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Prospective study comparing drug coated balloons versus balloon angioplasty for management of critical limb ischemia patients with tibial occlusive disease

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***Abstract*---**Background: For years interventionists have been searching for a technique of angioplasty to provide a reasonable patency without leaving something behind, and drug coated balloons came as the answer long waited with very promising preliminary results. This study aimed to compare between plain balloons and drug coated balloons as regard patency and limb salvage in treating tibial atherosclerotic occlusive disease. Methods: A prospective, randomized study. Patients with CTLI due to tibial atherosclerotic occlusive disease with or without concomitant inflow involvement are randomized into 2 groups, group A standard balloon angioplasty and group B drug coated balloons in a ratio of 2: 1. All patients were followed up for 12 months both clinically and radiologically for patency, limb salvage and wound healing. Results: No statistically significant differences were found regarding demographic data, co-morbidities, and risk factors between both groups. 93.3% of patients

were diabetics. The one-year primary patency rates differ between the two approaches only at 12 months and was better for the DCB group (P-value 0.004). The one-year limb salvage rates didn't differ between the two groups. Conclusion: Limb salvage rates were almost the same in the two groups, which is the most important clinical parameter in the CTLI populations, so DCB cannot be considered as a cost-effective modality and should not be used routinely in all cases. Large randomised controlled trials are needed to identify clear indication for the use of the DCB.

***Keywords*---**drug coated balloons, balloon angioplasty, critical limb ischemia, tibial occlusive disease.

Introduction

Rest pain or tissue loss are the main clinical presentations of critical limb ischemia (CLI) which are both limb and life threatening especially in the elderly with severe co-morbidity, so have high risk for surgery (Norgren er al., 2007, Bradbury et al., 2010). An important cause of CLI is isolated infrapopliteal arterial occlusive disease or combined with more proximal lesions (van Overhagen et al., 2013). It remains a challenge for vascular surgeons (Randon et al., 2010). For years interventionists have been searching for a technique of angioplasty to provide a reasonable patency without leaving something behind, and drug coated balloons came as the answer long waited with very promising preliminary results(Reekers et al., 2016). Our study aims at assessing safety and efficacy of both standard and drug coated balloons in the management of tibial occlusive disease, and to compare between both modalities as regard patency and limb salvage.

Methods

Study design: A prospective, randomized study performed at the Department Vascular Surgery in El-Sahel Teaching Hospital and the National Institute of Diabetes between January 2019 and September 2020. Patients were enrolled in this study if they fulfil the inclusion criteria (general and angiographic). Written consents were signed by the patients to verify their acceptance to share their information. Patients are randomized into 2 groups, group A standard balloon angioplasty and group B drug coated balloons in a ratio of 2: 1. Inclusion criteria: General inclusion criteria include: Patient is aged 18 years or more, presented with critical limb ischemia, accepting follow up and understanding the procedure. Angiographic inclusion criteria include lesions (high degree significant stenosis or occlusion) in one or more of the tibial arteries.

Exclusion criteria were: Severe renal impairment (creatinine more than 2.5), any degree of chronic ischemia yet not critical, patients with bleeding disorders and those with contraindications to antiplatelets and anticoagulants. Patients with arteritis and patients in poor general condition and short life expectancy were also excluded. All patients were categorized clinically according to Rutherford categorization of severity of ischemia. Color-flow duplex ultrasound imaging was

done. Interventions details: An Arterial Access is planned after review of the pre-operative imaging and the choice usually depends on the anatomy and operator preference. Antegrade, ipsilateral CFA puncture is preferred unless the lesion is within the first cm of the SFA origin. In this condition, contralateral CFA access and cross over technique is performed. Retrograde ipsilateral puncture of any of the tibial arteres is done if there is failure of antegrade crossing of the lesion. Access from the upper limb (to treat concometant iliac lesions). In case of retrograde access a micropuncture set is used. Crossing the lesions was done with a hydrophilic wire and Berenstein catheter or an angiographic balloon and support catheters were used selectively in cases with long occlusions. Balloons of appropriate diameter as judged by eyeing the normal vessel before or after the lesion. The longest balloon that covers most of the lesion is chosen to minimize the number of inflations. Overlaps of inflation are done until all the lesion is angioplasted. Reangioplasty may be done in segments with residual stenosis, sometimes with higher pressure and sometimes with longer inflation time. Residual stenosis of <30% is considered successful angioplasty. After the completion angiogram is satisfactory, the arterial sheath is removed and manual compression for 15 minutes is done. In the case of use of the DCB, it is inflated after the ordinary ballon angioplasty for 3 minutes. After revascularization, debridement is done to remove all gangrenous and necrotic tissue if present and standard wound care is done according to the standard wound care protocol at the institution.

