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Original Article

Efficacy and safety of drug-coated balloon versus non-drug-coated balloon combined with bare metal stent implantation in treatment of patients with occlusions of the superficial femoral artery: a retrospective study in clinical practice

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Abstract: Objective: To assess the efficacy and safety of drug-coated balloon and non-drug-coated balloon combined with bare metal stent implantation for the treatment of patients with occlusions of the superficial femoral artery. Methods: In this retrospective study, 83 patients with occlusions of the superficial femoral artery were included. Among them, 41 patients received paclitaxel drug coated balloon treatment combined with bare metal stent implantation treatment (experimental group), the remaining 42 received non-drug-coated balloon treatment (control group). Patients were followed up at 1, 6, and 12 months after surgery. The primary clinical assessments, including ankle brachial index (ABI), RutherFord grade, Doppler ultrasound, or CT angiography (CTA), were used to observe the patency of target vessels, perioperative and postoperative complications. Results: All the diseased vessels were successfully opened. There were no serious intraoperative complications such as vascular rupture or acute thrombosis. There was no significant difference in ankle brachial index, RutherFord grade, and total score between the two groups at one month and six months after operation (P>0.05). There was no significant difference in mortality, amputation rate, or thrombosis between the two groups (P>0.05). Twelve months after the operation, the ankle brachial index, Rutherford grade and total score of the experimental group were better than those of the control group (P<0.05). There was no significant difference in mortality, amputation rate, or thrombosis between the two groups (P>0.05). Conclusion: Paclitaxel coated balloon is safe and effective in the treatment of superficial femoral arteriosclerosis occlusion. It can significantly improve the ABI and Rutherford grades of patients, and it had a higher patency rate and lower reconstruction rate, but it may affect the healing ability of foot ulcer.

Keyword: Paclitaxel drug coated balloon, occlusions of the superficial femoral artery, balloon dilatation, bare metal support, safety

Introduction

Arteriosclerosis obliterans (ASO) is an ischemic disease of lower limbs caused by arterial stenosis and occlusion induced by peripheral atherosclerosis [1, 2]. It is the local manifestation of systemic arteriosclerosis obliterans in lower limbs [3]. Without effective treatment in time, it may lead to amputation and even death in some patients [4, 5]. Superficial femoral artery is the most common vessel that predispose to peripheral arteriosclerosis occlusion, so it has become the research direction [6, 7]. The treatment of superficial femoral artery disease includes traditional open surgery and minimally invasive endovascular treatment [8-10]. Traditional open surgery has the disadvantages of large trauma, multiple complications, and high perioperative mortality [11]. Minimally invasive endovascular therapy has become the main treatment for superficial femoral artery occlusion [12, 13]. Pericutaneous transluminal angioplasty (PTA) refers to the clearance of stenosis or occlusion of dilated blood vessels by insert-

ing balloons or stents into the cavity, which can effectively improve the limb blood supply after operation [14].

Although endovascular interventional technology represented by PTA has been widely used in the clinic, and the technology is becoming increasingly mature, there is a high possibility of re occlusion after unobstructed treatment of lower limb artery occlusion, which affects the clinical efficacy of this technology. Some studies have shown that 50%-60% of patients have restenosis or occlusion of vascular lumen within 1 year after PTA treatment [15, 16]. To solve the problem of restenosis after PTA or stenting, drug coated balloon technology was created, especially paclitaxel drug coating technology, which brings hope to solve the problem of restenosis after stenting [17].

After the drug coated balloon (DCB) reaches the lesion, the balloon expands and drug coating on its surface contacts with and adheres to the vascular wall of the lesion. The slow release of the drug inhibits the growth of intimal and smooth muscle cells and reduces the incidence of restenosis or occlusion [18]. Katsanos et al. [19] suggested that the use of paclitaxel balloon can increase its cure rate. Gray et al. [20] found that there was no difference in long-term mortality between drug balloon and ordinary balloon. Although many trials have confirmed that the efficacy of DCB is significantly better than that of PTA alone, there is little data on whether there is any difference between DCB and non-drug-coated balloon in combination with bare metal stent implantation.

