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Shady Hesham Ahmed Abd Elmohty
Department of Vascular and Endovascular Surgery Faculty of Medicine - Al-Azhar University in cairo , Egypt, shiko2016nono@gmail.com

Omar Mokhtar Ibrahim
Department of Vascular and Endovascular Surgery Faculty of Medicine - Al-Azhar University in cairo , Egypt

Mohamed Hamza Hamed
Department of Vascular and Endovascular Surgery Faculty of Medicine - Al-Azhar University in cairo , Egypt

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ORIGINAL ARTICLE

Drug-Coated Balloon versus Plain Balloon Angioplasty for Infrapopliteal Lesions in Patients with Critical Limb Ischemia

Shady Hesham Ahmed Abd Elmohty [a,*], Omar Mokhtar Ibrahim [a], Mohamed Hamza Hamed [b]

[a] Department of Vascular and Endovascular Surgery, Egypt
[b] Faculty of Medicine, Al-Azhar University, Cairo, Egypt

Abstract

Background: **Peripheral ischemia of the lower extremity is a condition that is prevalent worldwide and that is likely to increase with age. The increased prevalence of diabetes mellitus and hypertension in the population leads to increased proportion of peripheral arterial disease (PAD). The objective of this study is to compare the effects of paclitaxel-eluting balloon (PEB) and plain balloon (PB) angioplasty patency rate and efficacy in patients with critical infrapopliteal ischemic lesions.**

Materials and methods: **This randomized controlled trial followed, for 12 months, fifty patients with atherosclerotic disease of the infrapopliteal limb lesions, ischemic ulcer, tissue loss, and rest pain. Patients were categorized into groups A and B: group A received paclitaxel-eluting balloon angioplasty and group B received plain balloon angioplasty. An ipsilateral approach was used for stenotic lesion. This trial had been undergone at Al-Azhar University Hospitals. It lasted from May 2021 to May 2023.**

Results: **Paclitaxel-eluting balloon group showed a statistically marked decrease of restenosis compared with plain balloon at 12 months post treatment (*P*-value <0.05). However, there was no between-group difference post treatment in limb salvage rate, clinical improvement, and complete wound healing (*P*-value >0.05).**

Conclusion: **Angioplasty with balloon that is coated with paclitaxel drug decreases restenosis more than balloon that is uncoated in patients with critical infrapopliteal ischemic lesions.**

Keywords: Drug-coated balloon, Infrapopliteal lesions, Plain balloon angioplasty

1. Introduction

Peripheral artery disease (PAD) highest serious form is critical limb ischemia (CLI). The CLI is characterized by tissue loss and ischemic rest discomfort. It typically affects multiple levels of arteries, primarily the infrapopliteal arteries. Most CLI patients also have diabetes and other cardiovascular problems, which negatively reinforce one another.[1]

Obesity, sedentary lifestyle, and diabetes, as well as rising life expectancy, are likely to cause these estimations of CLI to rise up to 3 % in patients with PAD.[2]

When saving a limb is conceivable, guidelines call for infrapopliteal revascularization; cases of brief occlusions, stenosis, or who are at increased likelihood of open surgery should also take into account endovascular therapy.[1]

Paclitaxel-eluting balloons (PEBs) are currently being used to promote limb preservation, minimize artery restenosis, and maybe facilitate sustained wound healing.[3]

Drug-coated balloons (DCBs) that elute paclitaxel have showed potential in the treatment of PAD. Due to its lipophilic nature, the antiproliferative drug paclitaxel is a proven choice for this application. During DCB angioplasty, paclitaxel is injected into

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* Corresponding author at: Department of Vascular and Endovascular Surgery, Faculty of Medicine, Al-Azhar University, Cairo 11884, Egypt.
E-mail address: shiko2016nono@gmail.com (S.H.A.A. Elmohty).

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the vessel wall in combination with an excipient (carrier) molecule.[4]

This work aims to compare the effects of paclitaxel-eluting and plain balloon angioplasty on patency rate and efficacy in patients with 'infra popliteal arterial lesions' from 'critical limb ischemia'.

