Debulking plus Drug-coated Balloon Angioplasty versus Drug-coated Balloon Angioplasty alone for Femoropopliteal Tosaka III In-stent Restenosis Runing

Liqiang Li
Department of Vascular Surgery, Xuanwu Hospital and Institute of Vascular Surgery, Capital Medical University

Zhu Tong
Department of Vascular Surgery, Xuanwu Hospital and Institute of Vascular Surgery, Capital Medical University

Shijun Cui
Department of Vascular Surgery, Xuanwu Hospital and Institute of Vascular Surgery, Capital Medical University

Lianrui Guo (lianruiguosina.com)
Department of Vascular Surgery, Xuanwu Hospital and Institute of Vascular Surgery, Capital Medical University

Research Article

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Abstract

Objectives: 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.

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 80 patients with Tosaka III FP-ISR were included; 39 were treated with debulking plus DCB, in which 22 were treated with laser atherectomy (LA) plus DCB and 17 were treated with rotational atherectomy (RA) plus DCB. 41 were treated with DCB alone. 12-month primary patency was significantly different in the comparison of debulking+DCB with DCB group (87.2% vs. 65.9%, p=0.039). in the subgroup comparison, no significant difference was found in the LA+DCB and RA+DCB group (86.4% vs. 88.2%, p=0.842). 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: In this small preliminary experience, combined treatment with Debulking and DCB angioplasty is correlated with better outcomes in one-year primary patency for Tosaka III FP-ISR lesions.

Introduction

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 in two-year follow up.

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 Aug. 2020 were enrolled. The included criteria were as follows: (1) patients age 45 years or older; (2) subacute or chronic symptoms with Rutherford category II–III; (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 sub-neointimal recanalization was performed on in-stent total occlusions (using 0.035 or 0.018-inch hydrophilic guidewire. Debulking devices, including 2.3 or 2.5mm excimer laser (Spectranetics, USA), or 6F Rotarex catheter (Straub Medical, Switzerland) were employed at the discretion of the endovascular specialists. 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 (including stent-in-stent and stent distally or proximately to the ISR lesion) 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, Gemany) 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 Aug 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 (χ²) 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

eighty 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=39) 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 51 and 88 years, (mean age, 70.83±9.04 years). The baseline demographic and concomitant disease characteristics were similar in the two groups and two subgroups (Table 1, 2).

Table 1

<table>
<thead>
<tr>
<th>Characteristic Baseline in Patients Treated with Debulking plus DCB vs. DCB Alone</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline in Patients Treated with LA plus DCB</th>
<th>DCB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.87±8.13</td>
<td>69.83±9.82</td>
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</tr>
<tr>
<td>Gender (n, male/female)</td>
<td>28/11</td>
<td>32/9</td>
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</tr>
<tr>
<td>Hypertension (n, yes/no)</td>
<td>17/22</td>
<td>17/24</td>
<td>0.848</td>
</tr>
<tr>
<td>Diabetes (n, yes/no)</td>
<td>15/24</td>
<td>19/22</td>
<td>0.476</td>
</tr>
<tr>
<td>Smoker (n, yes/no)</td>
<td>17/22</td>
<td>16/25</td>
<td>0.678</td>
</tr>
<tr>
<td>Dyslipidemia (n, yes/no)</td>
<td>25/14</td>
<td>30/11</td>
<td>0.382</td>
</tr>
<tr>
<td>Coronary artery disease (n, yes/no)</td>
<td>10/29</td>
<td>12/29</td>
<td>0.716</td>
</tr>
<tr>
<td>Cerebrovascular disease (n, yes/no)</td>
<td>6/33</td>
<td>9/32</td>
<td>0.452</td>
</tr>
<tr>
<td>Rutherford classificationn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>28</td>
<td>26</td>
<td>0.424</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>10</td>
<td>0.678</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>5</td>
<td>0.502</td>
</tr>
</tbody>
</table>