The aim of this research was to assess the efficacy and safety of drug-coated balloon and non-drug-coated balloon in combination with bare metal stent implantation for treatment of patients with occlusions of the superficial femoral artery.

Data and methods

Clinical data

Eighty-three patients with lower extremity ASO treated in the Department of Vascular Surgery of the Affiliated Hospital of Qingdao University from January 2018 to December 2020 were included in this study. Among the 83 populations, 41 patients received paclitaxel-coated balloon treatment combined with bare metal stent implantation treatment (experimental group). The remaining 42 patients received the non-drug-coated balloon (control group). All clinical trials involved in this study were approved by the ethics committee of the Affiliated Hospital of Qingdao University (No.: 201801121), and all patients included in the trial signed an informed consent.

Inclusion and exclusion standard

Inclusion criteria: ① Age ≥18 years old; ② Moderate to severe intermittent claudication, ischemic resting pain, ulcer, or gangrene (Rutherford grade 2-6); ③ The degree of vascular stenosis of lower limbs was 70%~100% in single lesion, combined lesion, or series lesion. The total length of lesions was 10~300 mm; ④ Reference vessel diameter of 4-7 mm; ⑤ Angiography showed sufficient blood flow into the foot at the distal end (at least one autologous blood vessel of the lower leg [anterior tibial artery, posterior tibial artery, and peroneal artery] remained unobstructed, i.e. the stenosis diameter was less than 50%); ⑥ Life expectancy was expected to be more than 1 year.

Exclusion criteria: ① Patients had non lower extremity arteriosclerosis lesions, such as vasculitis; ② Patients developed stroke or ST segment elevation myocardial infarction (STEMI) within 3 months before admission; ③ Patients had a chronic renal insufficiency (serum creatinine >178.6 μmol/L; ④ Patients had signs of bleeding; ⑤ Patients had received major surgery or interventional treatment (such as heart, peripheral, or abdominal) within 30 days before operation; ⑥ Patients had received local or systemic thrombolytic therapy within 48 hours before operation; ⑦ Patients were allergic or sensitive to heparin, aspirin, other anticoagulant/antiplatelet therapies and/or paclitaxel; ⑧ Patients had unsuccessful delivery of the guide wire to pass through the target lesion (successful passing through the target lesion means that the head end of the guide wire can reach far away from the target lesion without current limiting interlayer or perforation); ⑨ Patients had acute or subacute thrombosis in target vessels; ⑩ Pregnant or lactating women.

Intervention

The Experimental group: The smallest drug coated balloon in the lesion area was selected for endovascular angioplasty. The expansion

Table 1. Clinical characteristics of two groups

		Experimental group (n=41 cases)	Control group (n=42 cases)	*P Value*
Gender	male	29 (70.7%)	27 (64.3%)	0.617
	female	12 (29.3%)	15 (35.7%)	0.817
Age		52-85	53-90	0.772
Risk factors				
Hypertension		28 (68.3%)	29 (69.0%)	0.905
Diabetes		27 (65.8%)	24 (57.1%)	0.663
Cardiovascular and cerebrovascular disease		19 (46.3%)	21 (50%)	0.835
Long-term smoking		16 (39.0%)	19 (45.2%)	0.819
Hyperlipidemia		11 (26.8)	12 (28.6%)	0.893

Table 2. Comparison of ABI between the two groups before and after intervention ($\bar{x}\pm s$)

	Experimental group (n=41)	Control group (n=42)	t/χ^2	*P*
Pre-operation	0.39±0.099	0.28±0.033	0.344	0.732
1 week after operation	0.84±0.035	0.87±0.025	0.528	0.600
3 months after operation	0.75±0.034	0.73±0.034	0.352	0.726
6 months after operation	0.70±0.039	0.68±0.031	0.820	0.415
12 months after operation	0.66±0.045	0.44±0.044	0.152	0.043

Note: Significant difference as P<0.05.

