Comparative study between drug-coated balloon angioplasty vs plain balloon angioplasty in management of venous stenosis in hemodialysis access circuit

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Introduction
Juxta-anastomotic venous stenosis is a major concern associated with arteriovenous fistulas, which is mainly a result of neointimal hyperplasia. Although balloon angioplasty remains the cornerstone treatment for vascular access stenosis, the combination of venous anatomy and physiology, with the pre-existing endothelial dysfunction of uremic patients, generally leads to poor mid-term and long-term results. Theoretically, vascular access patency may be optimized by a technology that would both block negative vessel wall remodeling and inhibit fibromuscular hyperplasia. One such approach could be the use of angioplasty with drug-coated balloon (DCB) angioplasty.
Patients and methods
Within a 10-month period, 80 patients with different types of hemodialysis access stenosis in whom percutaneous transluminal angioplasty (PTA) was indicated were prosTectively, randomized to have either DCB or plain balloon angioplasty (PBA). This study was designed to compare primary patency rates and target lesion revascularization of DCB vs PBA to preserve the patency of the vascular access circuit in patients undergoing hemodialysis after 1 year of follow-up.
Results
All patients enrolled in the study completed the 1-year follow-up period. Access circuit primary patency results were also significantly in favor of DCB angioplasty (DCB, 287 days, and PBA, 156 days; P=0.04). Target lesion revascularization-free survival was significantly superior in the DCB group according to the Kaplan–Meier survival analysis curve (DCB, 316 days, and PBA, 172 days; P=0.041). There was no statistically significant difference in this subgroup analysis (P>0.1).
Conclusion
In this two-center study, DCB angioplasty results in improved vessel patency and is superior to plain balloon dilation in the treatment of venous stenoses of failing native or prosthetic arteriovenous shunts used for dialysis access.

Keywords:
arteriovenous fistula, drug coated balloon, fistuloplasty, hemodialysis, neointimal hyperplasia

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Introduction

As the incidence of end-stage renal diseases (ESRD) has been escalating over the past years, the creation of hemodialysis access (the so-called 'lifeline' for dialysis patients) has become a common vascular procedure in the form of either an autologous arteriovenous fistula (AVF) or prosthetic arteriovenous graft (AVG) [1].

The autogenous AVF is considered as the optimum access for patients with ESRD on hemodialysis, as when the access matures, it results in higher patency rates and lower complication rates than the other dialysis options as the prosthetic grafts and cuffed, tunneled dialysis catheters [2]. However, juxta-anastomotic venous stenosis is a major concern associated with AVFs, which is mainly as a result of neointimal hyperplasia [3]. The presence of this occlusive neointimal hyperplasia at the anastomosis and/or the outflow veins, which may be accelerated by chronic kidney disease, has been considered to be the leading cause of AVF failure [4].

An established method of preserving failing dialysis access is plain balloon angioplasty (PBA) of significantly stenotic lesions occurring in the dialysis circuit of failing arteriovenous shunts. Although PBA remains the cornerstone treatment for vascular access stenosis because of its minimally invasive percutaneous nature and widespread availability, the combination of venous anatomy and physiology, with the pre-existing endothelial dysfunction of uremic patients, generally

leads to poor mid-term and long-term results, necessitating multiple repeat angioplasty sessions in the same circuit [1,2,5,6].

In an attempt to improve immediate technical success and long-term vascular patency, several methods have been applied in the past, with bare metal stents having been most widely tested, albeit with controversial outcomes [7–9].

Theoretically, vascular access patency may be optimized by a technology that would both block negative vessel wall remodeling and inhibit fibromuscular hyperplasia formation after standard balloon angioplasty. One such approach could be the use of angioplasty with drug-coated balloons (DCBs), which are already known to effectively inhibit neointimal hyperplasia and reduce vascular restenosis after angioplasty of the superficial femoral artery for leg ischemia [10].

DCB provides rapid delivery of the antiproliferative drug to the local vessel wall and inhibition of neointimal hyperplasia compared with PB [11].

Patients and methods

Study design

A total of 80 patients with different types of hemodialysis access venous stenosis in whom percutaneous transluminal angioplasty (PTA) was indicated were prospectively, randomized to have either DCB angioplasty (n=40 patients) or PBA (n=40 patients). Our study is approved by ethical committee in both vascular department in Al-Azhar University hospitals in Cairo, Egypt.

The study was performed at two Tertiary Referral Centers, Al-Azhar University Hospitals in Cairo (Egypt) and Prince Sultan Military Medical City in Riyadh (Saudi Arabia).

This prospective, multicenter, randomized study was designed to compare long-term angiographic and clinical outcomes of the application of DCB angioplasty vs PBA in the treatment of failing dialysis accesses with angiographic documentation of a significant venous stenotic lesion in patients with AVF or AVG circuits (Table 1).

Study devices

Drug-coated dilatation balloon catheters available in the market were used in patients randomized in the experimental comparator group (DCB group) according to the availability at the time of each procedure (Table 2).

Patients who were randomized to the control group (PBA group) underwent angioplasty with a variety of high-pressure balloon catheter brands.