2. Patients and methods

2.1. Patients

The study design was a 'randomized controlled trial'. It was undergone at Al-Azhar University – vascular surgery department. It included 50 patients suffering from infrapopliteal limb ischemic lesions in the form of ischemic ulcer, tissue loss, and rest pain. Patients were categorized into groups A and B: group-A patients received angioplasty with balloon eluted with paclitaxel drug and group-B patients received angioplasty with plain balloon. An ipsilateral approach was used for stenotic lesion.

2.2. Inclusion criteria

Symptomatic, atherosclerotic lesion of the infrapopliteal occlusion in the form of ischemic ulcer, tissue loss and rest pain, and patency of suprageniculer arterial lesions (iliac and common femoral artery, superficial femoral artery).

2.3. Exclusion criteria

Acute limb ischemia, abdominal aortic occlusion or aneurysm, combined multilevel lesions, prior surgery in the site, severe renal impairment, inability or unwillingness to complete the follow-up schedule, pregnancy, or breastfeeding are all risk factors for metastatic cancer.

This study was approved by Ethical Research Board of the Faculty of Medicine, Al-Azhar University.

2.4. Methods

2.4.1. Patient evaluation

The ABPI, duplex, lab's investigation, cardiology assessment (echo), computerized tomographic angiography (CTA), and MRI (if renal impairment) were carried out for the patients. Patients signed an informed consent before starting the procedures.

Detailed history (claudication pain, claudication distance, rest time, rest pain, and tissue loss), detailed general examinations, and lower limb examination to detect peripheral pulsation, ankle brachial pressure index (ABPI), and presence of tissue loss were taken. CTA was done for all patients to detect patency of the aorta, patency of common femoral artery, profunda and popliteal artery, and stenosis or occlusion of infrapopliteal tibial arterial lesions. The instruments used in operations were Angiosuit, sheath, balloons (drug-coated, plain), and 2.5, 3, guide wires (0.035).

2.4.2. Follow-up and assessments

The subjects were evaluated before and one year after the intervention. At baseline, medical history of ABPI and duplex imaging for measurement of peak systolic velocity were performed.

2.4.3. Point of success

Technical success is defined as uncomplicated revascularization and residual DS less than or equal to 30 %. While pain alleviation and wound healing following debridement or small amputation in patients with CLI are considered a success clinically. Patients who had tissue loss were frequently hospitalized and monitored until the wound contracted and granulation development was satisfactory. Following surgery, 100 mg of aspirin and 75 mg of clopidogrel were given as dual-antiplatelet medication, which was continued if side effects did not appear.

2.4.3.1. End point. The end point was reached after achieving pain reduction and wound healing.

2.4.3.2. Radiology assessment. Duplex ultrasound was utilized for measurement of peak systolic velocity, CT angiography was undertaken in cases of calcification and worsening of patient's condition. ABPI tests and ultrasonography were redone at 12 weeks' interval. Patients who have clinical symptoms that are getting worse get CT angiography.

2.4.4. Study outcome measure

Outcome measures for the current study were vascular patency and adverse events.

3. Results

3.1. Patients and lesion

Between May 2021 and May 2023, 50 participants in total were included in the trial and monitored for up to one year. Patients who presented with CLI were randomized to receive angioplasty with balloon that is eluted with paclitaxel drug (PEB) or with balloon that is uncoated (PB). Patients' baseline characteristics and clinical data, including mean

age, sex distribution, proportions of diabetes, hypertension, current smokers and ischemic heart disease (IHD), mean ABBI, and Rutherford category in both groups, are presented in Table 1.

This table shows that there were no significant differences between groups in the baseline characteristics and clinical data of the patients (*P*-value >0.05).

3.2. Angioplasty

Baseline lesion characteristics, including location, type, and length of lesion and runoff status are presented in Table 2.

This table shows that there were no significant differences between groups in the baseline lesion characteristics (*P*-value >0.05).

3.3. Procedure

Characteristics of the procedures for the patients of both groups are presented in Table 3 in detail.

This table shows that there were no significant differences between groups in the baseline procedural characteristics (*P*-value >0.05), except predication that was significant (*P*-value = 0.04) in favor of PEBA group.

3.4. Safety outcomes

During follow-up, groin hematoma (1 case), increased renal function (1 case in PEBA and 2 cases in PBA), and allergic reactions (1 case in the Posterior Tibial Artery (PTA)) were reported. In addition, death from organ failure (one in each group) and 3 above-knee amputations (2 in PBA and 1 in PEBA) were reported.