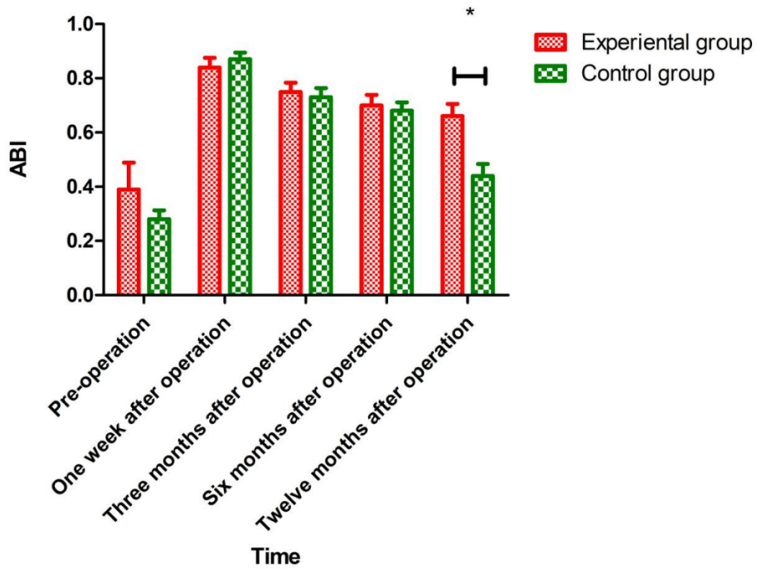

Figure 1. Comparison of ABI between the two groups before and after intervention. *P<0.05.

time was 3 minutes. Digital subtraction angiography was rechecked immediately after the operation to evaluate the treatment effect. If the stenosis was still more than 30% after balloon dilatation, a supplementary remedial bare metal stent (BMS) was applied. For UCB + BMS group, based on non-drug coated balloon expansion step by step, bare metal stents were placed in patients with infinite flow dissection and stenosis >30%. The patients in the two groups were administered aspirin 100 mg orally once a day for a specified time; and Clopidogrel 75 mg orally, once a day for 6 months.

The Control group: According to preoperative color Doppler ultrasound and CTA, the puncture site was selected, and a reasonable operation plan was formulated. After local anesthesia, the ipsilateral or contralateral common femoral artery was punctured by Seldinger technique, and the 6F arterial sheath was successfully inserted. The location, length, and distal outflow tract of the lesion were determined by angiography. Non-drug-coated balloons conforming to the length of the lesion segment (10 mm more than the proximal and distal ends of the target lesion) were selected for progressive preexpansion. The criteria for successful dilation of occluded vessels included [21]: ① Postoperative angiography confirmed that the blood flow was unobstructed; ② The modified TICI was grade III antegrade blood flow; ③ Residual stenosis was less than 50%.

Table 3. Comparison of RutherFord grading between the two groups before and after intervention ($\bar{x}$±s)

RutherFord grading	Groups	1	2	3	4	5	6
Pre-operation	Experimental group	0	0	15 (36.6%)	14 (34.1%)	7 (24.4%)	5 (12.2%)
	Control group	0	0	16 (38.1%)	15 (35.7%)	4 (9.5%)	7 (16.7%)
	t	-	-	2.124	1.395	1.753	2.645
	P	-	-	0.214	0.085	0.119	0.223
One week after operation	Experimental group	0	10 (24.4%)	10 (24.4%)	9 (21.9%)	7 (17.1%)	5 (12.2%)
	Control group	0	8 (19%)	13 (30.9%)	7 (16.7%)	4 (9.5%)	7 (16.7%)
	t	-	3.267	2.471	2.151	2.654	1.793
	P	-	0.093	0.095	0.078	0.088	0.913
Three weeks after operation	Experimental group	6 (14.6%)	9 (21.9%)	7 (17.1%)	8 (19.5%)	6 (14.6%)	5 (12.2%)
	Control group	7 (16.7%)	8 (19%)	8 (19%)	7 (16.7%)	3 (7.1%)	7 (16.7%)
	t	1.531	1.841	2.295	2.537	4.551	1.401
	P	0.931	0.881	0.065	0.751	0.093	0.071
Six weeks after operation	Experimental group	9 (21.9%)	11 (26.8%)	8 (19.5%)	3 (7.3%)	5 (12.2%)	5 (12.2%)
	Control group	8 (19%)	9 (21.4%)	10 (23.8%)	6 (14.3%)	2 (4.7%)	7 (16.7%)
	t	1.940	2.433	2.887	3.543	3.241	2.777
	P	0.066	0.102	0.221	0.199	0.079	0.084
Twelve weeks after operation	Experimental group	14 (34.1%)	13 (31.7%)	5 (12.2%)	3 (7.3%)	2 (4.9%)	5 (12.2%)
	Control group	9 (21.4%)	10 (23.8%)	10 (23.8%)	5 (11.9%)	0	7 (16.7%)
	t	7.776	3.219	6.392	1.887	1.221	1.423
	P	0.037	0.310	0.042	0.210	0.193	0.072