Outcome parameters

Technical success was defined as palpable distal pulsation and residual stenosis less than 30%.

Follow-up

Follow up was done at 3, 6, and 12 months. Pulses and vascularity were checked, and the wounds examined, and progress documented in Rutherford category. Also, any complications are documented especially in the first visit as access site complications or contrast induced nephropathy. Collected data was statistically analyzed.

Results

Demographic data

45 cases with 45 limbs were included. 60% were male (27 patients) with age ranged between 42-80 years (mean age was 65 years) (Tables 1,2). Risk factors were diabetes mellitus (93.3%), hypertension (80%), smoking (26.6%) and ischemic heart disease (57.7%). (Table 3,4).

Table 1
The distribution of gender in each group of the study groups

	Group		p-value
	DCB Group	PTA Group	

		Count	%	Count	%	
Gender	Male	12	80.0%	15	50.0%	0.053
	Female	3	20.0%	15	50.0%	

Table 2
The distribution of age

	Group										p-value
	Drug coated balloon group					PTA group					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	65.00	13.19	70.00	42.00	76.00	65.67	8.09	65.50	46.00	80.00	0.562

Table 3
Risk factors: overall

Risk factor	Number	Percent
Smoking	12	26.6%
Hypertension	36	80%
Diabetes mellitus	42	93.3%
Ischemic heart disease	26	57.7%

Table 4
Risk Factors per group

		Group				p-value
		DCB Group		PTA Group		
		Count	%	Count	%	
Diabetes	Y	12	80.0%	30	100.0%	0.032
	N	3	20.0%	0	0.0%	
Hypertension	Y	15	100.0%	21	70%	0.020
	N	0	0.0%	9	30%	
Smoking	Y	6	40.0%	6	20%	0.174
	N	9	60.0%	24	80%	
IHD	Y	9	60.0%	17	56.7%	0.831
	N	6	40.0%	13	43.3%	

Co morbidities

26 patients (57.7%) were cardiac of which five patients (11.1%) had previous coronary interventions (two patients had CABG and three patients had PTCA) and five patients (11.1%) had history of stroke all were of the PTA group. Two patients (4.4%) had contralateral major amputations (one above knee and one below knee) all were of the PTA group also. Five patients (11.1%) had previous peripheral angioplasty three patients of the DCB & two patients of the PTA group, and only one patient had previous open surgical revascularizations (femoro-crural bypass

contra-lateral limb). One patient only in the study had a large venous ulcer and was of the DCB group. Three patients have COPD, and all were of the PTA & four patients had mild renal insufficiency and all also were of the PTA group. (Table 5).

Clinical presentations

The preoperative assessment reported just one patient (2.2%) classified as Rutherford category 4 (rest pain), 38 patients (84.4%) as Rutherford category 5 (minor tissue loss) and 6 patients (13.3%) as Rutherford category 6 (major tissue loss) (Table 6). Sub-group analysis showed no patients in the DCB group with rest pain versus one patient in the PTA group. Regarding the minor tissue loss 14 patients were in the DCB group and 24 patients in the PTA group. All the 6 patients presented with major tissue loss were in the PTA group (Table 7).

Lesion allocation and configuration

In all cases total occlusion was found. 11 occlusions involve the superficial femoral artery, two occlusions of the popliteal artery, 37 occlusions involve the ATA, 28 occlusions involve the PERA and in all cases the PTA had occlusions. Runoff vessels analysis shows that 16 patients had 3 vessels runoff (35.5%), 13 patients had 2 vessels runoff (28.8%), 15 patients with single runoff (33.3%) and only 1 patient had no distal run off (Table 8,9). Subgroup analysis showed that the ATA was a run of in 12 patients of the DCB group & in 22 patients in the PTA group. The PTA was a runoff in 12 cases in the DCB group and 12 cases in the PTA group. The peroneal artery was a runoff in 12 cases of the DCB group and 20 cases in the PTA group. The only case with no distal run off was of the PTA group.