Index intervention

Detailed full medical history of the patient was taken, and a physical examination of the dialysis access circuit was performed in accord with the Kidney Disease Outcome Quality Initiative recommendations. A

Table 1 Inclusion and exclusion criteria for study enrollment

Inclusion criteria	Exclusion criteria
Age 18–90 years	Patient unable to provide informed consent
Autogenous arteriovenous fistula or prosthetic arteriovenous graft in the arm and forearm	Patient unable to abide with study follow-up protocol
Vascular access actively used for hemodialysis (≥1 successful session)	Patient participating in other relevant or conflicting studies
Clinical signs of failing access in the form of either poor thrill over the access or palpable pulse propagated over the access	Vascular access circuit placed in the lower extremities
Patient referred from HD unit with inefficient HD due to high percentage of recirculation (high venous pressure)	Bare metal stent or stent-graft placed previously
Angiographically proven venous outflow stenosis <50% as compared to proximal segment of the reference vein diameter. Aneurysmal venous segments were avoided	Metastatic cancer or other terminal medical condition
	Hemodynamically significant stenosis of the central venous system
	Limited life expectancy (<6 months)
	Blood coagulation disorders
	Sepsis or active infection
	Recent arm superficial thrombophlebitis (<6 months)
	Allergy or other known contraindication to iodinated contrast material, heparin, or paclitaxel
	Pregnancy

Table 2 Most common available drug-eluting balloon dilatation catheters

Company	Biotronic	Bard	Boston	Medtronic	Spectranetics
Device name	Passeo-18 Lux	Lutonix	Ranger	In.Pact	Stellarex
Catherter type	OTW	OTW	OTW/RX	OTW	OTW
Drug coating	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel	Paclitaxel
Drug concentration	3 μg/mm^2	2 μg/mm^2	2 μg/mm^2	3.5 μg/mm^2	2 μg/mm^2

single, intravenous 750 mg dose of cephalosporin was given as a prophylactic antibiotic against potential infection of the vascular access. Percutaneous access was gained in an appropriately chosen nonaneurysmal site of the dialysis access circuit with a micropuncture set after the application of local anesthetic (2–3 ml of 1% lidocaine). Vascular access was secured with the introduction of a 0.035-inch stiff hydrophilic guide wire (Terumo, Tokyo, Japan) and placement of a 6-F vascular sheath. Five thousand units of unfractionated heparin was administered intravenously to avoid thrombotic events, and selective digital subtraction angiography of the access circuit was performed to outline the anatomy and delineate the location and morphology of the stenosis. The lesion was crossed with routinely used catheters and guide wires, whereas the size of the DCB or plain high-pressure balloon was selected according to the reference diameter of the most proximal non-aneurysmal vein segment.

High-pressure (>18 atmospheres) balloon catheters were considered the instrument of choice for dilation of highly resistant venous stenoses that develop in AVFs or AVGs. In the active comparator group, DCB dilation was performed with predilatation using high pressure balloon.

According to protocol, duration of balloon inflation will be at least 1 min at the recommended nominal inflation pressure in all cases. A final angiogram of the entire dialysis vascular access, including the arterial inflow and the vein outflow circuit, was performed to exclude any immediate complications. After completion of the procedure, hemostasis was achieved with the use of a purse-string suture. Patients were prescribed daily antiplatelet therapy with clopidogrel (75 mg).

Follow-up

The follow-up protocol included the following:

(1) Clinical surveillance was performed during regular dialysis sessions with referral to vascular service if there is disappearance of thrill of AV fistula or increase in hemostasis time at the end of dialysis (>20 min or increase by >50% from usual hemostasis time).
(2) Measurement of access flow monthly was performed with referral for vascular surgery evaluation if flow is below 400 ml/min.
(3) Routine duplex ultrasound examination of AV access and inflow artery with measurement of PSV ratio of access every 3 months.
(4) Conventional angiogram of arteriovenous access was performed if there is evidence of significant restenosis (>50%) proven by duplex ultarsound (DUS).

Study end points and outcome measures

Procedural success was defined as a final angiogram with less than 30% residual stenosis after DCB application or PBA and at least one successful dialysis session using the treated AVF or AVG circuit. The primary end point was primary patency of the treated lesion and of the treated circuit at 6 months. Secondary end points included first, overall dialysis circuit survival, defined as a patent and functional vascular access regardless of the number of repeat surgical and/or percutaneous procedures in the interim, and second, major and minor complications, classified according to published international reporting standards. Primary patency was defined as the angiographic visualization of a patent lesion or circuit with less than 50% angiographic restenosis and no need for any repeat procedures during the entire follow-up period. Loss of primary patency was recorded in the event of significant binary restenosis, clinically driven surgical or percutaneous reintervention, or thrombosis of the target lesion or treated circuit. Angiographic restenosis was set at a binary 50% threshold. Both residual stenosis and restenosis were assessed on digital subtraction angiography using vessel analysis software tools (Allura Xper FD20, Xcelera Release 7.2; Phillips Medical Systems, Amsterdam, The Netherlands). Clinically driven reintervention was defined as the percutaneous or surgical treatment of a greater than or equal to 50% target lesion restenosis associated with clinical and/or hemodynamic abnormality of the dialysis circuit, whereas thrombosis was clinically evaluated as the presentation of an impalpable dialysis circuit, resulting in an inability to perform hemodialysis. Thrombosis of vascular access had to be further confirmed by duplex ultrasonography.

