Comparison of Therapeutic Efficacy of Debulking Plus Drug-coated Balloon Angioplasty Versus Drug-coated Balloon Angioplasty Alone for Femoropopliteal Tosaka Class Iii in-stent Restenosis Lesions

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Abstract

Background: Femoropopliteal (FP) Tosaka Class III in-stent restenosis (ISR) Lesions remain a significant clinical problem and optimal revascularization management including the use of drug-coated balloon (DCB) and debulking devices have the potential to improve the outcomes for these patients. However, few studies have been published comparing the debulking plus DCB with DCB alone in Tosaka III FP-ISR treatment. This study was to compare debulking plus DCB versus DCB alone for the treatment of Tosaka III FP-ISR lesions in patients.

Methods: This was a single-center retrospective study of patients Tosaka III FP-ISR who underwent endovascular interventions of debulking plus DCB or DCB alone for Tosaka III FP-ISR lesions. One-year primary patency was the main outcome. Other outcome measures are 12-month freedom from clinical-driven target lesion revascularization (f-CD-TLR), technical success rate, and periprocedural complications.

Results: A total of 70 patients with Tosaka III FP-ISR were included; 29 were treated with debulking plus DCB, in which 13 were treated with laser atherectomy (LA) plus DCB and 16 were treated with rotational atherectomy (RA) plus DCB. 41 were treated with DCB alone. Lesions in the debulking plus DCB group were significantly longer (16.45 ± 4.40 mm vs. 14.04 ± 3.67 mm, $p=0.015$). the 12-month primary patency was not significant different in the comparison of debulking+DCB with DCB group (75.9% vs. 73.2%, $p=0.798$). in the subgroup comparison, no significant difference was found in the LA+DCB and RA+DCB group (69.2% vs. 81.3%, $p=0.544$). There were also no significant differences in the group and subgroup comparison of 12-month f-CD-TLR, technical success rate, and periprocedural complications.

Conclusions: Debulking plus DCB or DCB alone are both safe and effective for Tosaka III FP-ISR lesions. Although no significant difference was seen, lesions in the debulking+DCB group were significantly longer, suggesting that debulking plus DCB treatment has possible superiority for longer lesions than DCB alone management.

Background

Femoropopliteal In-stent restenosis (FP-ISR) is a challenging issue to treat considering the poor short-term patency and high possibility of target lesion revascularization (TLR)[1]. Debulking treatment, has been attempted to improve patency by lessening restenotic tissue burden. However,

only few studies using debulking devices have reported good results[2]. Drug-coated balloon (DCB) is an emerging therapeutic means and several randomized controlled trials have shown its superiority compared to plain old balloon angioplasty (POBA) in FP-ISR treatment[3, 4]. The debulking of in-stent lesions may potentially improve DCB effects by reducing the thrombus or hyperplastic tissue and advancing paclitaxel dosage transit to the intima[5]. Multiple studies have demonstrated debulking plus DCB have better results than debulking alone[6, 7], Yet few studies have been published comparing the

debulking plus DCB with DCB alone in FP-ISR treatment. This paper aims to complete this comparison from our center experience.

Methods

Patient population and clinical characteristics

This is a single-center, retrospective study and ethical approval was obtained from the hospital review board and human investigations committee (protocol number: 2021152). Patients with Tosaka III FP-ISR lesions treated with debulking plus DCB or DCB alone from Jan. 2017 to Dec. 2019 were enrolled. The included criteria were as follows: (1) patients age 45 years or older; (2) subacute or chronic symptoms with Rutherford category I–II; (3) the presence of Tosaka III FP-ISR lesions; and (4) the lesions can be treated with the available debulking devices and Acotec Orchid DCB. According to the standard protocols, the patients' characteristics such as age, gender, morbidities, risk factors and Rutherford classification were collated. Patients with normal renal function also had computed tomographic angiography (CTA) to further assess the operation-detailed strategy including arterial anatomy, total occlusive lesions, calcified lesions, stent fracture and etc.

