Treatment of Infrainguinal Arterial Occlusive Disease by Acotec Drug-coated Balloon in 435 Patients

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Research

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Abstract

Background: At present, there are many clinical trials of drug coated balloon in the treatment of lower extremity arterial occlusive diseases, but there are not many clinical data in the real world study. Here we aimed to evaluate the efficacy and safety ofAcotec drug-coated balloon (DCB) for chronic ischemic disease in lower extremity.

Methods: Clinical data of 435 patientswith 564occlusive/stenotic lesions in 492lower extremities treated by DCB from April 2016 toApril2019 were retrospectively analyzed.The mean age was 63years.Rutherford stage 2, 3, 4, 5, and 6 were classified in 11, 167, 182, 109, and 23 limbs, respectively.The mean length of the targeted lesions was 179.6mm. Of all the lesions, 436 located at femoraland/or popliteal arteries, and 128 at infra-popliteal arteries. All the patients were followed up at 6-month intervals. The major evaluation endpoints included late lumen loss (LLL), target lesion restenosis, target lesion revascularization (TLR), and severe clinical events including mortality and major amputation.

Results: The technique success rate was 96.1%.Stents were placed in 57 (13.1%) cases for flow-limited dissections or remnant stenosisgreater than 50% after DCB angioplasty.The mean follow-up time was 28.5 ± 12.1 months (12-48 months). The meanLLLwas 1.1 mm, 1.8mm, and 2.8 mm, respectively, 1, 2, and 3 years after operation. The rate ofrestenosis and TLRwas 17.3%and8.2%, respectively, 1 year after operation; 20.6% and 11.6%, respectively, 2 years after operation; 29.4% and 18.3%, respectively, 3 years after operation.Fourteenpatientsdiedand 25received amputation.

Conclusion: AcotecDCBwas safe and effective in treating chronic ischemic diseases of lower extremities.A better clinical outcome was achieved in femoro-popliteal arteries, compared toinfrapopliteal arteries.

Background

Peripheral arterial occlusive disease is a serious threat to people's life and health, usually with high mortality and disability. Arteriosclerosis obliterans (ASO), thromboangitis obliterans (TAO), arteritis and acute arterial embolism are the common pathogenesis. While involving lower limb, ASO gives rise to arterial occlusion or stenosis, as well as limb ischemia. Compared with conventional surgery, endovascular treatment exhibits special advantages such as small trauma and fast recovery, which are of extraordinary values for the aged, high-risked, complicated patients. With the development of technology and equipment, the indications of endovascular surgery has been sufficiently broadened.

By far, percutaneous transluminal angioplasty (PTA) has been recognized as the mainstream treatment for chronic ischemic disease in lower limbs. The main disadvantage of PTA is the relatively high incidence of restenosis, which was reported to be up to 40% between 6 and 12 months after treatment[1]. Drug-coated balloons (DCBs) were developed to overcome these limitations. Many randomized controlled trials(RCTs)[2–6] have shown consistent superior outcomes of DCBs over uncoated balloons in femoropopliteal lesions, with data up to 5 years for some studies[7–10]. But,their application in lower

limbs is still insufficient. Acotec DCB is a new paclitaxel-coated balloon catheter manufactured in China. The purpose of this study is to evaluate the effectiveness and safety of Acotec DCB in treating chronic ischemic diseases in lower limbs.