Table 1. The patients' baseline characteristics and clinical data.

	PBA (n = 25)	PEBA (n = 25)	*P*-value
Age (y), mean (SD)	**60.1 (7)**	**59.8 (7.3)**	0.88
Sex			
Male, no (%)	20 (80 %)	18 (72 %)	0.5
Female, no (%)	5 (20 %)	7 (28 %)	
Diabetes (%)	18 (72 %)	19 (76 %)	0.74
Hypertension (%)	15 (60 %)	16 (64 %)	0.78
Current smoker (%)	11 (44 %)	10 (40 %)	0.78
IHD (%)	14 (56 %)	13 (52 %)	0.78
ABPI, mean (SD)	0.37 (0.07)	0.39 (0.1)	0.42
Category of Rutherford			
3	3 (12 %)	3 (12 %)	1
4	6 (24 %)	9 (36 %)	0.36
5	11 (44 %)	10 (40 %)	0.78
6	5 (20 %)	3 (12 %)	0.44

ABPI, ankle brachial pressure index; IHD, ischemic heart disease: PBA, plain balloon angioplasty; PEBA, paclitaxel-eluting balloon angioplasty; SD, standard deviation.

Table 2. Baseline characteristics of the lesions.

	PBA (n = 25)	PEBA (n = 25)	*P*-value
Lesion location			
Popliteal, tibial	3 (12 %)	5 (20 %)	0.44
Tibial	22 (88 %)	20 (80 %)	0.44
Lesion type			
Stenosis	7 (28 %)	6 (24 %)	0.76
Occlusion	18 (72 %)	19 (76 %)	0.74
Lesion length			
<5 cm	10 (40 %)	11 (44 %)	0.78
5–10	15 (60 %)	14 (56 %)	0.78
Status of runoff			
Good (2–3 vessels)	23 (92 %)	22 (88 %)	0.64
Poor (0–1 vessel)	2 (8 %)	3 (12 %)	0.64

PBA, plain balloon angioplasty; PEBA, paclitaxel-eluting balloon angioplasty.

3.5. Functional outcomes

Functional outcomes, including Rutherford stage, ankle brachial pressure index (ABBI), restenosis, limb salvage rate, clinically driven target lesion revascularization (TLR), target vessel occlusion, complete index ulcer healing, all-cause deaths, amputation-free survival (AFS), clinical improvement, and complete wound healing at one-year follow-up are presented in Table 4.

This table shows that there were no significant differences between groups in all the studied functional outcomes (*P*-value >0.05), except target vessel occlusion, ABPI, and restenosis that were significant (*P*-value <0.05) in favor of PEBA group.

Table 3. Baseline procedural characteristics.

	PBA (n = 25)	PEBA (n = 25)	*P*-value
Vascular access			
Ipsilateral	25 (100 %)	25 (100 %)	1
Successful guidewire crossing	25 (100 %)	25 (100 %)	1
Predication	21 (84 %)	25 (100 %)	**0.04**
Lesion crossing			
True lumen	9 (36 %)	10 (40 %)	0.78
Subintimal	16 (64 %)	15 (60 %)	0.78
Device success (%)[a]	25 (100 %)	25 (100 %)	1
Procedural success (%)[b]	24.5 (98 %)	24.75 (99 %)	0.78
Clinical success (%)[c]	24.25 (97 %)	24.75 (99 %)	0.62

PBA, plain balloon angioplasty; PEBA, paclitaxel-eluting balloon angioplasty.

[a] Defined as delivery, inflation, deflation, and retrieval of the balloon without burst.

[b] Defined as residual diameter stenosis less than or equal to 50 %.

[c] Defined as residual DS less than or equal to 50 % without complications as thrombosis before discharge.

Table 4. Functional outcomes at 12 months of follow-up.

