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Management of In-Stent Restenosis in Femoro-Popliteal Arteries; Drug-Coated Balloon, plain balloon, comparative study

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Abstract

Background: Management of In-Stent Restenosis (ISR) has a high rate of initial procedural success, but long-lasting sustainable patency is still difficult to obtain. This work aims to compare plain balloon(PTA) and drug-coated balloon (DCB) regarding patency rate and target lesion revascularization (TLR) and limb salvage in the management of femoropopliteal ISR lesions.

Methods: This prospective hospital-based study was conducted on 25 patients presenting with femoropopliteal ISR presented with Rutherford category 4 and category 5 and adequate distal run-off vessels. Patients were randomized simply by flipping a coin into two groups: the PTA group and the DCB group.

Results: Both groups exhibited a statistically significant difference regarding patency rate; however, no significant difference was found regarding limb salvage. Comparing the two groups revealed a statistically significant difference regarding the mean degree of stenosis, mean ankle pressure, and mean ankle-brachial index after 3, 6, 9, and 12 months postoperatively. In addition, the difference between the two groups was statistically significant in mean ankle pressure after 1 month and in mean ankle-brachial index postoperatively. Wound healing was statistically significantly lower in DCB than in PTA. There was a statistically significant difference regarding TLR. There was no statistically significant difference between both groups regarding preoperative ankle pressure, however, it was statistically significant in the DCB group postoperatively. In addition, there was a statistically significant difference between pre and post-operative ankle pressure in both groups.

Conclusions: DCB was superior to PTA results regarding patency rate, TLR, and limb salvage rate.

Keywords: In-stent restenosis, plain balloon, drug-coated balloon, femoropopliteal arteries
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Introduction

In-stent restenosis (ISR) is defined as a loss of luminal volume caused by cell, extracellular matrix, and thrombus growth inside the stented artery's cylinder and/or 5-mm margins distal and proximal to the Stent. [1, 2] ISR of the femoropopliteal region continues to be one of the most aggravating issues for endovascular specialists. Within the first year following femoropopliteal artery stenting, it occurs in 18% to 40% of patients, which is a rather high rate.[1, 3] Femoropopliteal ISR is more prev-alent following the stenting of larger

lesi-ons and may be associated with fracture of the stent.[4]

Tosaka et al.[5] offer a novel femoropopliteal ISR categorization system that relies on the length of the lesion and the existence of in-stent occlusion. Restenotic lesions with a diameter of 50 mm or less are classified as Class I (focal) lesions, while Class II (diffuse) lesions are longer than 50 mm at the stent body or stent edge. Total in-stent occlusions were classified as Class III lesions.

Although ISR treatment produces high initial procedural success, long-term patency remains challenging. In recent years, balloon angioplasty with an anti-proliferative agent coating on the balloon's surface has been linked to greater patency rates than conventional balloon angioplasty. As a result, drug-coated balloons (DCBs) were progressively accepted in the management of femoropopliteal blockages in several interventional centers. Schillinger M et al review the available data for drug-coated balloons in infrainguinal arteries and their use in specific lesion groups.[6]

The currently optimal strategy is to perform DCBs to prevent the recurrence of neointimal hyperplasia. This therapy method has previously been proven in coronary arteries. However, the patient suffers from an early re-occlusion rate. Drug-eluting stent(DES) does not seem to work well in ISR.[1, 2]The administration of paclitaxel-coated balloons dramatically reduced the occurrence of restenosis at six months of treatment as well as the rate of target lesion revascularization (TLR) at six, twelve, and twenty-four months.[1, 2]

The authors demonstrated that balloon angioplasty for lengthy ISR lesions (class II) was linked with comparable results as therapy for shorter lesions (class I). According to some experts, conventional balloon angioplasty produces poor outcomes in such diseases. The incidence of re-occlusion is quite high.[1, 2]

This work aims to compare plain balloon (PTA) and DCB regarding patency rate and TLR and limb salvage in the management of femoropopliteal ISR lesions.