Methods

General information

Between April 2016 and April 2019, we applied DCB treatment on 435 patients with chronic ischemic disease of lower limbs. Their mean age was 63 ± 15 years (range, 29–85 years). There were 317 men and 118 women, with 564 occlusive and/or stenotic lesions in 492 lower limbs. Computed tomographic angiography (CTA) scanning was given to all patients before treatment. Rutherford stage 2, 3, 4, 5, and 6 were classified in 11, 167, 182, 109, and 23 limbs, respectively. The mean preoperative ankle brachial index (ABI) was 0.43 ± 0.18. The lesion locations included 341 femoral, 36 popliteal, 59 femoral-popliteal, and 128 infrapopliteal arteries. The mean length of the lesions treated in this study was 179.6 ± 96.1 mm, and the percentage of total occlusions was 78.5%. There were 349 (80.2%) cases diagnosed with ASO, including 62 cases (14.3%) of in-stent restenosis (ISR). The left 86 (19.8%) cases were diagnosed with TAO. Among all the 435 cases, 298 had a history of smoking, 154 had concomitant hypertension, 95 had diabetes, 62 had coronary heart disease and 42 had cerebral infarction. Baseline characteristics are described in Table 1. This retrospective study followed the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Xijing Hospital, The Fourth Military Medical University.

Treatment

During hospitalization, all patients received oral aspirin (100 mg, qd) and clopidogrel hydrogen sulphate (75 mg, qd), and beraprost sodium tablets (40 μg, tid). Under local anaesthesia, femoral artery was punctured with Seldinger method. After transferring the guide wire into the true lumen of distal artery under ultrasound guidance, the length and diameter of stenosis was gauged. The most optimal length of balloon was 2–3 cm longer than that of lesion and the location of balloon should be in center during the process of expansion. The diameter of balloon was selected based on the Duplex measurement of normal vessel adjacent to the lesion. In case that the lesion was very serious, a smaller balloon was expanded first. DCB was expanded with the pressure of 6–10 atm and lasted for 2.5-3 min. Paclitaxel-coated peripheral balloon catheter (Acotec Scientific, Beijing, China) was used in all cases. The drug concentration was 3 $\mu g/mm^2$. For patients exhibiting residual stenosis greater than 50% or restrictive dissection after DCB expansion, stent implantation would be considered. Dissections were diagnosed by bidirectional flow pattern or divided flow with clearly different velocities as shown by color Doppler imaging. Low molecular heparin was injected after surgery to prevent thrombosis.

Follow-up and study endpoints

All the patients were followed up at 6-month intervals with color Doppler imaging in an outpatient department. The following indexes were evaluated: (1) late lumen loss (LLL), defined as the difference

between the minimal luminal diameter after operation and at follow up sonography (2) target lesion restenosis, defined as the degree of restenosis greater than 50%; (3) clinically driven target lesion revascularization (TLR), defined as reoperation deemed necessary; (4) Rutherford stage change, judged by evaluation of ulcer healing, claudication distance and rest pain; (5) severe clinical events, including major amputation and death.

Statistical method

Normal distribution data were represented by mean ± standard deviation. Student's t test was used to compare the mean after checking the homogeneity of variance. Enumeration data was compared using Fisher's exact test. $P < 0.05$ was considered statistically significant. SPSS 22 for windows was used for statistical analysis.

Results

Surgical results

The technical success was achieved in 473 (96.1%) limbs, with evident improvement of skin temperature and disappearance of rest pain. Eighteen patients received retrograde puncture on the popliteal (n = 16) or posterior tibial (n = 2) artery for failure in entering the true lumen by antegrade access. The average number of DCB used was 1.7 ± 0.8. The average DCB expansion time was 144 ± 27 sec, and the average expansion pressure was 6.5 ± 1.3 atm. The operating time varied from 7 to 160 min, with the average time of 40 ± 9 min. Stents were placed in 57 (13.1%) cases for flow-limited dissections or remnant stenosis greater than 50% after DCB angioplasty. The mean ABI was 0.82 ± 0.21, 3 days after operation, with dorsalis pedis palpable in 390 limbs.

Follow-up

The mean follow-up time was 28.5 ± 12.1 months (range, 12–48 months). Follow-up data at 1, 2, and 3 years were obtained from 391, 243, and 96 patients, respectively, with 448, 281, and 112 limbs. Rutherford stage was improved in 362 (80.8%) limbs 1 year after operation, and in 210 (74.7%) and 76 (67.9%) limbs, respectively, at 2 and 3 years. Up to one year of follow-up, ultrasonographic imaging detected 89 (17.3%) restenosis among 513 target lesions. The mean LLL was 1.1 mm. Forty-two (8.2%) restenosis underwent revascularization with 25 of them receiving stent implantation. The mean LLL was 1.8 mm and 2.8 mm, respectively, at 2 and 3 years. The rate of restenosis and TLR was 20.6% and 11.6%, respectively, 2 years after operation; 29.4% and 18.3%, respectively, 3 years after operation. A total of 14 patients died and 25 received amputation. Details of clinical results are shown in Table 2.

