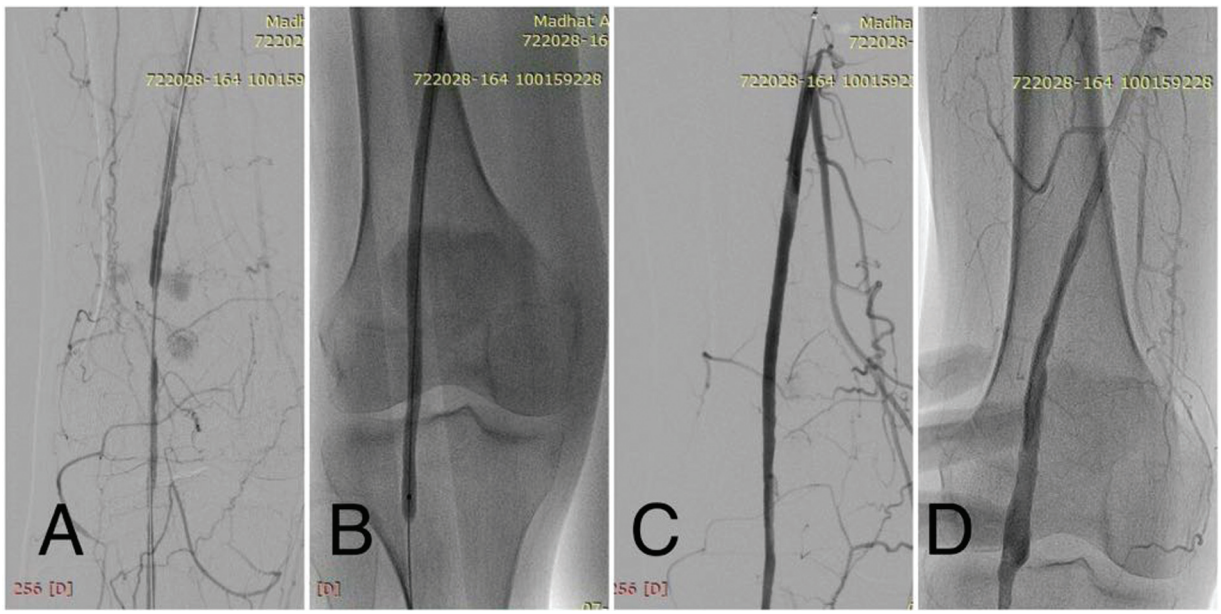
Over the past decades, endovascular repair has become the preferred treatment for femoral arterial obstructive

Figure 6



(a) Distal superficial femoral artery segmental occlusion; (b) full inflation of IN.PACT balloon; and (c) no residual postangioplasty dissection or stenosis.