Patients and Methods:

Study design

This prospective hospital-based study was conducted on 25 patients presenting with femoropopliteal ISR.

Study setting

This study was carried out at Sohag university hospital and Assuit university hospital.

Inclusion and exclusion criteria

Patients presenting with femoropopliteal ISR presented with Rutherford category 4 and category 5 and adequate distal run-off vessels were included. Exclusion criteria were patients with untreated iliac or aortic lesions, patients with tostada classification class III with failed crossing the occluded segment, patients with a life-threatening infection, and patients with non-salvageable limbs.

Informed and written consent was taken from all patients. This study was approved by the ethical and scientific committee of the Sohag Faculty of Medicine.

Data collection

Clinical evaluation

The first assessment includes a thorough history and physical examination to look for signs of critical limb ischemia, such as hair loss, peripheral pulses, skin color changes, and trophic changes. The vascular laboratory is the first stage in the non-invasive diagnostic evaluation of the site and degree of severity of arterial disease. These non-invasive examinations may also be performed over time to track disease development and outcome after revascularization.

Investigations: Ankle pressure and ankle brachial indices.

Imaging modalities include duplex, computed tomographic angiography (CTA), and direct angiography.

Patients were randomized simply by fliping a coin into two groups:

(a)plain balloon group.

Inflation of the balloon to its nominal pressure for 1-to-2-minute, diameter, and length of the balloon was determined according to reference vessel as well as lesion length. Repeated balloon inflation was done in cases of residual stenosis of more than 30% or occurrence of flow-limiting dissection in the stent edge. The most common types of used balloons are Merit, Boston, and Ivascular.