	PBA ($n = 25$)	PEBA ($n = 25$)	*P*-value
Rutherford stage			
Improved	16 (65 %)	21 (85 %)	0.1
Worsened	5 (20 %)	2 (10 %)	0.3
Equal	3 (15 %)	1 (5 %)	0.24
ABPI (mean)	0.6 (0.27)	0.84 (0.11)	**0.0002**
Restenosis	15 (63 %)	7 (30 %)	**0.02**
Limb salvage rate[a]	23 (95.7 %)	24 (96 %)	0.96
Clinically driven TLR[a]	6 (26 %)	3 (13 %)	0.24
Target vessel occlusion	13 (54 %)	4 (16 %)	**0.02**
Complete index ulcer healing	16 (66 %)	21 (85 %)	0.11
All-cause deaths	1 (5 %)	1 (5 %)	1
AFS	21 (84 %)	21 (85.5 %)	0.88
Clinical improvement[b]	21 (85 %)	22 (90 %)	0.6
Complete wound healing	19 (79 %)	20 (80 %)	0.94

ABPI, ankle brachial pressure index; AFS, amputation-free survival; PBA, plain balloon angioplasty; PEBA, paclitaxel-eluting balloon angioplasty; TLR, target lesion revascularization.

[a] Any re-intervention at the target lesion due to symptoms or drop of ABI of greater than or equal to 20 %.

[b] Decrease in ulceration depth and/or size or reduction of pain during rest.

3.6. Case 1

3.6.1. Past history and history of present illness

A 70-year-old female patient with hypertension, diabetes mellitus with dry gangrene of right little toe (Fig. 1), and O/E: bilateral, femoral, and popliteal pulse.

3.6.2. Access

Ipsilateral left femoral access by sheath 6 French.

3.6.3. Procedure

Introducing of burn 4 fr over 0.018 wire that passes the lesion of tibioperoneal trunk of popliteal artery and anterior tibial artery (ATA), ballooning of tibioperoneal trunk of popliteal artery, and ATA using 3- and 150-mm drug-coated balloon (Fig. 2).

Post-ballooning angiography showed good flow to ATA, tibioperoneal trunk, and peroneal artery as shown in Fig. 3.

3.6.4. End result

Patient regain of ATA and dorsalis pedis artery. Then, after 3 days of angioplasty, amputation of little toe was done as shown in Fig. 4.

Daily dressing shows granulating wound with minimal necrotic tissues was debridement at bedside as shown in Fig. 5. Then, after 2 weeks of angioplasty, it shows good granulating wound with decrease in size (Fig. 6). Daily dressing and follow-up at the outpatient clinic was shown good granulating and near to closed (Fig. 7). After 2 months, the wound closed completely (Fig. 8).

3.7. Case 2

3.7.1. Past history and history of present illness

A 65-year-old male patient, diabetic, hypertensive, with right CLI with second and third toes gangrene, O/E: bilateral, femoral, and popliteal pulse, and CTA: tibial vessel disease (Fig. 9).

3.7.2. Access

Ipsilateral right femoral access by sheath 6 French.

3.7.3. Procedure

Introducing of burn 4fr over 0.035 wire that passes lesion of PTA. Then, ballooning of PTA using 2- and 200-mm balloon was applied (Fig. 10).

Post-ballooning angiography showed good PTA filling with good flow to the foot as shown in Fig. 11. Then, debridement and amputation of second and

Fig. 1. Conventional angiography shows distal vessel disease, the patient was presented by little toe dry gangrene.

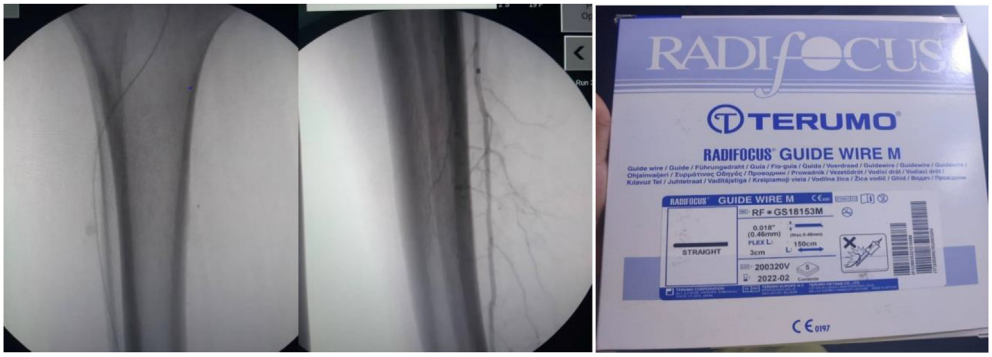

Fig. 2. Ballooning of tibioperoneal trunk of popliteal artery and anterior tibial artery using 3- and 150-mm drug-coated balloon using wire 0.018.