Note: Compared with the control group, Significant difference as P<0.05.

Table 4. Condition of the lesion in two groups ($\bar{x}$±s)

Condition of the lesion	Experimental group (n=41)	Control group (n=42)	*P* Value
The length of the lesion (mm)	65.20±28.37	51.84±30.67	0.685
Reference vessel diameter (mm)	4.8±0.5	4.8±0.4	0.793
The rate of severe calcification	11 (26.8)	8 (19.0)	0.435
The rate of complete occlusion	27 (65.9%)	25 (59.6%)	0.605

Note: Significant difference as P<0.05.

Observation index

The primary observation indices were ankle brachial index (ABI), ulcer healing rate, primary patency rate of target vessels, and reprocessing rate of target lesions at the 24-month follow-up. Primary patency rate of target vessels was defined as free of stenosis or binary restenosis, which was defined as a duplex ultrasonography peak systolic velocity ratio of >2.4 or a >50% diameter stenosis from the angiography. The ankle brachial index (ABI) measured in normal people at rest is 0.9-1.3. Lower than 0.8 indicates moderate lesions of lower limb arteries. Lower than 0.5 indicates severe lesions of lower limb arteries. Patients with ABI of 0.35-0.9 usually have intermittent claudication, and those below 0.4 often complain about lower limb resting pain. If it is not treated in time, there may be the risk of amputation. The Würzburg Wound Scale (WWS) was applied to assess wound healing. The WWS consists of 17 Likert-scaled items divided into the following subscales: physical complaints (seven items), occupational and everyday life (three items), social life (three items), psyche (two items), and stress caused by therapy (two items).

The secondary endpoints were occurrence of major adverse events (hematoma and distal arterial embolism), and improvement of the Rutherford grade at 12 months. Rutherford grading criteria: asymptomatic is grade 0, mild intermittent claudication is grade 1, moderate intermittent claudication is grade 2, severe intermittent claudication is grade 3, resting pain is grade 4, slight tissue defect is grade 5, and tissue gangrene and ulcer are Grade 6. The higher the grade is, the more serious the patient's Ischemia and the more serious the symptoms. After operation, patients were fol-