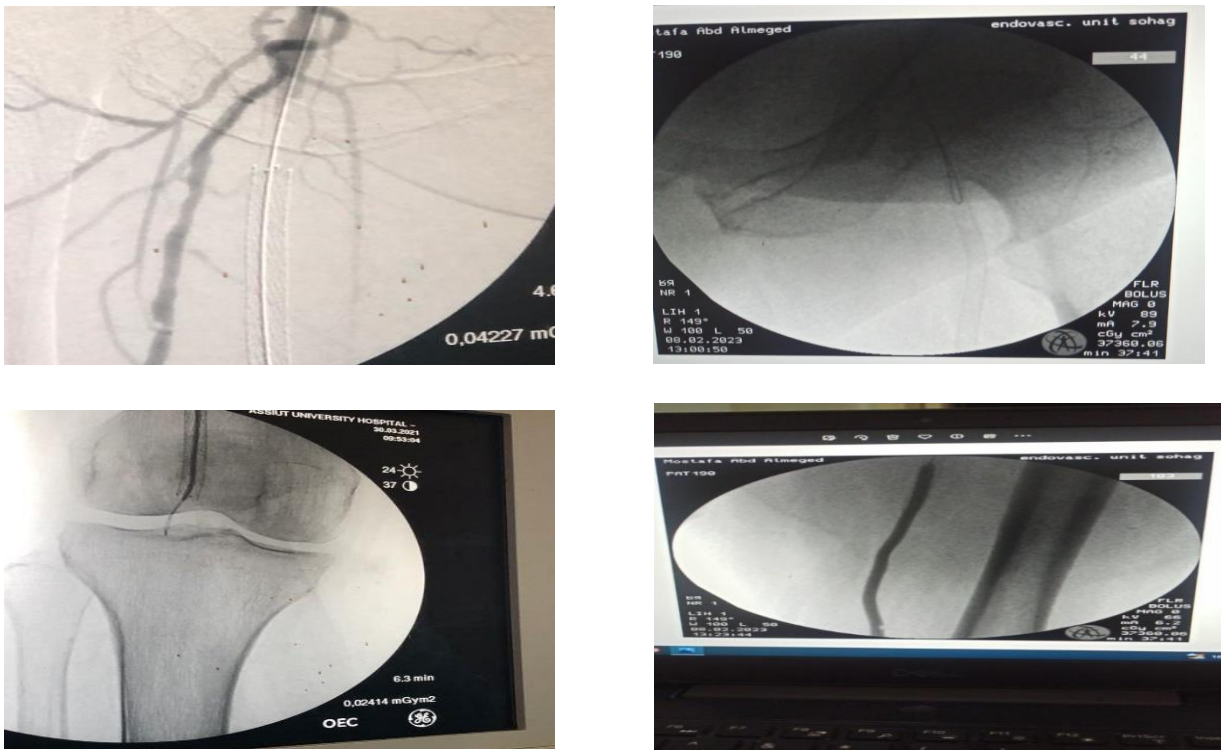


Figure.1 Plain ballon

(B) DCB group,

Pre-dilatation with a plain balloon was done in all cases to decrease friction at DCB and equal distribution of the excipient. Inflation of DCB for 3 minutes. DCB used were Medtronic, Admiral vascular, santa clara USA, paclitaxel and urea 3.5. In cases of long stenotic segment 2 DCB was used with at least 0.5 cm overlap to avoid geographic miss. In cases of residual stenosis, reinflation was done for 5 minutes (Schemit), if resistant, stenting–stent was done. In some cases we used Bail- out stent in patients with dissection at the stent edge or in patients with residual stenosis, we used BMS(Bare Metal Stent).