Table 5
Co-Morbidities

		Group				p-value
		Drug coated balloon group		PTA group		
		Count	%	Count	%	
COPD=BA	Y	0	0.0%	3	10%	0.540
	N	15	100.0%	27	90%	
Renal insufficiency	Y	0	0.0%	4	13.3%	0.285
	N	15	100.0%	26	86.7%	
Stroke	Y	0	0.0%	5	16.7%	0.153
	N	15	100.0%	25	83.3%	
History of amputation	Y	0	0.0%	2	6.7%	0.545
	N	15	100.0%	28	93.3%	
Previous angioplasty	Y	3	20.0%	2	6.7%	0.315
	N	12	80.0%	28	93.3%	
History of open bypass	Y	0	0.0%	1	3.3%	1
	N	15	100.0%	29	96.7%	
Coronary intervention	Y	0	0.0%	5	16.7%	0.153
	N	15	100.0%	25	83.3%	

Table 6
Patient's clinical presentation by Rutherford categories

Rutherford category	Number	Percent
Rutherford category 4	1	2.2%
Rutherford category 5	38	84.5%
Rutherford category 6	6	13.3%

Table 7
Clinical presentations

		Group				p-value
		Drug coated balloon group		PTA group		
		Count	%	Count	%	
Rest pain	Y	9	60.0%	25	83.3%	0.140
	N	6	40.0%	5	16.7%	
Ulcer	Y	6	40.0%	20	66.7%	0.088
	N	9	60.0%	10	33.3%	
Minor tissue loss	Y	9	60.0%	23	76.7%	0.304
	N	6	40.0%	7	23.3%	
Major tissue loss	Y	0	0.0%	6	20%	0.157
	N	15	100.0%	24	80%	

Table 8
Number of runoff vessels

Number of runoff vessels	Number			Percent
	DCB	PTA	Total	
3 vessels	9	7	16	35.5%
2 vessels	3	10	13	28.8%
Single vessel	3	12	15	33.3%
No run off	0	1	1	2.2%

Procedure
Access used

Most of the patients (38 cases representing 84.4%) had an ipsilateral antegrade femoral access. All the DCB group had ipsilateral femoral access (15 patients). On the other hand, 10 cases (15.5%) were done via a contralateral crossover femoral approach to treat concomitant SFA proximal lesions and all belongs to the PTA group. Only 3 (6.6%) cases had additional retrograde access due to failure of the antegrade trial to cross the lesion and all were of the PTA group (Table 10).

Table 9
Run off vessels

		Group				p-value
		Drug coated balloon group		PTA group		
		Count	%	Count	%	
ATA (Runoff)	Y	12	80.0%	22	73.3%	0.726
	N	3	20.0%	8	26.7%	
PTA (Runoff)	Y	12	80.0%	12	40%	0.011
	N	3	20.0%	18	60%	
PER (Runoff)	Y	12	80.0%	20	66.7%	0.492
	N	3	20%	10	33.3	

Table 10
Types of access used

Access	**Number**	**Percent**
Ipsilateral CFA	38	84.4%
Contralateral CFA	7	15.5%
Retrograde access	3	6.6%

Site of PTA

In the DCB group, the ATA was a site of the angioplasty in all cases, the PTA in 9 cases and the peroneal artery in 3 cases. In the PTA group, SFA angioplasty was done in 14 cases, POPA angioplasty in 4 cases, ATA in 20 cases, PTA in 6 cases & the peroneal artery in 18 cases. 0.35 wires were used in 9 cases all were of the PTA group, 0.018 wires in 22 cases, 12 of the DCB group and 10 of the PTA group. 0.014 wires in 21 cases, 3 of the DCB group and 18 of the PTA group (Table 11).

Table 11
Wire size used

	DCB	PTA	Total
0.35	0	9	9
0.018	12	10	22
0.014	3	18	21

In 34 cases a crossing catheter has been used to cross the lesion, 12 cases of the DCB group and 22 cases of the PTA group. The number of dilatations was significantly higher in the PTA group (Table 12). Stents were used in 10 cases all belongs to the PTA and all were used to treat SFA diseased segments. All the stents were self-expanding stents and of 6 mm diameter. The amount of dye used was significantly higher in the PTA group (Table 13).