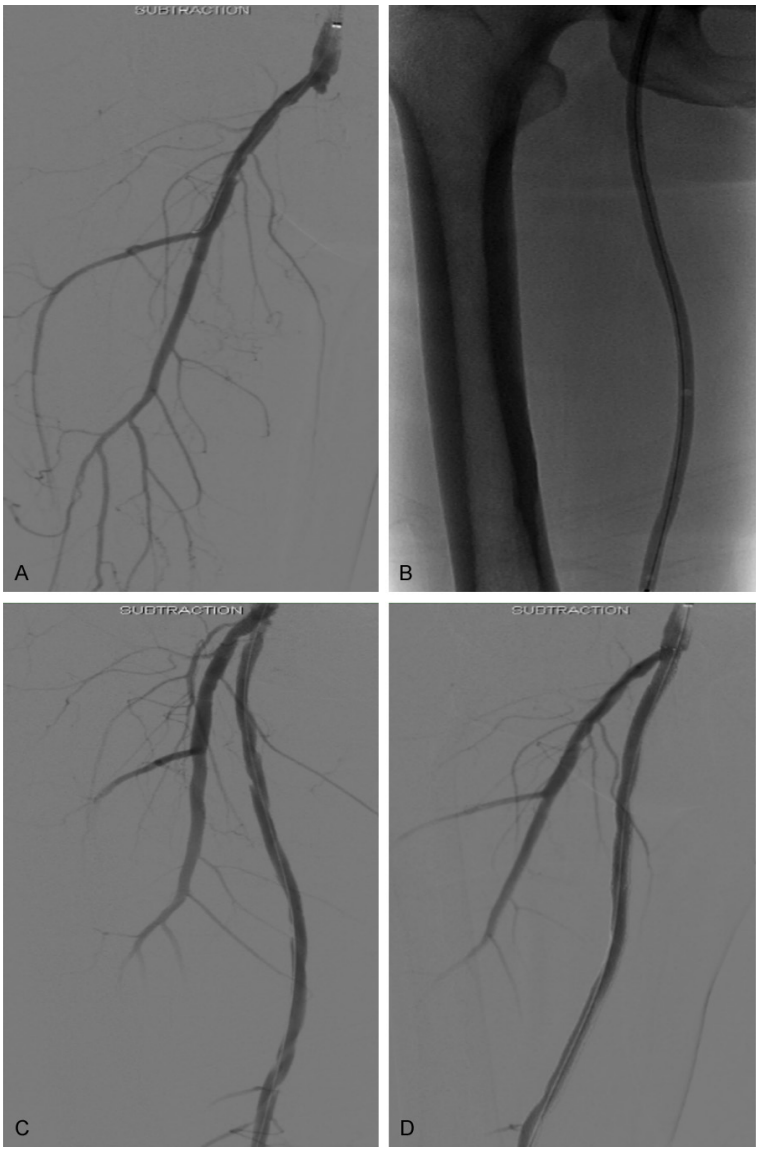

Figure 2. Preoperative examination and intraoperative angiography. A: The condition of preoperative angiography. B: After full pre expansion, exchange drug coated balloon (5*300 mm) to dilate the superficial femoral artery for 3 minutes. C: After balloon dilation, more dissections were found, and stenting was decided. D: Salvage stenting of superficial femoral artery.

lowed up at 1, 3, 6, and 12 months, and evaluation indicators were analyzed up to 12 months.

Statistical analysis

The count data were expressed as (n, %), and the comparison was performed by χ^2 test. The measured data were expressed by mean ± standard deviation (x ± SD). The measured data among groups were compared by independent t test or one-way ANOVA test followed by LSD test. Pairwise comparison between groups was performed using t test. Data were analyzed using the SPSS 19.0 software (SPSS for Windows software, SPSS Inc., Chicago, IL).

Results

Clinical characteristics

The average age of the experimental group was (70.6±10.2) years old. Among them, there were 29 cases of hypertension, 27 cases of diabetes mellitus, 19 cases of cardiovascular and cerebrovascular diseases, 8 cases of hyperlipidemia, and 16 cases of long-term smoking. There was no significant difference in general data, complications, cardiovascular and cerebrovascular risk factors, preoperative ABI, and Rutherford clinical grade between the two groups (all P>0.05) (**Table 1**).

Comparison the ABI and RutherFord grading between two groups

As shown in **Table 2** and **Figure 1**, the level of ABI had no significant difference between the two groups at one week, three months, and six months after operation (all P>0.05), but it was obviously higher in the experimental group at 12th month after operation as compared with that in the control group (P<0.05). The number of patients with Rutherford grade 1 and 3 in the experimental group was significantly higher than that in the control group at 12 month after intervention (all P<0.05) (**Table 3**).