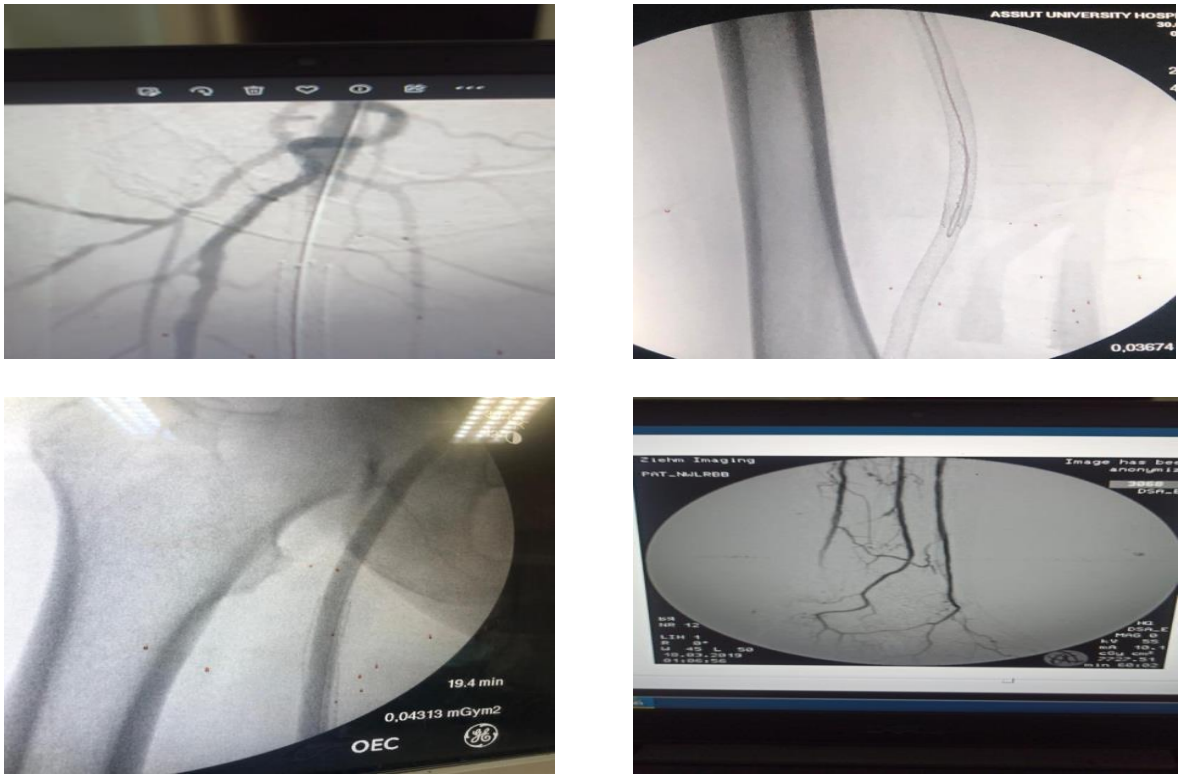


Figure.2 Drug-coated balloons

The Follow up was done after one month, 3 months, 6 months, 9monthes, and one year.
Ankle-brachial index duplex was done (to assess the degree of re-stenosis, clinical evaluation, and wound assessment.
Cut–off point: after one year of follow-up and after major amputation.

Wound management
In our study there are some cases presented with stage 5 Rutherford, some cases needed just daily dressing, some other cases needed minimal debridement, others needed toe or more amputation and some cases needed trans metatarsal amputation.
Then daily dressing with betadine solution, amikacin spray, honey, silver preparations, and VAC therapy till the wound became clean and granulating plastic consultation was done for grafting.

Definitions:
Technical success: patent target vessel with residual stenosis less than 30%.
Clinical success: improvement in the Rutherford category, foot ulcer healing and increase ABI after intervention.
TLR: any lesion required reintervention within the targeted lesion because of the return of ischaemic manifestations or decrease of ABI by more than 20% as reported by Zeller et al.
Vessel patency: absent hemodynamically significant stenosis by duplex ultrasound and peak systolic velocity (PSVR) less than 2.4
Reocclusion: more than 50% stenosis by duplex or angiography.
Minor amputation: occurring distal or through the tarsometatarsal joint (forefoot, trans metatarsal, and Lisfrance).
Major amputations: are those that occur proximal to the transmetatarsal joint (Chopard, Boyd, Syme, below the knee and above the knee).
Study outcome: one-year recurrent occlusion, TLR, and limb salvage rate.

Statistical analysis
The SPSS v25 program from IBM Inc. in Chicago, Illinois, USA, was used for the statistical study. The mean and standard deviation (SD) of quantitative variables were provided. The frequency and percen-

tage (%) of qualitative characteristics were reported. Pearson Chi-Square, Fisher's Exact Test, and Mann-Whitney U Test, wherever possible, the U test or independent sample t-test were utilized. A two-tailed P value of < 0.05 was deemed significant.

Results

There were no statistically significant differences between the two groups regarding demographic characteristics, clinical history, Rutherford classification, and surgical and operative characteristics. (Table1)

Table (1): Demographic characteristics, clinical history, Rutherford classification, surgical and operative characteristics of studied patients

Item		DCB cases N =11		PTA cases N =14		P value
		No.	%	No.	%	
Gender	***Female***	2	18.2%	4	28.6%	0.6
	Male	9	81.8%	10	71.4%	
Age by years	***Mean ± SD***	61.27 ± 9.91		58.50 ± 6.28		0.4
D.M		9	81.8%	12	85.7%	0.79
Smoking		8	72.7%	10	71.4%	0.94
Dyslipidemia		4	36.4%	6	42.9%	0.7
HTN		6	54.5%	8	57.1%	0.89
Cerebrovascular disease		3	27.3%	4	28.6%	0.9
IHD		7	63.6%	7	50.0%	0.49
Obesity		3	27.3%	3	21.4%	0.7
Renal impairment		2	18.2%	1	7.1%	0.3
Rutherford classification						
stage 4		3	27.27%	4	28.57%	0.7
stage 5		8	72.72%	10	71.42%	
Approach	Ipsilateral	1	9.1%	1	7.14%	0.89
	contralateral	7	63.6%	9	64.2%	
	Combined contralateral and Retrograde (popliteal)	1	9.1%	1	7.14%	
	Combined ipsilateral and Retrograde (pedal)	1	9.1%	2	14.2%	
	trans brachial	1	9.1%	1	7.1%	
Length of ISR	Long(>10cm)	5	45.5%	8	57.1%	0.6
	Short(<10cm)	6	54.5%	6	42.9%	
Runoff vessels	One vessel	4	36.4%	6	42.9%	0.9
	Two vessels	6	54.5%	7	50.0%	
	Three vessels	1	9.1%	1	7.1%	
Angiographic pattern	diffuse	9	81.8%	10	71.4%	0.54
	focal	2	18.2%	4	28.6%	