Endovascular procedures

Before the endovascular procedure, all the patients were prescribed dual-antiplatelet therapy of aspirin 100 mg/day and clopidogrel 75mg/day for at least 3 days. Patients were treated by experienced team in endovascular suite under local anesthesia or intravenous sedation when necessary. During the procedures, 6-8 French sheaths were used for artery access. True luminal or subintimal recanalization was performed on in-stent total occlusions (using 0.035 or 0.018-inch hydrophilic guidewire. Debulking devices, including excimer laser (Spectranetics, USA), or Rotarex catheter (Straub Medical, Switzerland) were employed at the discretion of the endovascular specialists. Distal protective devices (EV3, USA) were used in the procedure of LA with excimer laser, while not used in the RA with Rotarex catheter. At least one plain balloon was used for vessel-preparation before DCB dilations. All patients were treated with Orchid DCB (Acotec, China) coated with 3.0µg paclitaxel per mm² and magnesium stearate as the excipient. The diameter of the DCB was equal or 0.5mm larger than the plain balloon. The length of the all DCB used was sufficient to cover the entire lesions. The successful procedure was defined as residual stenosis ≤ 30%. bailout stenting was deployed according to the endovascular surgeon's judgment as to the optimal treatment of the lesions. Self-expanding stents (Medtronic, USA; Bard, USA; Biotronik, Germany) were available in diameters of 4-6 mm and in lengths up to 150mm. Associated blow-the-knee lesions were allowed to be treated with plain balloon in order to obtain the good runoffs.

Follow-up

All patients were prescribed dual-antiplatelet therapy at least 6 months after the procedure and changed to one agent after that. All patients underwent color coded Doppler ultrasound (CDUS) surveillance when 3, 6, 12 months and subsequently, annually after the procedure, or anytime when suffering limb

discomforts. The deadline for follow-up was August, 2021, when scheduled follow-up for all patients was longer than 12 months.

Endpoints and periprocedural data

The main outcome measure was 12-month primary patency defined by freedom from restenosis of the target lesion during follow-ups. Restenosis was defined as ≥50% diameter reduction based on criteria of a proximal systolic peak flow velocity ratio ≥2.4 detected by CDUS[8]. Other outcome measures are freedom from 12-month f-CD-TLR, technical success rate, periprocedural complications such as death, limb-threatening ischemia, embolization and hematoma. Lesion length and bailout stent implantation were also recorded in the procedure.

Statistical analysis

Statistical analysis was performed by SPSS version 19.0 (IBM SPSS, Armonk, NY, USA). Comparison of the categorical variables between the two groups was performed using a Chi-square (χ^2) test (using Fisher test when n<30). Comparison of continuous variables was investigated using t-test for independent-samples. Time-to-event end-point analysis was analyzed by using Kaplan–Meier (log-rank) method. P-value <0.05 indicated a statistically significant difference.

Results

Patient characteristics

seventy patients were included by this retrospective study with completion of scheduled follow-ups. The subjects were divided into two groups on the basis of procedure method: Debulking+DCB group (n=29) and DCB group (n =41). In order to distinguish the debulking approach, Debulking+DCB group was then divided into the subgroups of LA+DCB and RA+DCB. Overall patients were aged between 49 and 88 years, (mean age, 70.56±9.59 years). The baseline demographic and concomitant disease characteristics were similar in the two groups and two subgroups (Table 1, 2).

Table 1 Characteristic Baseline in Patients Treated with Debulking plus DCB vs. DCB Alone

	Debulking+DCB	DCB	p
Age, y	72.03±8.52	69.51±10.26	0.282
Gender (n, male/female)	22/7	32/9	0.830
Hypertension (n, yes/no)	11/18	17/24	0.766
Diabetes (n, yes/no)	10/19	19/22	0.321
Smoker (n, yes/no)	12/17	16/25	0.843
Dyslipidemia (n, yes/no)	21/8	30/11	0.944
Coronary artery disease (n, yes/no)	7/22	12/29	0.634
Cerebrovascular disease (n, yes/no)	6/23	9/32	0.899
Rutherford classification(n)			
Ⅱ	19/10	26/15	0.856
Ⅲ	7/22	10/31	0.981
Ⅳ	3/26	5/36	1.000

Table 2 Characteristic Baseline in Patients Treated with LA plus DCB vs. RA plus DCB