Considering the particularity of arteries beneath the knee (BTK), we divide the patients into two groups according to the location of targeted lesions: femoropopliteal group and BTK group. BTK group included lesions beneath the knee and necessary to be treated, meanwhile without severe stenosis in femoral or popliteal arteries. Baseline data of the two groups are listed in Table 1. Compared to femoropopliteal

group, BTK group were younger ($P < 0.001$), with lower incidence of diabetes ($P = 0.003$) and hypertension ($P < 0.001$). At every time-point during follow-up, femoropopliteal group showed significantly lower restenosis rate and TLR rate. The comparison between two groups are listed in Table 2.

Table 1
Baseline patient characteristics

	Total (patients, n = 435)	**Femoropopliteal group (Patients, n = 344)**	**BTK group (Patients, n = 91)**	***P* value**
Age (Years)	63.4 ± 15.1	67.8 ± 14.8	45.63 ± 10.3	< 0.001
Male	317 (72.9%)	246 (71.5%)	71 (78.0%)	0.054
Diabetes	95 (21.8%)	85 (24.7%)	10 (11.0%)	0.003
Hypertension	154 (35.4%)	139 (40.4%)	15 (16.5%)	< 0.001
Smoking	298 (68.5%)	232 (67.4%)	66 (72.5%)	0.059
Rutherford stage	(Limbs, n = 492)	(Limbs, n = 387)	(Limbs, n = 105)	
2	11 (2.2%)	9 (2.3%)	2 (1.9%)	0.980
3	167 (33.9%)	133 (34.4%)	34 (32.4%)	0.907
4	182 (37.0%)	151 (39.0%)	31 (29.5%)	0.086
5	109 (22.2%)	77 (19.9%)	32 (30.5%)	0.192
6	23 (4.7%)	17 (4.4%)	6 (5.7%)	0.948
ABI	0.43 ± 0.18	0.45 ± 0.19	0.38 ± 0.12	0.163
Lesion number	564	436	128	
Lesion length	179.6 ± 96.1	181.7 ± 107.5	173.3 ± 61.7	0.784
Abbreviation: ABI, ankle brachial index; BTK, beneath the knee.				

Table 2
Follow up results

	Total	Femoropopliteal group	BTK group	*P* value
1 year				
Number of patient/limb/lesion	391/448/513	307/350/393	84/98/120	
Late lumen loss (mm)	1.1 ± 0.6	1.1 ± 0.6	0.9 ± 0.5	0.605
Target lesion restenosis	89 (17.3%)	61 (15.5%)	28 (23.3%)	< 0.001
Target lesion revascularization	42 (8.2%)	23 (5.9%)	19 (15.8%)	< 0.001
Rutherford stage change	362 (80.8%)	294 (84.0%)	68 (69.4%)	< 0.001
2 year				
Number of patient/limb/lesion	243/281/320	192/221/246	51/60/74	
Late lumen loss (mm)	1.8 ± 0.9	1.9 ± 1.1	1.5 ± 0.9	0.076
Target lesion restenosis	66 (20.6%)	43 (17.5%)	23 (31.1%)	< 0.001
Target lesion revascularization	37 (11.6%)	23 (9.3%)	14 (18.9%)	0.002
Rutherford stage change	210 (74.7%)	171 (77.4%)	39 (65.0%)	< 0.001
3 year				
Number of patient/limb/lesion	96/112/126	76/89/95	20/23/31	
Late lumen loss (mm)	2.8 ± 1.3	2.9 ± 1.4	2.1 ± 1.3	0.024
Target lesion restenosis	37 (29.4%)	24 (25.3%)	13 (41.9%)	0.001
Target lesion revascularization	23 (18.3%)	15 (15.8%)	8 (25.8%)	0.008
Rutherford stage change	76 (67.9%)	63 (70.8%)	13 (56.5%)	0.003
Abbreviation: BTK, beneath the knee.				