No statistically significant difference was observed between both groups regarding preoperative clinical parameters (Table 2)

Table (2): Comparison between DCB cases and PTA cases as regard the Clinical parameter pre-operative

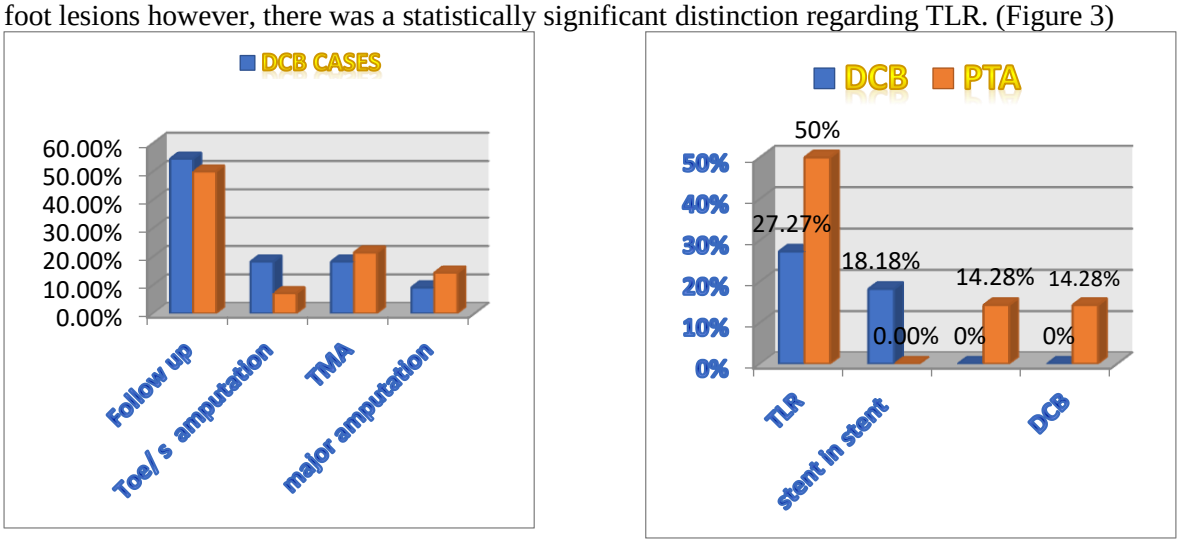
		DCB cases N =11		PTA cases N =14		P value
		No.	%	No.	%	
Tosaka classification	Class I	3	27.3%	7	50.0%	0.5
	Class II	7	63.6%	6	42.9%	
	Class III	1	9.1%	1	7.1%	
Mean ankle pressure	Mean ± SD	55.45 ± 19.29		57.50 ± 24.79		0.8
Mean PSV ratio	Mean ± SD	2.45 ± 0.33		2.56 ± 0.30		0.3
Number of previously deployed stents	Mean ± SD	1 ± 0		1.4 ± 1		0.5
The interval of stent placement and ISR in months	Mean ± SD	7 ± 2		6 ±3		0.1

There was a statistically significant distinction between the two groups in terms of patency rate, however, there was no statistically significant distinction detected in terms of limb salvage. (Table 3)

Table (3): Comparison between DCB cases and PTA cases as regard patency rate and limb salvage after 12 months, n=25