	LA+DCB	RA+DCB	p
Age, y	72.31±7.96	71.81±9.20	0.880
Gender (n, male/female)	10/3	12/4	0.626
Hypertension (n, yes/no)	5/8	7/9	0.537
Diabetes (n, yes/no)	5/8	9/7	0.282
Smoker (n, yes/no)	6/7	8/8	0.566
Dyslipidemia (n, yes/no)	11/2	11/5	0.292
Coronary artery disease (n, yes/no)	3/10	6/10	0.336
Cerebrovascular disease (n, yes/no)	4/9	6/10	0.507
Rutherford classification (n)			
Ⅱ	8/5	10/6	0.628
Ⅲ	3/10	5/11	0.474
Ⅳ	2/11	1/15	0.420

Follow-up results and operative details

Measurement Results and Operative Details were shown in the Table 3 and 4. Twelve-month primary patency rate was 75.9% (22/29) in the Debulking+DCB group, and 73.2% (30/41) in the DCB group (Figure 1). In the analysis of subgroups, the twelve-month primary patency LA+DCB and RA+DCB group were 69.2%(9/13) and 81.3%(13/16) respectively (Figure 2). There was no significant difference between the two groups and subgroups in the patency ($p=0.798$ and 0.544). The Debulking+DCB group have a longer lesion length than DCB group ($16.45\pm4.40\text{mm}$ vs. $14.04\pm3.67\text{mm}$, $p=0.015$). In DCB group, one patient suffered acute thrombosis 2 days after procedure and received re-intervention by in-stent catheter-directed thrombolysis and bailout stent. embolization was seen in below-the-knee artery and removed by 4F catheter in two patients of DCB group, one patient in LA+DCB group, and three patients in RA+DCB group. Three hematoma was all healed by conservative observation and pressure therapy.

Table 3 Outcome Measures in Patients Treated with Debulking plus DCB vs. DCB Alone

	Debulking +DCB	DCB	p
Technical success, %	100	100	-
Lesion length(mm)	16.45±4.40	14.04±3.67	0.015
Bailout stent (n, yes/no)	7/22	10/31	0.981
12-month primary patency	22/29=75.9%	30/41=73.2%	0.798
12-month f-CD-TLR	25/29=86.2%	35/41=85.4%	0.909
Periprocedural complications			
Death	0	0	-
Limb-threatening ischemia	0	1	1.000
embolization	4	2	0.379
Hematoma	2	1	0.758

Table 4 Outcome Measures in Patients Treated with LA plus DCB vs. RA plus DCB

	LA+ DCB	RA+DCB	p
Technical success, %	100	100	-
Lesion length (mm)	16.07±4.87	16.76±4.13	0.683
Bailout stent (n, yes/no)	3/10	5/11	0.474
12-month primary patency	9/13=69.2%	13/16=81.3%	0.544
12-month f-CD-TLR	11/13=84.6%	14/16=87.5%	0.848
Periprocedural complications			
Death	0	0	-
Limb-threatening ischemia	0	0	-
embolization	1/12	3/13	0.383
Hematoma	1/12	1/15	0.704

Discussion

in-stent FP occlusion, or Tosaka ✎ FP-ISR remains a significant clinical challenge for the endovascular specialists, and there is still no consensus as to the best approach of treating it. Stent implantation triggers reorganization of the atherosclerotic plaque and durative barotrauma to the intima layer, which leads to complex pathophysiological processes initiating smooth muscle cell migration, proliferation, and over-production of extracellular matrix. The resulting intimal hyperplasia causes in-stent lumen loss that causes the occurrence of clinically restenosis or occlusion[9]. Inadequate antithrombotic treatment, lack of response to drugs, elastic characteristics, poor below-the-knee runoff, length and fracture of the stent, and control of cardiovascular risk factors are some of the predictors associated with low patency in previous studies[10]. Although bypass surgery is still considered the good treatment of Tosaka ✎ FP-ISR, many patients are not candidates for the traditional surgery due to severe comorbidities or high surgical risk.

In 2012, Tosaka et al have reported results of POBA for FP-ISR, proposing Tosaka classification system to define the patterns of restenosis. In their observation, the totally-occluded stents (class III ISR) were associated with an increased risk of recurrent ISR/occlusion and revascularization, compared to the restenotic groups (classes I and II ISR). This confirms the inadequacy of POBA and the need for better endovascular techniques to improve the results in the Tosaka ✎ FP-ISR lesions.