Results

Patients

A total of 80 patients (46 men=57.5%; mean age 63.1 ±13.8) (Table 3, Figs 1–4) with hemodialysis-dependent ESRD were enrolled in the study which was performed at two Tertiary Referral Centers, Al-Azhar University Hospitals in Cairo (Egypt) and Prince Sultan Military Medical City in Riyadh (Saudia Arabia).

In total, 40 patients were randomly assigned to group A (PBA) (36 AVFs and four AVGs) and 40 patients to group B Drug eluting balloon (DEB) (33 AVFs and seven AVGs).

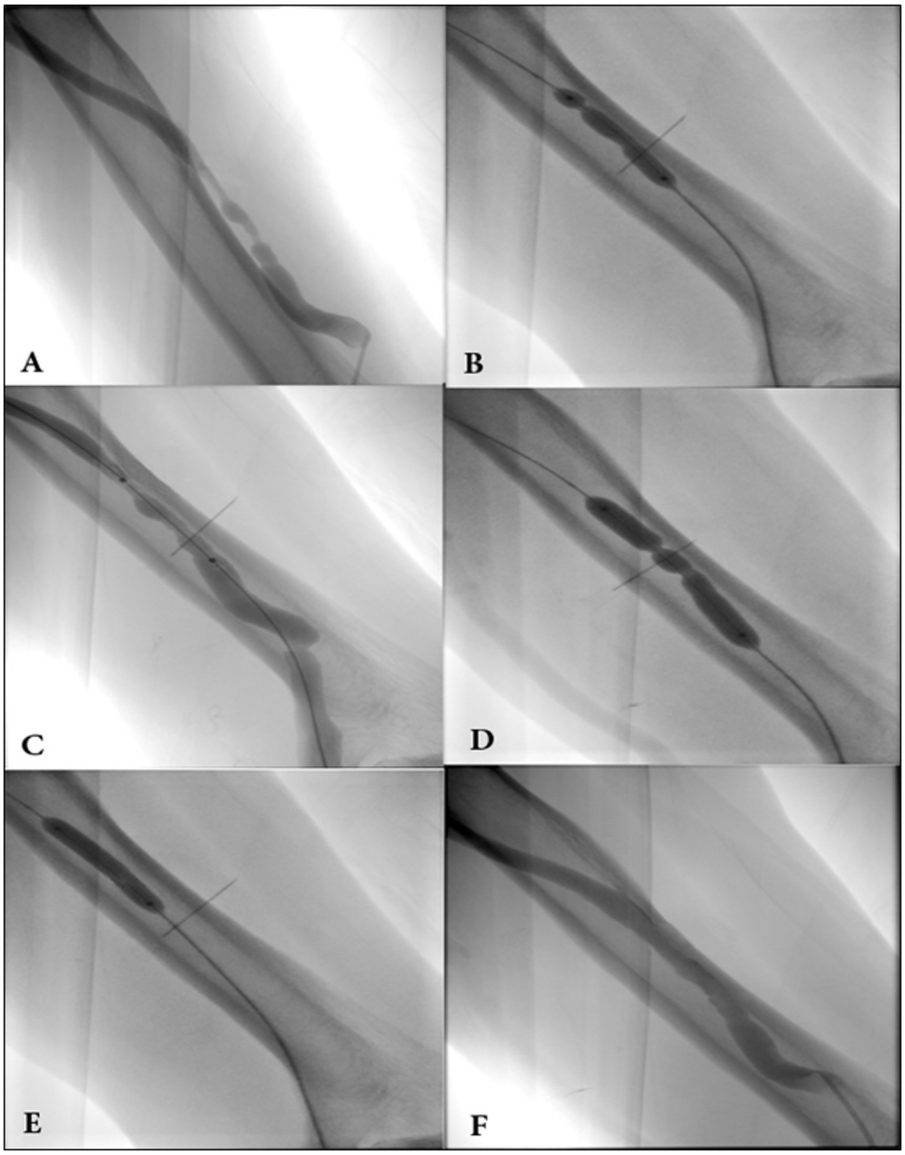
Baseline and procedural variables were comparably distributed in DEB and PBA groups.

(1) Group A: (PBA group) included 21 males and 19 females (Fig. 5).