	DCB cases N =11		PTA cases N =14		P value
	No.	%	No.	%	
Patent	8	72.7%	5	35.71%	0.05
Re-occluded within one year	3	27.2%	9	64.28%	
Stent in stent	2	18%	0	0%	
Bypass	0	0%	2	14.28 %	
DCB	0	0%	2	14.28 %	
Claudication and conservative	0	0%	2	14.28 %	
Major amputation	1	9.09%	3	21.43%	
Limb salvage	10	90.9%	11	87.57%	0.4
Major amputation	1	9.1%	3	21.43%	

There was no statistically significant distinction between the two groups regarding the management of foot lesions however, there was a statistically significant distinction regarding TLR. (Figure 3)



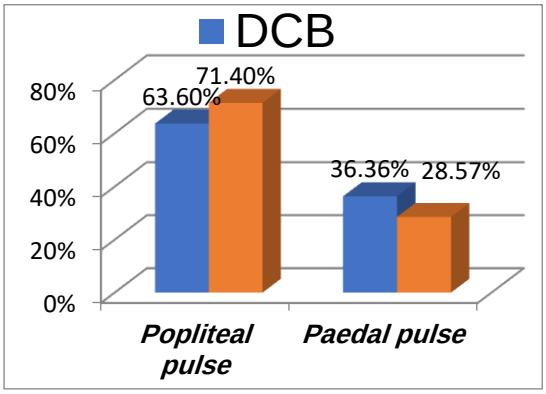
(A) (B)

Figure (3): Comparison between two study groups regarding the management of foot lesion (A) and target lesion revascularization (B).

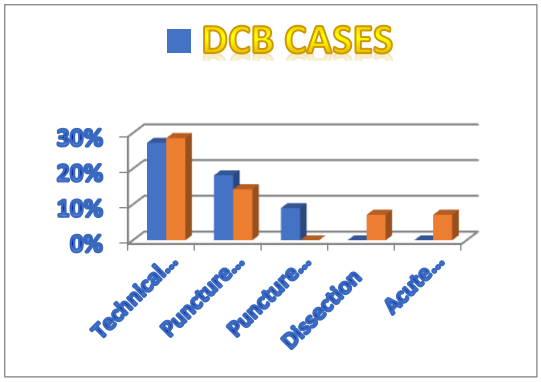
DCB: drug-coated balloon, TLR: target lesion revascularization, PTA: plain balloon, TMA: trans-metatarsal amputation

There was no statistically significant distinction between the two groups regarding the level of distal pulsation.

As regards technical complications: in the DCB group in 2cases puncture site hematomas were treated conservatively and in one case exploration of hematoma and repair of CFA was done. In the PTA group:2 cases puncture site hematoma occurred and conservative treatment was done, in one case dissection occurred and was treated conservatively and in one case thrombosis occurred and thrombolysis was done. (Figure 4)



(A)



(B)

Figure (4): Comparison between both groups regarding the level of distal pulsation (A) and complications (B) after treatment.

DCB: drug-coated balloon

There was a statistically significant distinction between the two groups regarding the mean degree of stenosis, mean ankle pressure, and mean ankle-brachial index after 3, 6, 9, and 12 months postoperatively. In addition, there was a statistically significant difference between both groups in mean ankle pressure after 1 month and in mean ankle-brachial index postoperatively. Wound healing was statistically significantly lower in DCB compared to PTA. (Table 4)

Table (4): Comparison between both groups regarding the mean degree of stenosis, mean ankle pressure and mean ankle-brachial index overtime