Debulking devices, including Strub Rotarex, excimer laser, letstream, Silverhawk and et al have been confirmed to be feasible for FP-ISR treatment with variant results of primary patency and f-TLR, and superior to those of conventional POBA[11–14]. To some extent, debulking techniques could improve the results of FP-ISR treatment by acquiring more lumen gain compared with POBA. However, A systematic review and meta-analysis including 12 studies with 743 patients showed that the 12-month primary

patency of debulking treatment was 58.3% and the f-TLR was 68.2%[2]. Therefore, debulking techniques still revealed relatively high restenosis rates and are not considered to be routine ISR managements.

DCB, firstly used in percutaneous coronary intervention, delivers pharmaceutical ingredients, usually paclitaxel at the de novo or ISR of lesions, which could inhibit smooth muscle cell proliferation and therefore reduce or delay the restenosis[15]. In the following years, DCB was tentatively used in the treatment of de novo or ISR of FP lesions. In comparison to POBA, DCB had a higher patency rate and f-TLR at 6- and 12-months follow-up in FP-ISR management, and there was no difference in incidence of amputation, all-cause adverse events and mortality [16]. In the IN.PACT Global Study ISR Cohort[17], a total of 131 subjects with 149 ISR lesions were included and mean lesion length was 17.17 ± 10.47 cm. The 12-month primary patency was 88.7% and freedom of clinically driven TLR was 7.3%. There were no major amputations or deaths, and a low (0.8%) thrombosis rate. Moreover, several studies suggested debulking plus DCB angioplasty has a distinct superiority compared to debulking alone[7, 18].

However, the comparison of debulking plus DCB versus DCB alone for Tosaka III FP-ISR lesions are few. In 2013, a single-center, prospective, randomized study compared debulking using laser atherectomy plus DCB versus DCB alone included 48 patients. In the Debulking+DCB group, the primary patency rate at 12 months was 66.7%, significantly higher than 37.5% in the DCB only patients[19]. the patency rate was not good and the perhaps reason could be that the early product of DCB was not effective from the fabrication process and usage method (only 1 min DCB dilatation in this study, while 3 mins in the recent standard). In our study, Debulking+DCB and DCB group both have good 12 month patency. Although no significant difference was found between the two groups, the mean lesion length in Debulking+DCB group was longer than that of DCB group, suggesting that operators tend to use Debulking treatment for longer lesions. Therefore, we assume that debulking+DCB group has superiority to DCB group. The reason may be that debulking modifies the atherosclerotic plaque, exposing endothelial micropores whereby paclitaxel could more easily permeate through the neointimal tissue.

Conclusion

Debulking plus DCB or DCB alone are both safe and effective for Tosaka III FP-ISR lesions. Although no significant difference was found in the efficiency and safety, lesions in the debulking+DCB group were significantly longer, suggesting that debulking plus DCB management has a possible superiority compared with DCB alone for longer lesions. High-quality randomized clinical trials (RCTs) are needed to evaluate these two methods.

Abbreviations

FP: Femoropopliteal; ISR: in-stent restenosis; DCB: drug-coated balloon; f-CD-TLR: freedom from clinical-driven target lesion revascularization; LA: laser atherectomy; RA: rotational atherectomy; POBA: plain old balloon angioplasty; CTA: computed tomographic angiography; CDUS: color coded Doppler ultrasound; RCTs: randomized clinical trials

Declarations

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Not Applicable.

Authors' contributions

The following authors contributed to the preparation of the manuscript as follows: LL: Study design, manuscript editing, interpretation of data, literature search. ZT and SC: Statistical analysis, manuscript editing, literature search. YG and LG: Study design and concept, manuscript editing, interpretation of data, literature search. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki. The Institutional Review Board of Xuanwu Hospital, Capital Medical University, Beijing, China, approved the study and waived the consent because of the retrospective nature. Ethic Name: Drug-Coated Balloon for the Treatment of Femoropopliteal Tosaka Class III In-stent Restenosis Lesions. Ethic Number: 2021152.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Figures

Figure 1

Kaplan-Meier curves showing 12-month primary patency of patients treated with debulking plus DCB and DCB alone.

Figure 2

Kaplan-Meier curves showing 12-month primary patency of patients treated with LA+DCB and RA+DCB.