Table 3 Sex distribution and cerebrospinal fluid causes among patients in our study

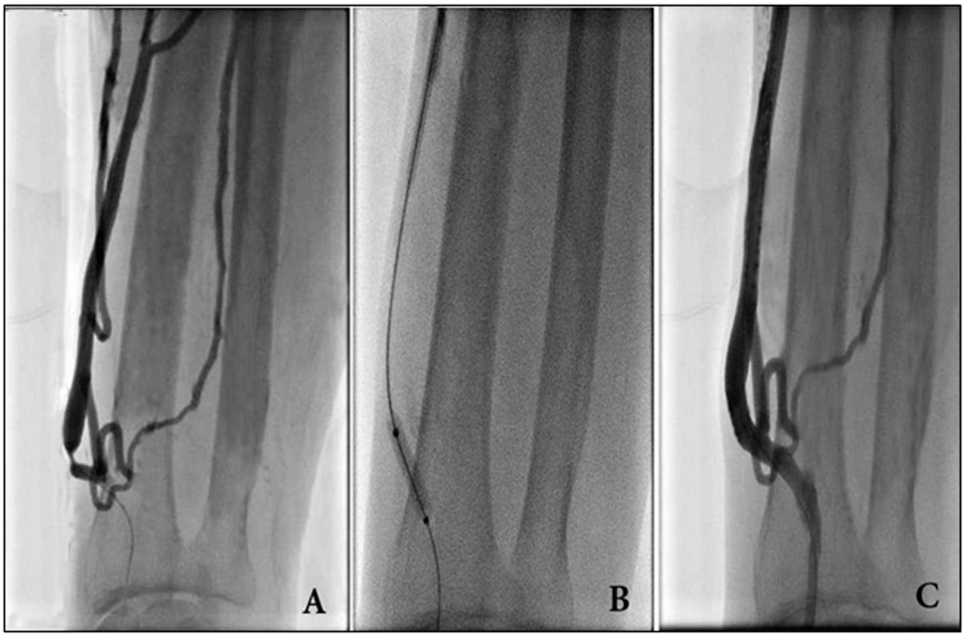
	n (%)
Male	46 (57.5)
Female	34 (42.5)
Diabetes	40 (50)
Hypertension	17 (21.25)
Uropathy	12 (15)
Lupus nephropathy	11 (13.75)

Figure 1



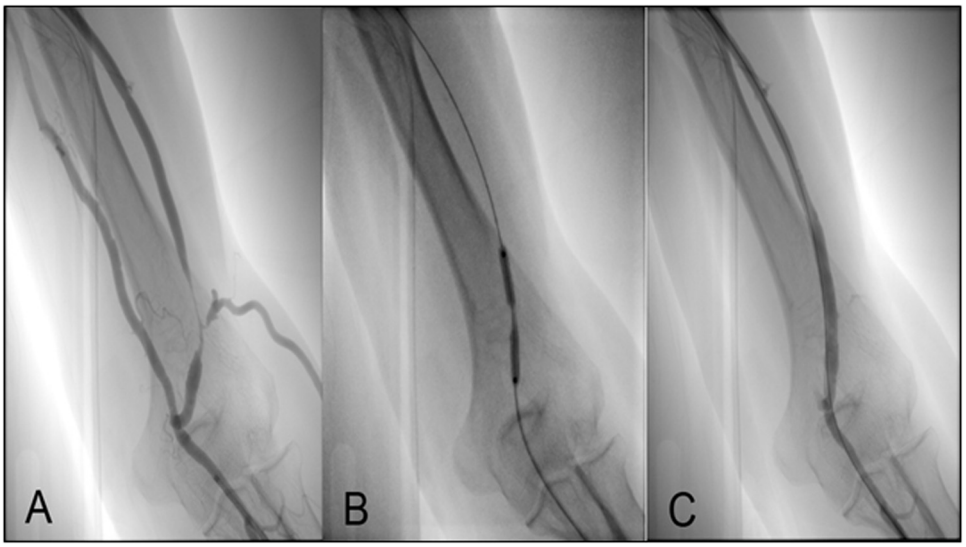
Serial fistulograms depict the study procedures in (a) two stenotic lesions of the main cephalic vein stem which have been selected for dilatation by drug-coated balloon. (b) The two lesions have been simultaneously predilated using Armada 0.35 balloon 5 mm diameter×80 mm length with apparent two waists. (c) Residual stenoses post dilatation in the venography. (d) Repeat dilatation by using Dorado conventional balloon at 18 atmospheres with gradual disappearance of the two waists. (e) Dilation with IN.PACT balloon size 5 mm diameter×70 mm length). (f) Final postdilatation venogram showing full dilatation of the mid-vein stenotic lesions and rapid flow of the injected dye.

Figure 2



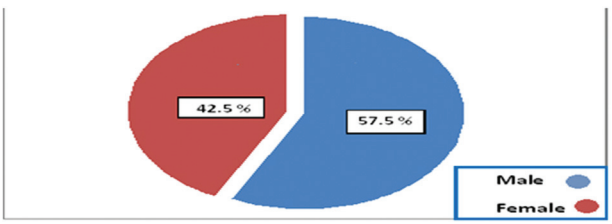
Tight stenosis of radiocephalic fistula vein (a) was dilated with 4/20 mm drug-coated balloon (b) with successful result as shown in the postdilatation venography (c).

Figure 3



Dilatation of the juxta-anastomotic cephalic vein segment stenosis (a) using drug-coated balloon 4×70 mm (b) with successful postdilatation venography (c).