The mean degree of stenosis	DCB cases N =11		PTA cases N =14		P
	mean	SD	mean	SD	
Follow up duplex after 3 months	34%	7%	40%	5%	<0.004
Follow up duplex after 6 months	40%	5%	72%	7%	<0.001
Follow up duplex after 9 months	53.6%	4%	80.7%	8%	<0.001
Follow up after 1 year	60%	8%	85.2%	6%	0.007
Mean ankle pressure after 1m	99	16	74	28	0.01
Mean ankle pressure after 3m	80	17	60	25	0.004
Mean ankle pressure after 6m	70	5	48	8	0.001
Mean ankle pressure after 9m	65	5	40	6	0.005
Mean ankle pressure after 12m	55	7	35	6	0.01
Mean ABI pre-operative	0.41	0.1	0.43	0.1	0.6
Mean ABI immediate post-operative	0.83	0.10	0.7	0.1	0.003
Mean ABI after 3m	0.6	0.1	0.4	0. 1	0.0001
Mean ABI after 6m	0. 5	0.1	0.3	0.1	<0.001
Mean ABI after 9m	0.45	0.1	0.2	0.1	<0.001
Mean ABI after 12m	0.4	0.1	0.20	0.1	<0.001
Wound healing time (weeks)	4.6	1.14	6.1	1.95	0.03

There was no statistically significant difference between both groups regarding preoperative ankle pressure, however, it was statistically significantly higher in the DCB group postoperatively. In addition, there was a statistically significant difference between pre and post-operative ankle pressure in both groups. (Table 5)

Table (5): Preoperative and postoperative ankle pressure among both groups

parameter	DCB cases N =11	PTA cases N =14	p-value
	Mean ± SD	Mean ± SD	
Pre-operative ankle pressure	58.18± 17.2	60.7 ± 24.6	0.7
***Post-operative ankle pressure	98.18± 17.8	77.1 ± 26.1	0.03
P1 value	<0.0002	<0.0001	

Discussion

Treatment options for the management of ISR are numerous but there is no ideal strategy for its treatment. Currently, available algorithms for management are unclear. Endovascular management is the choice for symptomatic femoropopliteal disease[7, 8]. Percutaneous transluminal angioplasty (PTA) is commonly used with
a high intraoperative success rate, but it is with a suboptimal long-term patency rat.[9] Drug coated balloon (DCB) has been developed and this enabled the delivery of anti-proliferative drugs to the ISR [10]. It has been associated with favorable clinical and angiographic success in the management of de novo lesions of femoropopliteal arteries and ISR[11].

The mean ankle pressure was reduced more among patients after six and twelve months of follow-up. Also, the mean stenosis degree was increased on follow-up at the same period.

A comparison between PTA patients and DCB patients was performed and it was found both groups were matched with insignificant p-value regarding demographic data and clinical presentation, type of stenosis, number of previously deployed stents, mean ankle pressure, and interval of stent placement.

Our study showed that no statistically significant difference was found between both groups regarding demographic characteristics, clinical history, Rutherford classification, interventional characteristics as regards risk factors, diabetes mellitus, and smoking were the predominant risk factors. As regards the Rutherford category: 7 cases were stage 4 (28%), 3(12%) of them were enrolled in the DCB group and 4 (16%)were enrolled in the PTA group, 18 cases were stage 5(72%) 8 (32%) of them were enrolled in the DCB group and 10 (40%)were enrolled in PTA group.

No statistically significant difference was observed between both groups regarding preoperative clinical parameters (Tosaka classification, mean ankle pressure, mean PSV, number of previously deployed stents and interval of stent placement and ISR in months) Regarding Tosaka classification most prevalent was class 2(diffuse >5cm) 13 cases.

Patency rate at one year was reported in 72.7% of patients in the DCB group while in the PTA group, it was recorded in 35.71% of patients. These results were compared with the results of Armstrong et al.[12] and Liao et al.[13] were 90%,60% and 87.9%, and 51.6% respectively.

In the DCB group, 3 patients were occluded one had a severe infection and ended by major amputation, stent –in- stent was used in two cases. In the PTA group 9 patients were occluded, in 2 patients femoropopliteal bypass was done, in 3 cases major amputation due to severe uncontrollable infection, in 2 patients DCB treatment and conservative treatment in 2 cases as they were claudication.