Comparison of condition of the lesion between the two groups

The length of the lesion, reference vessel diameter, rate of severe calcification, and rate of complete occlusion were not statistically different between the two groups (all P>0.05) (**Table**

Table 5. Comparison of WWS score between the two groups

Wound evaluation points	Experimental group (n=41)	Control group (n=42)	*P* value
Pre-operation	18.78±0.29	19.15±0.35	0.768
1 week after surgery	17.21±0.21	17.37±0.28	0.617
3 weeks after surgery	10.11±1.87	13.59±2.11	0.032
6 weeks after surgery	4.76±1.06	7.59±2.15	0.012

Note: Compared with the control group, P<0.05.

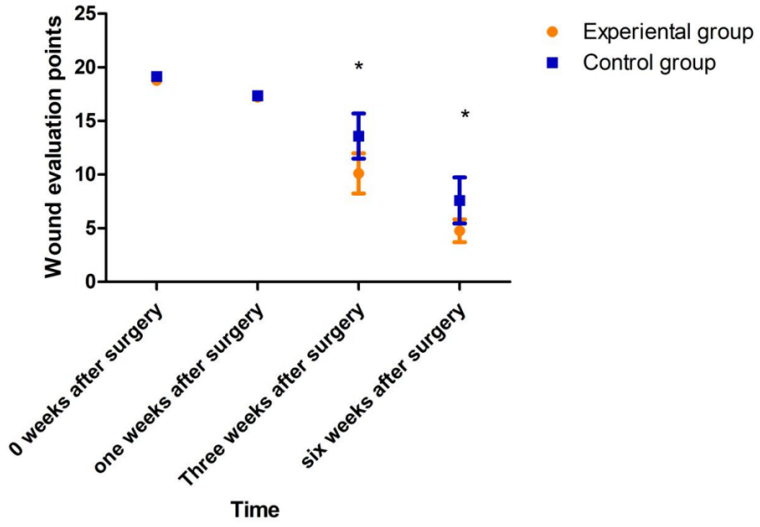

Figure 3. Comparison of wound evaluation points between the two groups. *P<0.05.

4). We recorded the vascular condition during the preoperative examination and intraoperative angiography. The results showed that the vascular blood flow was unobstructed after drug-coated balloon intervention (**Figure 2**).

Comparison of Würzburg Wound Scale (WWS) score between the two groups

As shown in the **Table 5** and **Figure 3**, the WWS score after treatment in the experimental group was significantly lower than that in the control group at three and six weeks after the surgery [(10.11±1.87) vs (13.59±2.11); (4.76±1.06) vs (7.59±2.15); all P<0.05], but there was no significant difference between the two groups at one week after surgery [(17.21±0.21) vs (17.37±0.28), P>0.05].

Comparison of safety index between the two groups

There were no serious surgery or surgical instrument related postoperative complications or death in the two groups. Two patients (5.4%) in the control group had limb amputation, which was significantly higher compared with the experimental group (P< 0.01). There was no death caused by other causes in both groups (**Table 6**).

Comparison of patency rate and reprocessing rate of target lesions between the two groups

As shown in the **Table 7**, the patency rate at 12th month after the operation in the experimental group was significantly higher than that in the control group [(82.9%) VS (64.3%), P<0.05]. The reprocessing rate of target lesions at 12th month after operation was also significantly higher than that in the control group [(71.4%) VS (60%), P<0.05] (**Table 8**).

Discussion

Femoral popliteal artery occlusion is a common disease in lower extremity arteriosclerosis occlusive diseases. Without timely and effective treatment, it can lead to lower extremity ischemia necrosis and even amputation. In recent years, the development of endovascular therapy has been continuously improved. Its advantages of small trauma and repeatable intervention, has made it become the first choice for the treatment of femoral popliteal artery occlusion [22, 23]. Due to the restenosis caused by the wide application of stents, the curative effect of patients is seriously affected. A commonly used drug for DCB is an antiproliferative drug called paclitaxel, which plays an important role in preventing intravascular restenosis [24]. It is highly lipophilic, promotes absorption, and protects the integrity of vascular wall tissues, and resists the scouring of blood flow [25]. Most of its drugs can quickly penetrate the arterial wall to prevent postoperative restenosis by inhibiting and delaying the migration and proliferation of smooth muscle cells through anti-proliferation and anti-inflammatory effects [26, 27]. Most foreign trials support the efficacy and safety of DCB plasty [28-

Table 6. Comparison of adverse events after treatment between the two groups

Indicator	1 month after operation		3 months after operation		6 months after operation		12 months after operation	
	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
serious adverse event	0	0	0	1	0	1	0	0
Target limb amputation	0	0	0	0	0	1	0	1
Surgery-related deaths	0	0	0	0	0	0	0	0

Note: Compared with the control group, P<0.05.