Figure 4



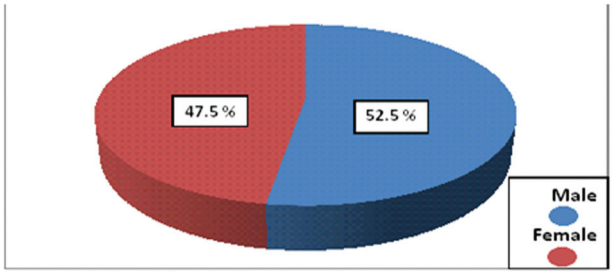
Sex distribution among patients in our study.

(2) Group B: (DEB group) included 25 males and 15 females (Fig. 6).

Sex distribution among patients in our study was as follows:

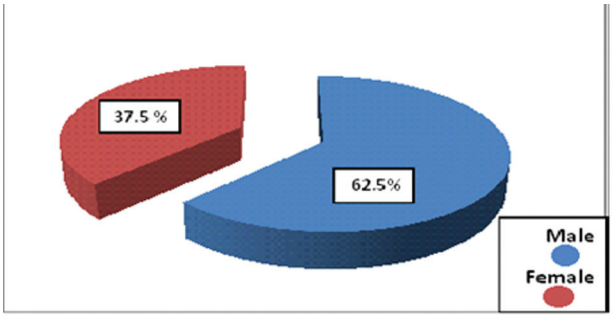
(1) Group A treated by PBA had a mean age of 62.7 years, with a range of 48–82 years.
(2) Group B treated by DEB had a mean age of 62.4 years with a range of 52–78 years (Table 4).

Figure 5



Male to female ratio in group A.

Figure 6



Male to female ratio in group B.

Table 4 Age distribution among both groups

Age (years)	Groups [*n* (%)]	
	Group A: PBA	Group B: DEB
40–50	3 (7.5)	4 (10)
51–60	10 (25)	9 (22.5)
61–70	11 (27.5)	13 (32.5)
71–80	11 (27.5)	10 (25)
81–90	5 (12.5)	4 (10)

DEB, drug eluting balloon; PBA, plain balloon angioplasty.

Table 5 Distribution of etiology of dialysis-dependent end-stage renal disease in both groups and their percentage

Etiology of dialysis-dependent ESRD	Group A [*n* (%)]	Group B [*n* (%)]
DM	19 (47.5)	21 (52.5)
Hypertension	10 (25)	7 (17.5)
Uropathy	5 (12.5)	7 (17.5)
Lupus nephropathy	6 (15)	5 (12.5)

DM, diabetes mellitus; ESRD, end-stage renal disease.

Age distribution among both groups was as follows:

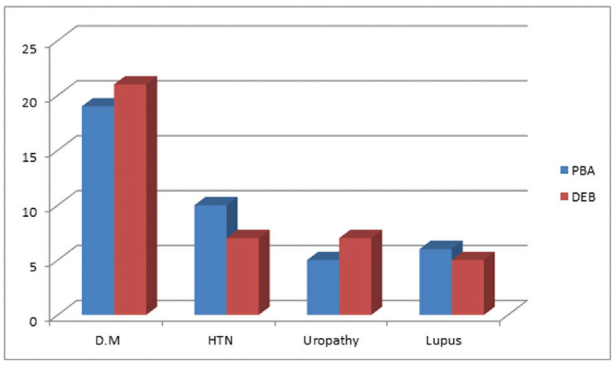
Distribution of etiology of dialysis-dependent ESRD in both groups and their percentage (Table 5 and Fig. 7) was as follows:

The site of access lesion in each group is shown in Table 6.

Table 6 The site of access lesion in each group

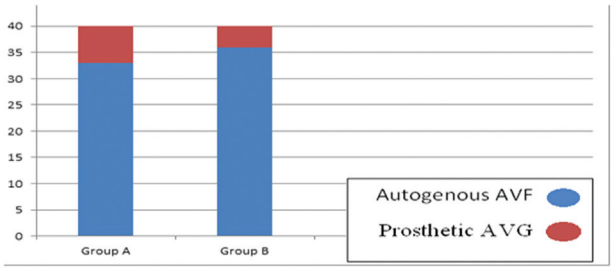
The site of access lesion	Group A [*n* (%)]	Group B [*n* (%)]
Cephalic vein	34 (47.5)	30 (52.5)
Arm basilic vein	3 (12.5)	5 (17.5)
Axillary vein	3 (15)	5 (12.5)

Figure 7



Distribution of etiology of dialysis-dependent end-stage renal disease in both groups and their percentage.

Figure 8



Type of vascular access in each group.

The type of vascular access in each group is shown in Fig. 8.

There were no significant differences in the overall length of the treated target vein lesion in both groups:

(1) The mean overall length of the treated target vein lesion (cm) calculated by pre-procedural angiogram in group A (PBA) was 5.4±1.6 cm.
(2) The mean overall length of the treated target vein lesion in group B (DEB) was 5.2±1.4 cm.
(3) There was no effect of overall length of the treated target vein lesion on the primary success in the present study in both groups.