**Table 2**

Characteristic Baseline in Patients Treated with LA plus DCB vs. RA plus DCB
<table>
<thead>
<tr>
<th></th>
<th>LA+DCB</th>
<th>RA+DCB</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.36±8.96</td>
<td>72.53±7.12</td>
<td>0.663</td>
</tr>
<tr>
<td>Gender (n, male/female)</td>
<td>16/6</td>
<td>12/5</td>
<td>0.883</td>
</tr>
<tr>
<td>Hypertension (n, yes/no)</td>
<td>10/12</td>
<td>7/10</td>
<td>0.789</td>
</tr>
<tr>
<td>Diabetes (n, yes/no)</td>
<td>9/13</td>
<td>10/7</td>
<td>0.267</td>
</tr>
<tr>
<td>Smoker (n, yes/no)</td>
<td>11/11</td>
<td>9/8</td>
<td>0.855</td>
</tr>
<tr>
<td>Dyslipidemia (n, yes/no)</td>
<td>17/5</td>
<td>13/4</td>
<td>0.953</td>
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<tr>
<td>Coronary artery disease (n, yes/no)</td>
<td>7/15</td>
<td>6/11</td>
<td>0.819</td>
</tr>
<tr>
<td>Cerebrovascular disease (n, yes/no)</td>
<td>8/14</td>
<td>6/11</td>
<td>0.945</td>
</tr>
<tr>
<td>Rutherford classification n/mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>14/8</td>
<td>11/6</td>
<td>0.945</td>
</tr>
<tr>
<td>II</td>
<td>6/16</td>
<td>5/12</td>
<td>0.883</td>
</tr>
<tr>
<td>III</td>
<td>2/20</td>
<td>1/16</td>
<td>0.709</td>
</tr>
</tbody>
</table>

**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 87.2% (34/39) in the Debulking+DCB group, and 65.7% (27/41) in the DCB group, with significant difference (p=0.039). In the analysis of subgroups, the twelve-month primary patency LA+DCB and RA+DCB group were 86.4% (19/22) and 88.2% (15/17) respectively, with no significant difference (p=0.842). There was no significant difference between the two groups and subgroups in the 12-month f-CD-TLR (p= 0.172 and 0.820). One patient suffered acute thrombosis 2 days after the procedure and received re-intervention by in-stent catheter-directed thrombosis and bailout stent. Embolization was seen in below-the-knee artery and removed by 4F catheter in two patients in 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**
## Table 4

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

<table>
<thead>
<tr>
<th></th>
<th>LA+ DCB</th>
<th>RA+DCB</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical success, %</td>
<td>100</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>16.89±5.07</td>
<td>15.14±3.86</td>
<td>0.245</td>
</tr>
<tr>
<td>Bailout stent (n, yes/no)</td>
<td>6/16</td>
<td>5/12</td>
<td>0.883</td>
</tr>
<tr>
<td>12-month primary patency</td>
<td>19/22=86.4%</td>
<td>15/17=88.2%</td>
<td>0.842</td>
</tr>
<tr>
<td>12-month f-CD-TLR</td>
<td>20/22=90.9%</td>
<td>15/17=88.2%</td>
<td>0.820</td>
</tr>
<tr>
<td>Periprocedural complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Limb-threatening ischemia</td>
<td>0</td>
<td>0</td>
<td>0.326</td>
</tr>
<tr>
<td>embolization</td>
<td>4</td>
<td>2</td>
<td>0.361</td>
</tr>
<tr>
<td>Hematoma</td>
<td>2</td>
<td>1</td>
<td>0.527</td>
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</tbody>
</table>

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 re-stenotic 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%. 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 ± 10.47cm. 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 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
In our study, Debunking+DCB and DCB group both have good early-term patency. 12-month primary patency of debunking + DCB group was better compared with DCB group (87.2% vs. 65.9%, p = 0.039).

Our study has a number of limitations. First of all, selection bias cannot be completely excluded. Second, this was a retrospective study and it should be evaluated in the context of retrospective research and its limitations. In addition, it involved only a relatively small group of patients and 1-year follow-up, more subjects and longer-term follow-up perhaps leaded to different conclusions.

Conclusion

Debunking plus DCB or DCB alone are both safe and effective for Tosaka III FP-ISR lesions. Combined treatment with Debunking and DCB angioplasty is correlated with better outcomes in one-year primary patency for Tosaka III FP-ISR 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

Acknowledgements

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 informed consent was waived because of the retrospective nature. Protocol number: 2021152.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no conflict of interest.

**Author details**

1 Department of Vascular Surgery, Xuanwu Hospital and Institute of Vascular Surgery, Capital medical University, 45 Changchun Street, 100053, Beijing, China.

**References**


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.