Discussion

Previous studies showed that although PTA could be used for most of chronic ischemic diseases in lower extremity, up to 40% of cases developed restenosis 6 to 12 months after operation[1]. Currently, it has been widely accepted that vascular endothelial hyperplasia is the main mechanism of restenosis. Sufficient inhibition of endothelial cell proliferation will be helpful to reduce the demand for TLR. Lipophilic paclitaxel is one of the most promising agents for serving this goal[11]. In vivo experiments confirmed that intraoperative application of paclitaxel, either added in the contrast medium or coated onto angioplasty balloons, could effectively inhibit vascular endothelial hyperplasia. Paclitaxel is hydrophobic, making it easy to gathering upon the arterial intima and exerting a long-time influence. After

releasing, paclitaxel may produce direct inhibition on arterial intima, thereby reducing the occurrence of restenosis and improving the long-term patency[12–14].

Recently, several randomized clinical trials applying DCB for the treatment of chronic ischemic diseases in lower extremity have been reported. THUNDER trial was a multicenter, randomized controlled study. A total of 154 patients were randomly divided into three groups. One group was treated with paclitaxel-coated balloons (n = 48), a second group was treated with uncoated balloons with paclitaxel dissolved in the contrast medium (n = 52), and the control group was treated with uncoated balloons and standard nonionic contrast medium (n = 54). The mean lesion length was 7.4 cm. At 6 months, the mean LLL was 1.7 mm in the control group, as compared with 0.4 mm ($P < 0.001$) in the DCB group and 2.2 mm ($P = 0.11$) in the group treated with paclitaxel in the contrast medium. The mean TLR at 6 months was 37% in the control group, 4% in the DCB group ($P < 0.001$), and 29% in the group treated with paclitaxel in the contrast medium ($P = 0.41$)[9]. DCBELLUM trial was a prospective, randomized controlled study, consisting of 50 patients and 122 lesions (including femoropopliteal and infrapopliteal lesions). At 12 months, LLL was 0.64 mm in DCB group vs. 1.81 mm in the conventional PTA group ($P = 0.01$). The TLR was 12.2% for DCB and 35.3% for PTA ($P < 0.05$). Amputation rate was 4% for DCB vs. 12% for PTA ($P = 0.36$)[15]. The IN.PACT SFA trial was a prospective, multicenter, single-blinded, randomized trial in which 331 patients with intermittent claudication or ischemic rest pain attributable to superficial femoral and popliteal artery disease were randomly assigned in a 2:1 ratio to treatment with DCB or conventional PTA. Mean lesion length and the percentage of total occlusions for the DCB and PTA arms were 8.94 and 8.81 cm ($P = 0.82$) and 25.8% and 19.5% ($P = 0.22$), respectively. One year follow-up results showed that DCB resulted in a higher primary patency versus PTA (82.2% vs. 52.4%; $P < 0.001$), After 36 months of follow-up, the results were still statistically different (69.5% versus 45.1%; log rank $P < 0.001$). The rates of clinically driven TLR(12 mouths) were 2.4% and 20.6% for the DCB and PTA groups, ($P < 0.001$), and the results of 36 mounths were 15.2% and 31.1% ($P = 0.002$) [2, 8]. Similar results were also observed in Lutonix Global SFA Registry [16] ,DEBATE SFA trial[17] and ISAR-PEBIS[18].