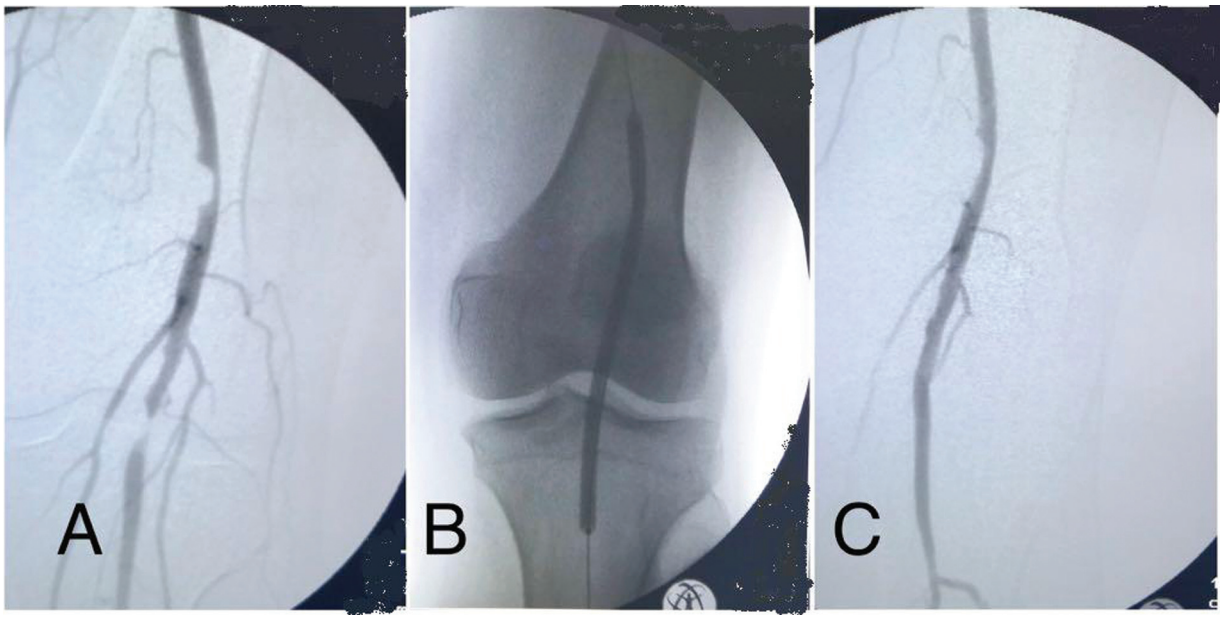
Figure 7



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

disease. No definitive consensus has emerged concerning the best endovascular strategy, like the added value of stenting [11]. The past decade has welcomed a greater understanding of PAD, the continued refinement of endovascular techniques, and the evolution of technology with the associated vicissitude of new angioplasty balloons, stent designs, and delivery systems for the revascularization of patients with PAD. The advancements in catheter-based technologies and the accretion of advanced antegrade, brachial, tibial, pedal, and digital access have greatly increased the treatment options for patients with peripheral vascular disease and have led to increase in the number of endovascular procedures performed annually [12]. Despite enhanced immediate technical success, neointimal hyperplasia, stent fracture, and restenosis remain the Achilles' heel of endovascular interventions [13].

Figure 8



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

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 carry paclitaxel as a cytotoxic agent. The difference between the balloons lies in the dose of paclitaxel drug delivery, ranging from 2 to 3.5 μg/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, polysorbate, shellac, and butyryl trihexyl citrate [7,8].

We tried to assess the efficacy and safety of IN.PACT paclitaxel-coated balloon angioplasty vs UCB for symptomatic femoropopliteal arterial disease. We found that 12-month primary patency and angiographic outcome of the target lesion were significantly better with DCB group compared with UCB group, and the rate of cdTLR was slightly higher in the UCB patients, however, not statistically significant as compared with DCB group. The use of DCB was safe and did not increase the major adverse clinical events such as death, MI, and minor or major amputation when compared with those seen with the use of the uncoated balloons.

We did not find a statistically significant difference between both groups regarding the clinically driven target lesion revascularization at 12-month follow-up (27 vs 20% for UCB and DCB, respectively (P=0.12), and this did not match with the results of other DCB trials in which target lesion revascularization rate was significantly lower in the paclitaxel balloon groups [14–16].

The findings of a better primary patency but no significant difference in cdTLR at 12 months between both groups in our study can be explained by several factors. First, the sample size was small, but we noted a lower cdTLR rate in the DCB compared with UCB, which might have been statistically significant if more patients have been enrolled. Second, the healing response after angioplasty begins immediately after the angioplasty and may last for weeks or months, after the cytotoxic drug paclitaxel has accomplished its action on the wall of the targeted artery. Third, there are different contributing factors other than lumen patency that may affect healing of diabetic foot wounds, such as infection, neuropathy that lead to the loss of protective sensation, the degeneration of sympathetic innervation of arteriovenous shunts, bone or tendon exposure, persistent pressure, or friction. Finally, the outflow of below-knee arteries (occlusive disease in the pedal arteries) was not assessed in our study. These results are consistent with the LEVANT II trial (a single-blind, randomized trial of 476 patients compared Lutonix DCB (Bard PV, Tempe, Arizona, USA) with UCB angioplasty for PAD that also failed to demonstrate a significant difference in the clinically improvement end

points of target lesion revascularization at 12 months [14].Several trials have shown that after balloon angioplasty, restenosis occurs in ~50% of cases within the first 6 months. The explanation 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). Many 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 UCB are approximately parallel [6,17].

Our study demonstrated that the IN.PACT DCB is superior to UCB in terms of primary patency in patients with PAD Rutherford stage 3, 4, and 5 with short SFA occlusions (>10 cm) or stenotic lesions of the SFA and popliteal artery (>15 cm), and this matches with many studies. We did not include longer occlusive lesions as it is difficult to control the release of the drug from the balloon while observing the balloon reaching the target lesion and inflating there, added to that while treating long lesions, inadequacies relating to carriers may make the drug level in the vessel wall at a subtherapeutic level, which is why DCB may not attain their expected primary patency rates [18,19].

The results of our study are promising but do not provide definitive guidelines in managing PAD. We do agree that the studied patients' groups were relatively small. 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 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.

Conclusion

DCBs can be safely used in the treatment of patients with symptomatic femoropopliteal disease. IN.PACT paclitaxel-coated balloons effectively inhibit restenosis and provide a better primary patency rate compared with standard UCBs at 12 months. DCB showed no clinical benefit over UCB at this 12-month follow-up period.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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