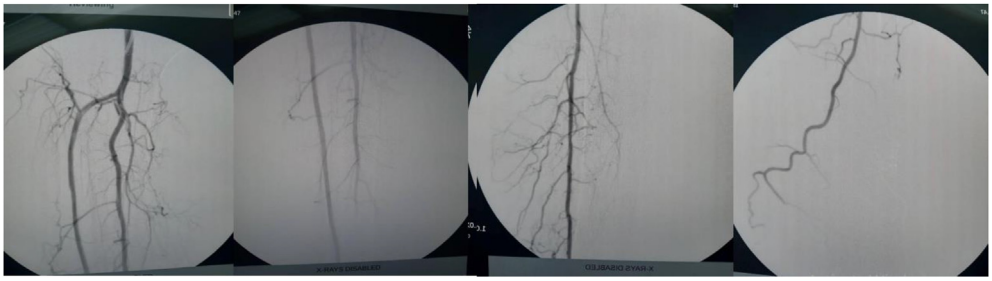

Fig. 3. Postballooning angiography showed good flow to anterior tibial artery, tibioperoneal trunk, and peroneal artery.

Fig. 4. After 3 days of angioplasty, amputation of little toe was done.

Fig. 5. By daily dressing, it shows granulating wound with minimal necrotic tissues was debridement at bedside.

Fig. 6. After 2 weeks of angioplasty, it shows good granulating wound with decrease in size.

Fig. 7. Daily dressing and follow-up at the outpatient clinic was shown good granulating and near to closed.

Fig. 8. After 2 months, the wound closed completely.

third toes of the foot were applied that leads to good granulating and vascularity wounds (Fig. 12). After that, another debridement and amputation of fourth and fifth toes of the foot after one week of angioplasty were done with complete healing (Fig. 13).

4. Discussion

Critical ischemia of the lower extremity is the highly prevalent causative factor for revascularization and amputation. The majority of patients with critical ischemia of the lower extremity of CLI have diabetes mellitus, leading to ulcers that resist healing.[5]

So, revascularization for patients with critical ischemia of the lower extremity is critical to prevent amputation that occurs in about 40 % of cases with pain during rest ischemic ulcer that does not heal, and digits with gangrene.[6]

Our thesis aim is to evaluate the vascular outcome of post-arterial segments' revascularization of the infrapopliteal arteries comparing angioplasty with balloon that is uncoated versus paclitaxel coated with CLI due to distal vessel diseases.

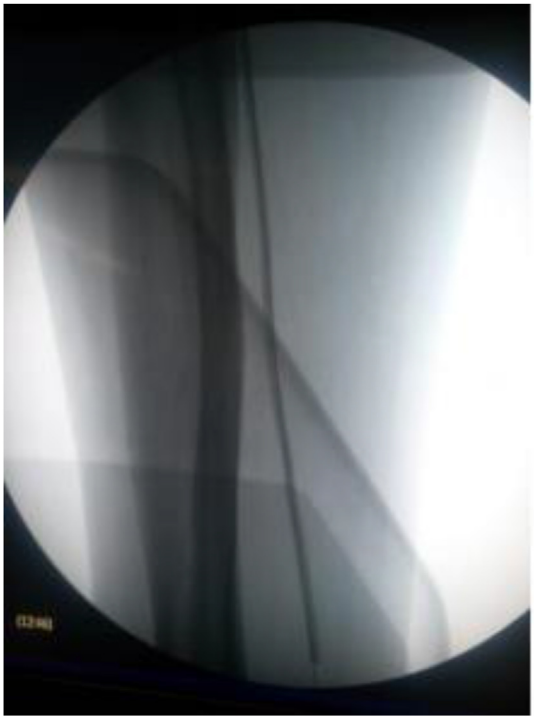

Fig. 10. Ballooning of PTA using 2- and 200-mm balloon.