In this study, the rate of target lesion restenosis at one year follow-up was 17.3%, similar to IN.PACT SFA trial (17.8%)[2]. Considering the longer length of treated segment (179.6 vs. 89.4 mm) and higher percentage of total occlusions (78.5% vs. 25.8%) in our trial, it seems possible to speculate that Acotec DCB is superior to Medtronic DCB used in IN.PACT SFA. The proportion of stent implantation was 13.1%, higher than that in the IN.PACT SFA trial (7.3%)[2]. The reason is likely to be the worse situation of patients at baseline, such as long length of target lesions, in our study. Rutherford stage improvement was observed in 80.8%, 74.7% and 67.9% of limbs, respectively, 1, 2 and 3 years following treatment. Clinically driven TLR was 8.2% at the first year, relatively higher than DCB arm reported in the IN.PACT SFA trial (2.4%)[2] and the BIOLUX P-III study(6.9%)[19], whereas significantly lower than PTA arm (20.6%). In this study ,freedom from clinically driven TLR was 88.4% at 2 years which was higher than IN.PACT Global Study(83.3%)[20].

Statistical analysis revealed that patients with femoropopliteal artery lesions were likely to obtain better outcomes in comparison with those with infrapopliteal lesions. The restenosis rate at 1, 2 and 3 year was

15.5% vs. 23.3% ($P < 0.001$), 17.5% vs. 31.1% ($P < 0.001$), and 25.3% vs. 41.9% ($P = 0.001$), respectively, in femoropopliteal and BTK arm, and the TLR rate was 5.9% vs. 15.8% ($P < 0.001$), 9.3% vs. 18.9% ($P = 0.002$), and 15.8% vs. 25.8% ($P = 0.008$), respectively. In the IN.PACT DEEP trail ,Freedom from clinically driven target lesion revascularization through 5 years was 70.9%[21]. The results of the IN.PACT DEEP randomized controlled trial showed comparable effectiveness and safety outcomes for the DCB and PTA arms. The paclitaxel-coated IN.PACT Amphirion DCB was not efficient in terms of reducing restenosis and TLR rates compared with PTA.

There were some shortcomings in this study. First, it was a single-center and retrospective study. Second, some participants were lost to follow-up. For instance, 133 patients underwent DCB treatment before April 2017. Except for 6 death and 11 amputation, 20 cases were lost to follow-up, leaving 96 cases whose data could be collected for 3-year analysis. Third, based on clinical data published recently that conventional PTA was evidently inferior to DCB, we did not used it in treatment as control.

Conclusions

Acotec DCB is safe and effective in the treatment of chronic ischemia of lower extremities. Lesions located at femoropopliteal arteries may achieve better outcomes compared to those at infrapopliteal arteries. Further studies are recommended to confirm these findings.

List Of Abbreviations

Acotec drug-coated balloon (DCB)

Late lumen loss (LLL)

Target lesion revascularization (TLR)

Arteriosclerosis obliterans (ASO)

Thromboangitis obliterans (TAO)

Percutaneous transluminal angioplasty (PTA)

Drug-coated balloons (DCBs)

Computed tomographic angiography (CTA)

Ankle brachial index (ABI)

In-stent restenosis (ISR)

Target lesion revascularization (TLR)

Declarations

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None.

Competing interests

None.

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Authors' contributions

Fengqiang Cui, Jianghao Chen,Ling Wang andRui Ling participated in the study design, performed data analysis and datainterpretation. Fengqiang Cui wrote the manuscript. Hui Wang,Wenlong Shi, Yanjie Li participated indata collection assisted in literature search. Zenghui Han andJing Yuprovided critical revision of themanuscript for important intellectual content. All authors read and approvedthe final manuscript.

Availability of data and materials

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

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Xijing Hospital, and the written informed consent was collected from each participant.

Consent for publication

Not applicable.

References

1. Thukkani AK, Kinlay S. Endovascular intervention for peripheral artery disease. Circulation research. 2015;116:1599–613.
2. Tepe G, et al. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation. 2015;131:495–502.