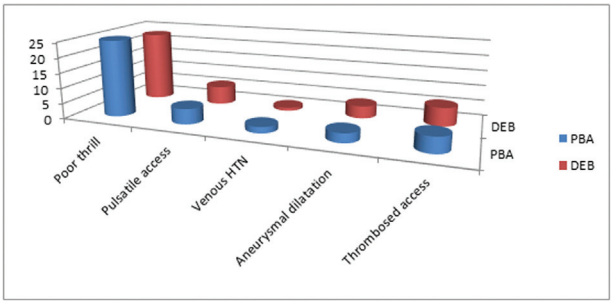
The results of access failure presentation number and percentage in each group (Table 7, Fig. 9) are as follows:

Table 7 Access failure presentation number and percentage in each group

Access failure presentation	Group A [*n* (%)]	Group B [*n* (%)]
Poor thrill	25 (62.5)	23 (57.5)
Pulsatile access	5 (12.5)	6 (15)
Venous HTN	2 (5)	1 (2.5)
Aneurysmal dilatation	3 (7.5)	4 (10)
Thrombosis	5 (12.5)	6 (15)

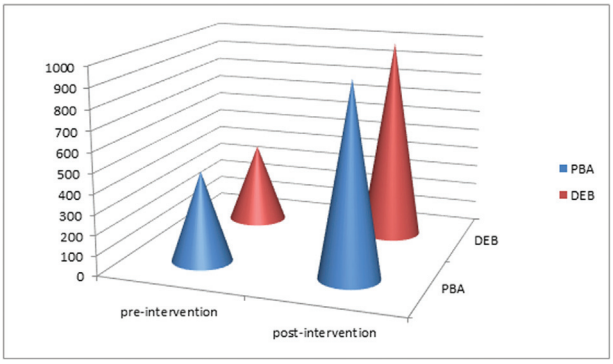
HTN, hypertension.

Figure 9



The relation between patients' number and access failure presentation.

Figure 10



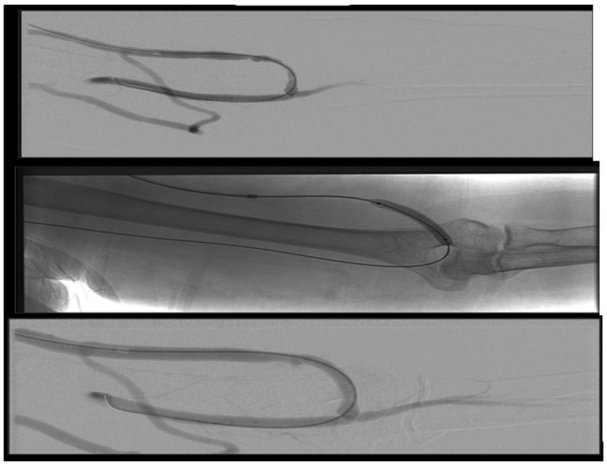
The mean access flow before and after intervention.

(1) The mean access flow at time of presentation in group A (PBA) was 450 ml/min, whereas the mean access flow in group B (DEB group) was 400 ml/min.
(2) The mean access flow during first HD session after intervention in group A (PBA) was 950 ml/min, whereas the mean access flow during first H.D session after intervention in group B was 1100 ml/min (Figs 10 and 11).

The mean degree of stenosis (%) of the treated target vein lesion calculated by pre-procedural angiogram in group A (PBA) was 75±8.47%.

The mean degree of stenosis (%) of the treated target vein lesion calculated by pre-procedural angiogram in group B (DEB) was 72±9.21%.

Figure 11



Dilation of juxta-anastomotic 75% stenosis in brachiocephalic arteriovenous fistula using 6×40 mm conventional balloon.

Table 8 Numbers and percentages of sites of stenosis in hemodialysis circuit in each group

Site of stenosis in hemodialysis circuit	Group A [*n* (%)]	Group B [*n* (%)]
Juxta-anastomotic (±3 cm from AV anastomosis)	24 (60)	23 (57.5)
Main vein segment used for puncture sites	16 (40)	17 (42.5)

Numbers and percentages of sites of stenosis in hemodialysis circuit in each group (Table 8) were as follows:

there were no significant differences between two groups in age of the treated vascular access circuit.

Mean age of dialysis access in group A (PBA) was 2.9 ±1.94 years, whereas the mean age of dialysis access in group B (DEB) was 3.2±1.62 years.

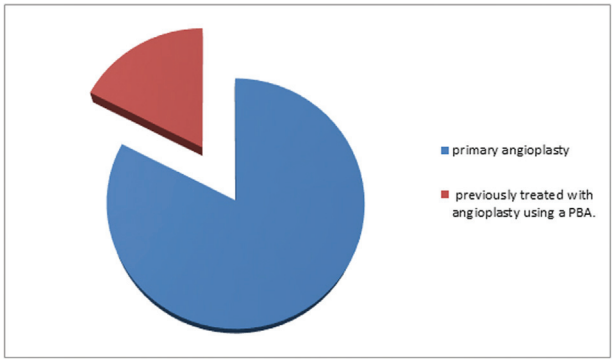
There were six cases in the PBA group (15%) and nine cases in the DEB group (22.5%) in which lesions had been previously treated with angioplasty using a PBA (Figs 12 and 13). There was no statistically significant difference in this subgroup analysis ($P>0.1$).

All patients enrolled in the study have been completed the 1-year follow-up period.

Device success rates were 100% in the both groups with routine predilation in DEB group.