This prospective study is to follow patients with arterial vessel disease who will be identified. Fifty patients were eligible for the study. They were categorized into two groups of 25 patients each.

In this trial, 'drug-coated balloon angioplasty' significantly reduced stenosis compared with 'plain balloon angioplasty' in subjects with symptomatic distal PAD. There was marked decrease in restenosis and the need for TLR at one year after application of 'drug-coated balloon angioplasty'.

The findings of the current study agree with Ipema et al.[7] who documented that TLR rate was 14.0 % for DCB versus 27.8 % for PTA. While, in this study, revascularization rate of the target lesion was 13 % versus 26 %, respectively.

Fig. 9. Conventional angiography shows tibial vessel disease, with Right Critical Limb Ischemia (RT CLI) with second and third toes gangrene.

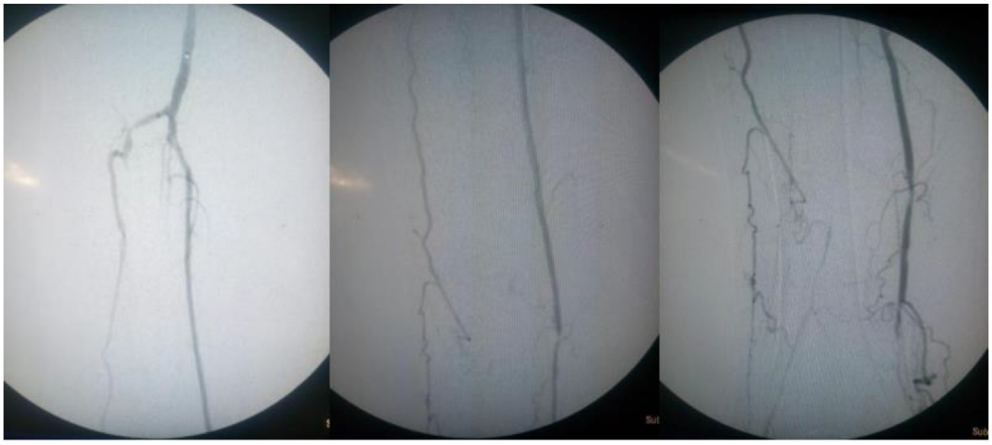

Fig. 11. Post-ballooning angiography showed good PTA filling with good flow to the foot.

This study showed significantly reduction of restenosis in PEBA versus plain balloon (32.9 %) versus (62.0 %), while in our study, (30 %) versus (63 %), respectively.

Ipema et al.[7] trials are also similar with our study in limb-salvageable rate uncoated versus PEBA (95.7 %) versus (94 %), (95.7 %) versus (96 %), respectively.

The results of this study are supported by Karnabatidis et al.[8] in reduction of restenosis of DCB versus plain balloon in distal vessel diseases (29 %) versus (67 %), respectively.

Our study provided increase, but nonsignificant, in 'the rate of complete index ulcer healing' at one year 85 % versus 66 %, respectively, in favor of PEBA.

The DEB is beneficial in improving restenosis through its significant effect on reduction of clinically driven TLR. The TLR has a crucial prognostic value for patients with CLI as 'early failure of endovascular recanalization' was reported to predict amputation. Treatments with repeated exposures to contrasts are dangerous to patients with severe comorbidities like those in our study that may lead them to death.[9]

Based on the finding of the current study, both interventions (DEB and PTA) have similar safety, because there are no cases of acute thrombosis reported.

Paclitaxel drug-eluting balloons are more beneficial in reducing stenosis, TLR, and occlusion of the target vessel than plain balloon angioplasty in

Fig. 12. Postdebridement and amputation of second and third toes of the foot with good granulating and vascularity wounds.

Fig. 13. Another debridement and amputation of fourth and fifth toes of the foot after one week of angioplasty with complete healing.

diabetic patients with 'critical limb ischemia' at 12 months of follow-up restenosis.[9]

4.1. Conclusion

In conclusion, angioplasty with paclitaxel-eluting balloons and plain balloons is similarly effective in improving limb salvage rate, clinical status, and wound healing. However, angioplasty with paclitaxel-eluting balloons is superior in decreasing restenosis in patients with CLI.

Conflicts of interest

None declared.

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