TLR was reported in DCB in 27.27% of patients in 2 patients stent in-stent was used and in the other below knee, amputation was done due to poor distal runoff. These results are matched with Qato et al.[14]in which TLR was reported in 35%. In the PTA group, it was recorded

in 64.28% of patients, in 2 cases femoropopliteal bypass was done one of them needed major amputation, in another 3 cases DCB was used, in 2 cases stent in-stent treatment, and 2 cases below knee amputation were done due to ascending infection in one case and poor distal run off in the other case. (total number of major amputations in PTA cases was 3). Osama et al.[15] reported 40% TLR in the PTA group and 28% in the DCB group.

DCB achieves highly significant performance in short lesions compared to long lesions ISR, p value= <0.05In some other trials, Cao et al.[16] found that the use of DCB was associated with significantly reduced risk of TLR at 12 months(p value <0.00001)

As regard limb salvage it was 90.9%in the DCB group while in the PTA group, it was 87.57%.

This is matched with Krankenberg et al.[17] who showed that there was no significant difference in the ipsilateral amputation rate (p-value =.91)

These results were matched with other literature.[11] that reported 18.2% in his series in the DCB group were subjected to TLR and 40% in the PTA group were subjected to TLR while Armstrong et al. [12] and Liao et al.[13]PACUBA trial[18] recorded an 86.6% occlusion rate of plain balloon angioplasty in mean long lesions 18.4cm. Variation in these percentages can be attributed to the small number of patients in this series as well as the type of DCB balloon and its dose of paclitaxel covering.

Other literature.[11]compared the results of DCBand PTA in the management of femoropopliteal ISR and classified ISR lesions into long and short lesions(short less than 10 cm and long more than 10 cm) and they reported that patency rates were in the DCB group(87.5%in short lesion and63.6% in the long lesion. While in the PTA group, patency rate was reported (42.9% in short lesions and40% in the long lesion and they appreciated the role of DCB in short lesions as it offers significant results compared to long lesions which recorded -significant results between PTA and DCBgroup.

Long-term follow-up of more than one year remains essential to establish DCB effectiveness. ISAR-PEBIS trial[19] documented a high patency rate of up to 2 years although the LEVANT "1" trial[20] had reported that there was no significant difference at 2 years between the DCB group and plain balloon group regarding TLR; 36% vs. 49%, p-value = 0.23. Cassese et al.[21] denied the DCB value in certain circumstances e.g. uncontrolled diabetes, long calcified lesions, and completely occluded vessels. Unfortunately, 2017 European guidelines[22] have recently assigned a weak recommendation (class IIb) for DCB angioplasty in patients with femoropopliteal ISR.

Correlation of occlusion with Tosaka classification, it was noticed that occlusion is more common in class III than in other groups, 00%, 20%, and 80% in class I, II, and III respectively in DCB group while in plain balloon group, it was 14.3%, 14.3%, 71.4% in class I, II, III respectively. Liistro et al.[23] confirmed that in Tosaka class III, DCB treatment was independently associated with recurrent ISR, and therefore class III lesions treated with DCBs only without adjuvant modalities are exposed to 4-times higher risk of occlusion and therefore, they preferred its use in combination with atherectomy devices. The limitations of this study include the small sample size, the length of stenosis wasn't determined, and the follow-up period of only one year, whereas better findings can be assessed at longer periods of follow-up. Another limitation is the distance of walking by patients wasn't estimated as well as their performance. Strengths of this study include it is one of the few studies that compared DCB and PTA outcomes in Egypt. The study was simple and the results are easy to understand. The study included prospective and retrospective methods for gathering data.

Further studies including larger sample sizes are recommended with the assessment of the performance of patients and long-term follow-up.

Conclusions

Patients who underwent DCB showed that DCB was superior to PTA results regarding patency rate, TLR, and limb salvage rate.

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Conflict of Interest: Nil

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