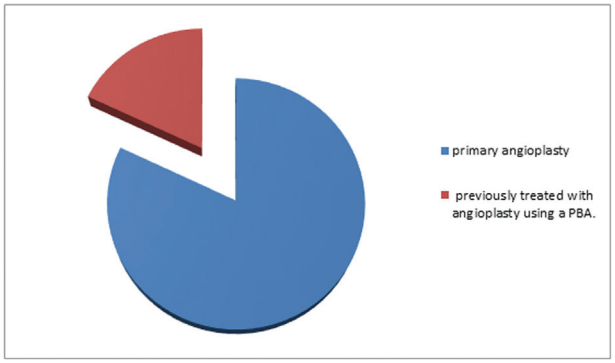
Anatomic and clinical success rates were 100% in both groups. No minor or major procedure-related complications occurred in either group (Table 9).

Figure 12



Percentage of primary angioplasty to previously treated lesions in group A.

Figure 13



Percentage of primary angioplasty to previously treated lesions in group B.

Table 9 Procedural primary and secondary outcome measures at 12-months for DEB vs plain balloon angioplasty groups

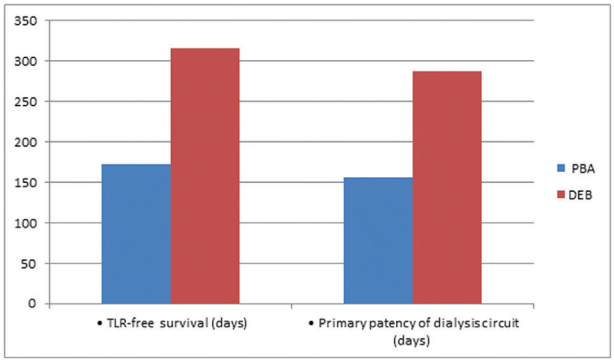
Outcome	DCB (*n*=40)	PBA (*n*=40)	*P* value
Completed 12-month follow-up	40	40	–
Device success (residual target lesion stenosis <30% without any further PBA postdilatation)	40	40	<0.001
Technical success (<30% remaining stenosis after postdilatation)	40	40	–
Procedural success	40	40	–
Major complication	0	0	-
Minor complications	0	0	-
TLR-free survival (days)	316	172	0.041
Primary patency of dialysis circuit (days)	287	156	0.040

DCB, drug-coated balloon; DEB, drug eluting balloon; PBA, plain balloon angioplasty; TLR, target lesion revascularization.

Access circuit primary patency results were also significantly in favor of DCB angioplasty (DCB, 287 days, and PBA, 156 days; *P*=0.04) (Fig. 14).

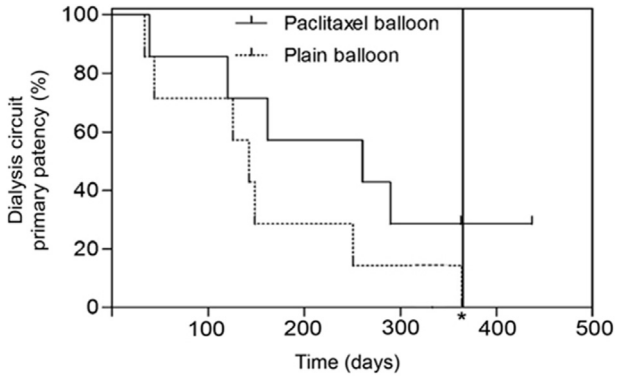
Target lesion revascularization-free survival was significantly superior in the DCB group according to the Kaplan–Meier survival analysis curve (DCB, 316 days, and PBA, 172 days; *P*=0.041) (Figs 15 and 16).

Figure 14



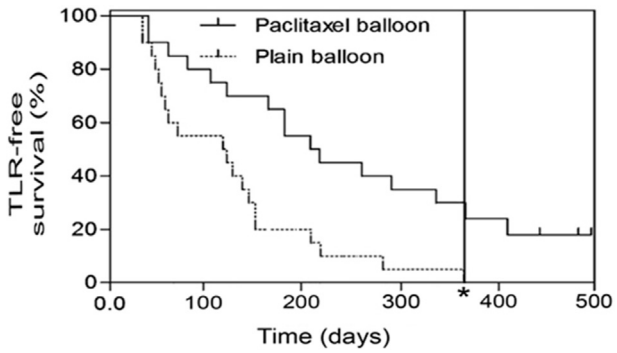
Target lesion revascularization survival and primary patency in both groups.

Figure 15



Kaplan–Meier survival plots of dialysis circuit primary patency. Vertical line with asterisk (*) represents 1-year time point. Subjects at risk are presented for intervals of 100, 200, 300, and 400 days.

Figure 16



Kaplan–Meier survival plots of target lesion revascularization-free survival. Vertical line with asterisk (*) represents 1-year time point. Participants at risk are also presented.

Discussion

ESRD is typically characterized by a state of massive endothelial dysfunction, which in turn is associated

with vascular inflammation, oxidative stress, and reduced flow-mediated vasodilatation. In addition, diabetes mellitus, which is the most common cause of ESRD, is a group of chronic metabolic diseases that is characterized by dysfunction of endothelial cells and SMCs, as well as by deceased vessel wall dilation [12].