3. Scheinert D, et al. Paclitaxel-releasing balloon in femoropopliteal lesions using a BTHC excipient: twelve-month results from the BIOLUX P-I randomized trial. Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists. 2015;22:14–21.
4. Rosenfield K, et al. Trial of a Paclitaxel-Coated Balloon for Femoropopliteal Artery Disease. N Engl J Med. 2015;373:145–53.
5. Schroe H, et al. Stellarex drug-coated balloon for treatment of femoropopliteal arterial disease-The ILLUMENATE Global Study: 12-Month results from a prospective, multicenter, single-arm study. Catheterization cardiovascular interventions: official journal of the Society for Cardiac Angiography Interventions. 2018;91:497–504.
6. Tepe G, et al. Angiographic and Clinical Outcomes After Treatment of Femoro-Popliteal Lesions with a Novel Paclitaxel-Matrix-Coated Balloon Catheter. Cardiovasc Interv Radiol. 2017;40:1535–44.
7. Albrecht T, et al. Two-Year Clinical Outcomes of the CONSEQUENT Trial: Can Femoropopliteal Lesions be Treated with Sustainable Clinical Results that are Economically Sound? Cardiovasc Interv Radiol. 2018;41:1008–14.
8. Schneider PA, et al. Treatment Effect of Drug-Coated Balloons Is Durable to 3 Years in the Femoropopliteal Arteries: Long-Term Results of the IN.PACT SFA Randomized Trial. Circulation Cardiovascular interventions. 2018;11:e005891.
9. Tepe G, et al. Angioplasty of femoral-popliteal arteries with drug-coated balloons: 5-year follow-up of the THUNDER trial. JACC Cardiovascular interventions. 2015;8:102–8.
10. Laird JA, et al. Long-Term Clinical Effectiveness of a Drug-Coated Balloon for the Treatment of Femoropopliteal Lesions. Circulation Cardiovascular interventions. 2019;12:e007702.
11. Axel DI, et al. Paclitaxel inhibits arterial smooth muscle cell proliferation and migration in vitro and in vivo using local drug delivery. Circulation. 1997;96:636–45.
12. Scheller B, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med. 2006;355:2113–24.
13. Scheller B, et al. Paclitaxel balloon coating, a novel method for prevention and therapy of restenosis. Circulation. 2004;110:810–4.
14. Tepe G, et al. Local delivery of paclitaxel to inhibit restenosis during angioplasty of the leg. N Engl J Med. 2008;358:689–99.
15. Fanelli F, et al. The "DEBELLUM"–lower limb multilevel treatment with drug eluting balloon–randomized trial: 1-year results. J Cardiovasc Surg. 2014;55:207–16.
16. Thieme M, et al. The 24-Month Results of the Lutonix Global SFA Registry: Worldwide Experience With Lutonix Drug-Coated Balloon. JACC Cardiovascular interventions. 2017;10:1682–90.
17. Liistro F, et al. Drug-eluting balloon in peripheral intervention for the superficial femoral artery: the DEBATE-SFA randomized trial (drug eluting balloon in peripheral intervention for the superficial femoral artery). JACC Cardiovascular interventions. 2013;6:1295–302.

18. Ott I, et al. ISAR-PEBIS (Paclitaxel-Eluting Balloon Versus Conventional Balloon Angioplasty for In-Stent Restenosis of Superficial Femoral Artery): A Randomized Trial. Journal of the American Heart Association 2017;6.
19. Tepe G, et al. Paclitaxel-Coated Balloon for the Treatment of Infrainguinal Disease: 12-Month Outcomes in the All-Comers Cohort of BIOLUX P-III Global Registry. Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists. 2020;27:304–15.
20. Micari A, et al. Drug-Coated Balloon Treatment of Femoropopliteal Lesions for Patients With Intermittent Claudication and Ischemic Rest Pain: 2-Year Results From the IN.PACT Global Study. JACC Cardiovascular interventions. 2018;11:945–53.
21. Zeller T, et al. The IN.PACT DEEP Clinical Drug-Coated Balloon Trial: 5-Year Outcomes. JACC Cardiovascular interventions. 2020;13:431–43.