Table 7. Comparison of patency rate between two groups

Primary patency rate	Experimental group (n=41)	Control group (n=42)	*P* value
One week after operation	41 (100%)	42 (100%)	1
Three months after operation	39 (92.8%)	38 (90.4%)	0.793
six months after operation	37 (88.1%)	34 (80.1%)	0.435
twelve months after operation	34 (82.9%)	27 (64.3%)	0.025

Note: Compared with the control group, P<0.05.

Table 8. Comparison of reprocessing rate of target lesions between two groups

reprocessing rate of target lesions	Experimental group (n=41)	Control group (n=42)	*P* value
Three months after operation	41 (100.0%)	3 (75.0%)	0.768
six months after operation	3 (75.0%)	6 (75.0%)	1
twelve months after operation	5 (71.4%)	3 (60.0%)	0.032

30]. There are still many trials that hold different conclusions about the clinical relevance of DCB plasty in the treatment of ASO. The use of drug-coated balloon in the treatment of diseased vessels has a high patency rate. It could avoid the risk of stent rupture. Kayssi [31] et al. found that the use of paclitaxel coated devices for the treatment of femoral popliteal artery disease increased all-cause mortality compared with uncoated devices, which raised concerns about the safety of drug coated devices.

In our study, the results demonstrated that paclitaxel coated balloon could affect the healing ability of foot ulcer. The results are different from the others [32, 33]. We infer that the possible reasons are: ① The coated drugs flow to the distal limb with the blood flow, which may lead to distal thromboembolism [34]. ② Vasculitis may occur after DCB treatment, which affects ulcer healing. Although it can effectively inhibit the proliferation of vascular smooth muscle cells, it also inhibits the growth of vascular intimal cells and hinders the process of vascular re-endothelialization after treatment. After the efficacy of the coating disappears or weakens, the blood vessels without vascular endothelial cells will be followed by thrombosis, resulting in restenosis or even occlusion of the lumen [35].

In view of the possible risks of paclitaxel balloon to patients, many trials are promoting the improvement scheme of DCB. If non PTX compounds such as "LIMUS" drugs are used in DCB, they have a larger treatment window and may be superior to PTX in safety. Many studies have combined DCB with assistive devices such as atherosclerotic plaque resection or stent implantation to improve the long-term patency rate. In a central study, directional atherosclerotic plaque resection was combined with DCB, and the results showed that rates of target lesion revascularization (TLR) decreased significantly at 12 months [36]. At present, the low-dose drug coated peripheral balloon for reducing paclitaxel adverse reactions has been applied in clinics. The product adopts the design of ultra-low drug loading (0.6 ug/mm^2) without affecting the drug transfer density.

There were limitations in our study. This study had a short follow-up time and a small sample size. The experimental time was short. We did not observe the long-term efficacy and recurrence of the patients. A larger, placebo-controlled, perspective study is needed to evaluate the efficacy and mechanism of the efficacy and safety of drug-coated balloon versus non-drug-coated balloon combined with bare metal stent implantation for treatment in patients with occlusions of the superficial femoral artery.

In conclusion, the therapeutic effect of patients in the drug-coated balloon group was significantly better than that in the non-drug-coated balloon combined with bare metal stent implantation group, but we have to pay attention to its safety. For example, some trials have concluded that paclitaxel coated devices have increased all-cause mortality compared with uncoated devices. A larger sample size is needed to draw a final and more reliable conclusion. In view of the slow healing of ulcer caused by paclitaxel, we can reduce the risk by reducing the dose of paclitaxel and replacing non paclitaxel drugs.

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Disclosure of conflict of interest

None.

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