In a newly formed hemodialysis access, neointimal hyperplasia may develop at the anastomotic site and lead to outflow stenosis, which prevents flow-mediated vasodilation, enlargement, and maturation in the case of AVFs; in venous juxta-anastomotic AVG stenoses, it may cause poor graft flow and early thrombosis [13]. Mild neointimal hyperplasia may also lead to a tight AVF stenosis if dilatation fails, whereas significant neointimal hyperplasia may not result in venous stenosis if it is compensated by outward positive vascular remodeling or vein dilatation. Other factors inculpated as primary irritators leading to neointimal hyperplasia formation include vascular trauma during access creation, vessel and injury from needle punctures. Events that may contribute to early AVF failure include small vessel diameter, surgical injury during AVF creation, previous venopunctures, newly developed accessory veins after surgery, fluid shear stress at the anastomosis, genetic predisposition to vasoconstriction and neointimal hyperplasia, and pre-existing venous neointimal hyperplasia [14].

In late AVF failure, the increased shear stress in the thin-walled outflow vein causes fibromuscular hyperplasia (fibrotic lesion formation) and consequent blood flow reduction (and stasis) that finally leads to thrombus formation [15]. The initial events of neointimal hyperplasia include trauma at the time of vascular access creation, elevated hemodynamic shear stress across the dialysis circuit, vessel injury from dialysis needle punctures, uremia resulting in endothelial dysfunction, and repeated angioplasties that may exacerbate endothelial injury [16]. The vessel injury leads to downstream events (oxidative stress, inflammation, endothelial dysfunction, and alternative origins for neointimal cells) that trigger the migration of vascular SMCs from the media to the intima, precipitating neointimal hyperplasia [17]. The same causes generally account for venous AVF stenoses and for venous juxta-anastomotic AVG stenoses, as well as for hemodynamically significant venous stenoses that may develop at any point along the venous outflow circuit [1]. In uremic patients, the endothelial dysfunction may exaggerate any preexisting venous neointimal hyperplasia, medial hypertrophy, and vessel wall intima-media thickening that may be present even before vascular access formation [18].

Most critical venous stenoses develop either along the venous outflow tract of the AVF or at the venous juxta-anastomotic site of the AVG. However, angioplasty itself can cause intima-media rupture, followed by neointimal hyperplasia (normal vessel response to the injury), and subsequent development of restenosis with recurrent vascular access failure. Therefore, BA of the vascular access is characterized by poor midterm patency, with an increasing rate of repeat procedures [19].

Several devices and techniques such as cutting balloons and cryoplasty have been used in the past in an attempt to improve patency outcomes of conventional percutaneous transluminal angioplasty in failing dialysis vascular access [20]. Recent outcomes from a multicenter randomized controlled trial demonstrated that stent-grafts perform better than percutaneous transluminal angioplasty in the management of AVG juxta-anastomotic stenosis. To our knowledge, no equivalent data are available for AVFs. Although etiology of stenosis in the latter case is considered a multifactorial trait, extending from circuit age and lesion length to vascular wall level changes, it is mainly attributed to aggressive neointimal hyperplasia. With neointimal hyperplasia being the main contributing factor to restenosis, the use of a local drug-delivery device that has been proven to inhibit this process in other vascular beds would be of interest [10].

Excitement has been fueled recently by a multicenter, controlled trial focusing on treatment of the venous anastomotic stenoses of AVGs. The trial compared the effectiveness of traditional BA with that of BA followed by the insertion of a self-expanding stent-graft at the stenosed venous anastomotic site of the AVG. Of interest, 6-month primary patency rates of both the treatment area and the entire treated access circuit were significantly superior, that is, approximately double in the stent-graft group [51 vs 23% (P=0.001) and 38 vs 23% (P=0.008), respectively] [21].

Drug-coated balloon technology has emerged during the recent years as a potential solution to the limitations presented by the use of drug-eluting stents (DES) in the management of atheromatous cardiovascular disease. DES technology was revolutionary as it both eliminated early elastic recoil with vessel scaffolding and significantly inhibited neointimal hyperplasia with

elution of antirestenotic agents. However, the need for long-term antiplatelet therapy and the risk of abrupt late stent thrombosis remain fundamental limitations of DES technologies [11].Theoretically, the absence of any source of chronic inflammation, such as the metal stent or polymeric coating material, avoids an exaggerated vessel reparative process responsible for the phenomenon of restenosis and acute late thrombosis. To date, positive results have been obtained with the application of DCB angioplasty for the treatment of leg ischemia owing to peripheral artery disease and recurrent coronary obstructions owing to in-stent stenosis. A strong and significant reduction in angiographic late lumen loss, which is a surrogate quantitative endpoint of late vascular restenosis, was achieved in both disease conditions with the use of DCB technologies [22].

Conclusion

In this two-center study, drug-coated balloon angioplasty results in improved vessel patency and is superior to plain balloon dilation in the treatment of venous stenoses of failing native or prosthetic arteriovenous shunts used for dialysis access.

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Conflicts of interest

There are no conflicts of interest.

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