Table 12
Number of dilatations

	Group										p-value
	Drug coated balloon group					PTA group					
	Mean	± S.D	Median	Minimum	Maximum	Mean	± S.D	Median	Minimum	Maximum	
No of dilatations	1.00	0.00	1.00	1.00	1.00	1.55	0.69	1.00	1.00	3.00	0.003

Table 13
Amount of dye

	Group										p-value
	Drug coated balloon group					PTA group					
	Mean	±SD	Median	Minimum	Maximum	Mean	±SD	Median	Minimum	Maximum	
Amount of dye (1=50 ml)	1.00	0.00	1.00	1.00	1.00	1.23	0.43	1.00	1.00	2.00	0.044

Complications

The mortality rate was 13.3% (only 6 cases). The complications were present in 8 patients (17.7%) (Fig. 1). All access hematomas were mild to moderate in size and were treated conservatively, one of them was associated with scrotal hematoma which also treated conservatively. CFA pseudoaneurysms occurred in 3 cases and in all duplex guided compression were done successfully. In 2 cases recoil had occurred and treated with prolonged balloon inflation (5 min) with a higher pressure.

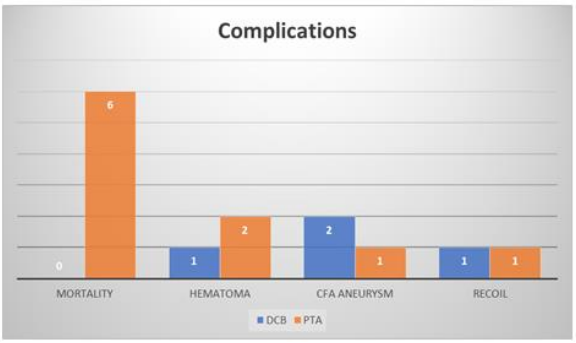

Fig 1. Complications

Technical success

Technical success was 97.7% (44 cases out of 45 cases). The only case with failure of crossing was of the PTA group and ended by AKA. Retrieval of pulse occurred in 12 cases of the DCB group and 8 cases of the PTA group only (Fig. 2).

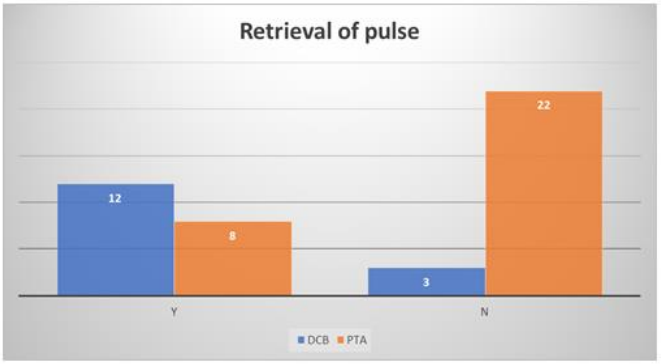

Fig. 2. Retrieval of pulse

Debridement and minor amputation rates

Debridement was done in 32 cases (71.1%), 6 cases in the DCB group and 26 cases in the PTA group. Toes amputation was done in 4 cases all belongs to the PTA group (8.8%) and trans-metatarsal amputation in 10 cases (22.2%) 7 in the PTA group and 3 in the DCB group (Table 14).

Table 14
Debridement

		Group				p-value
		Drug coated balloon group		PTA group		
		Count	%	Count	%	
Debridement	Y	6	40.0%	26	86.7%	0.004
	N	9	60.0%	4	13.3%	

Follow-up

Only one case excluded from the study from the start due to failure to cross the lesion and it ended up by major amputation after one week. It was of the PTA group. 44 patients completed the 3 months follow up, 40 patients completed the 6 months follow up and 37 patients completed the 12 months follow up. All the 15 cases of the DCB group completed the 12 months follow up, while in the PTA group 29 cases completed the 3 months follow up, 25 cases completed the 6 months follow up and 22 cases completed the 12 months follow up.

Patency rates

The 3 months follow up results shows that the primary patency was 100% in the DCB group and 96.7% in the PTA group. The 6 months follow up results shows

that the primary patency was 100% for the DCB group and 76.7% for the PTA group. The 12 months follow up results shows that the primary patency was 80% in the DCB group and 30% in the PTA group. The one-year primary patency rates differ between the two approaches only at 12 months and was better for the DCB group (p-value 0.004) (Fig. 3).

Fig. 3. Primary patency rates

Limb salvage

For the PTA group the limb salvage rates were 96.7% at 3 months, 80% at 6 months and 66.7% at 12 months, while for the DCB group the rates were 100% at 12 months. The one-year limb salvage rates didn't differ between the two groups up to 6 months, (p-value 0.272) YET there was a significant difference between the limb salvage at 12 months favouring the DCB group (p-value 0.029) (Fig. 4).

Fig. 4. Limb salvage rates

Discussion

In patients with CLI due to infrapopliteal arteries atherosclerosis, balloon angioplasty is the first choice due to its low cost and high success rate, low cost, yet with scarce durability (Anderson et al., 2013, Cassese et al., 2016). Newer technologies, although safe and feasible, did not show superiority over standard balloon angioplasty and so the extra cost is not justified (Michael et al., 2015). FDA recommended the use alternative treatment to DCB after the preliminary

results of 50% mortality in patients exposed to paclitaxel coated devices. Studies included in the FDA decision were mainly in the femoropopliteal segment (Katsanos et al., 2018). We believe that the high percentage of diabetic patients in our study (93.3%) has a noticeable effect on the results. Our mortality rate was 13.3% and the overall complication rate was 17.7% which is higher than the meta-analysis done by Cassese et al. (2016) (it was 11.5%), mostly due to diabetes related co morbidities (Cassese et al., 2016). The distal pulse retrieved in only 44.4% of cases and this is mostly due to the arterial wall calcifications in the diabetic patients. We didn't include the ABI as a parameter in our study, as many studies did, as this was not possible in our study due to the predominance of diabetes with a false high ABI. As our study was about CLI and 44 cases out of 45 were classified as Rutherford class 5 and 6, it is normal that nearly all had foot surgery after revascularization especially as we are a developing country and most of the patients seeks medical care in a little bit late stage.

The primary patency didn't differ between the two groups at 3 and 6 months, yet the primary patency rate at 12 months for the DCB group was 80%, while for the PTA group was 30%, showing a statistical significance between the two approaches (P value 0.004). The overall primary patency after 12 months was 42.5%. Even when we exclude the 6 cases of mortality in the PTA group and the case excluded due to failure of crossing the lesion, the primary patency for the PTA group will be 39% which is also significantly lower than that of the DCB. Restenosis rate of 68.8% after 3 months of plain balloon angioplasty was demonstrated by Schmidt et al.(2011), 50% of those needed reintervention (Laird and Armstrong 2014). They also demonstrated better results in the subgroup treated with DCB with restenosis rate only 27.4 with a reduction of 17.3% of TLR (Laird and Armstrong 2014). Similar results also have been demonstrated by Liistro et al. (2013) with reduction in 12-month restenosis (27% vs. 74%) (Cassese et al., 2016) .

Our limb salvage rates were higher than patency rates, based on the concept of situational perfusion enhancement, in which the wound demands are higher early with extensive wounds with infection & necrosis, and once the wounds gets cleaner and smaller, the demand get lower and so even if the angioplastied vessels are occluded, the wound completes its journey to complete healing and closure and the collaterals are enough for the viability of the foot without a wound or gangrene. Again, the limb salvage didn't differ between the two groups at 3 and 6 months, yet the limb salvage at 12 months for the DCB group was 100%, while for the PTA group was 66.7% (P= 0.029). But, if we excluded the 6 mortalities and the case excluded because of failure of crossing the lesion and calculated the limb salvage we will find it about 87%, so there was no statistical significance between the two approaches. In the literature, one-year, and limb salvage rate of 66% to 100%, respectively, have been reported [8]. In a large meta-analysis of series using PTA as the primary treatment modality, the 3-year limb salvage rate was 82.4% [8].A limitation in our study is that we didn't use a classification for the severity of the tibial arteries disease. Anyhow in our study all the cases had occlusions. Other limitation is the small number of cases (45 cases).

Conclusion

Both plain and drug coated balloon angioplasty are safe and effective in treating infrapopliteal atherosclerotic occlusive disease with high technical success and limb salvage rates for 12 months. The one-year patency rate was significantly higher for the treatment with the drug coated balloons than the treatment with the plain balloon angioplasty, yet, although the patency rate was higher with the use of the DCB, the limb salvage rates did not differ significantly between the two modalities of management. As the limb salvage rates was almost the same in the two groups, which is the most important clinical parameter in the CLI populations, DCB cannot be considered as a cost-effective modality in treatment and should not be used routinely in all cases. Larger randomised controlled trials are needed to identify clear indication for the use of the DCB, that's to say when we should use it to be a cost effective.

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