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Original Article

Drug-coated balloon in the treatment of coronary artery de-novo large lesions angiography

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Abstract

The superiority of drug-coated balloon (DCB) in treating small vessels, branching lesions, and high-risk bleeding lesions in coronary heart disease patients has been confirmed. However, its safety and efficacy in large vessels are still unclear. We aimed to investigate whether the efficacy of DCB in large vessels is not inferior to that of drug-eluting stent (DES). From November 2019 to April 2022, a total of 88 patients in our hospital who underwent coronary angiography for the first time and decided to receive DCB or DES treatment were selected. Indicators including late lumen loss (LLL), major adverse cardiovascular event (MACE) rate, major bleeding and all-cause mortality were evaluated at 9 months and 1-year post percutaneous coronary intervention (PCI) therapy. The primary endpoint of 9-month LLL was -0.07 in the DCB group and 0.19 mm in the DES group (p value<0.001). 1-year cumulative MACE rates were similar in the DCB and DES groups (3.03% vs. 7.23%, P=0.519), TLR rates were similar (3.03% vs. 7.23%, P=0.519), Major bleeding was similar (3.03% vs. 5.45%, P=0.580), and 1 case of Cardiac death in DES group. For LLL, the DCB-only strategy was non-inferior to DES in treating de novo large lesions in the coronary arteries. Furthermore, the efficacy of DCB was comparable to DES at 1 year of follow-up for secondary clinical endpoints.

Keywords: Angioplasty, Coronary artery disease, Drug-coated balloon, Drug-eluting stent, Large lesion.

1. Introduction

With the development of stent technology, drug-eluting stents have become one of the main means of coronary heart disease treatment [1]. However, stent placement can still lead to a number of complex complications, including restenosis, high risk of bleeding due to prolonged dual antiplatelet therapy [2], advanced in-stent thrombosis [3], hypersensitivity to stent materials, and even stent fracture [4].

Drug-coated balloons are a new concept for the treatment of Coronary artery disease in recent years, which is based on the use of specific excipients to rapidly deliver highly lipophilic drugs to the blood vessel wall after balloon inflation, thereby achieving inhibition of vascular endothelial proliferation [5]. Due to its advantages such as no foreign body implantation and short dual antiplatelet therapy time after surgery, it is a new alternative treatment option in selected patient subgroups (e.g. In-stent restenosis (ISR), high bleeding risk, and small-vessel coronary artery disease) [6, 7]. For small-vessel coronary artery disease, a large number of studies have been conducted to follow up on its short- and long-term prognosis [8–13]. Meanwhile, one study has found that the incidence of postoperative MACE in DCB is comparable to DES in de novo large vessels after successful pre-dilatation [14]. Encouraged by these studies, several smaller studies have begun to be conducted on the large coronary vessels and have produced some promising findings [15, 16]. Subsequently, a few studies have slowly started to investigate the efficacy of DCB in de-novo coronary artery disease studies [14, 17–19]. On the one hand, studies on large vessels are relatively limited, and on the other hand, some of the studies were conducted on de novo vessels and did not distinguish between large and small vessels, as the efficacy of small vessels has been well established and therefore may have an impact on the final results of the trials.

In this study, we retrospectively analyzed the prognosis of 88 patients with coronary artery disease who underwent percutaneous Coronary Intervention (PCI) from November 2019 to April 2022 at the Cardiovascular Center of Suzhou Municipal Hospital, using patients suffering from coronary artery de novo large vessels vascularization in Suzhou, aiming to further investigate the safety and efficacy of DCB in large vessel.

2. Materials and methods

2.1. Study design

A total of 88 patients in the Cardiovascular Center of

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Suzhou Municipal Hospital were enrolled in a randomized, retrospective, single-center trial investigating the efficacy and safety of the DCB (drug-coated balloon, Sequent Please Paclitaxel) compared with the DES (drug-eluting stent, Firebird). The study was performed according to the Declaration of Helsinki and World Health Organization guidelines. This study was approved by the Ethics Committee of Suzhou Municipal Hospital and all patients gave written informed consent.

2.2. Inclusion and exclusion criteria

Patients who underwent elective PCI at Suzhou Municipal Hospital were screened. The target lesions should be larger than 2.75mm and not be intervened before. Patients at least 18 years of age with clinical evidence of stable or unstable angina or a positive functional study, coronary angiography has been performed and only one lesion was treated with DCB or DES were considered for enrollment. Major clinical exclusion criteria were ST-segment elevation myocardial infarction within the past 72 h; previous PCI or CABG, renal insufficiency with serum creatinine levels >2.0 mg/dl; known hypersensitivity or contraindications to aspirin, heparin, clopidogrel, ticagrelor, paclitaxel, or sirolimus; sensitivity to contrast media not amenable to pre-medication.

2.3. Procedure

After assessment for angiographic and clinical inclusion and exclusion criteria, patients were chosen from 2019-11 to 2022-04. Patients who used DCB were treated with the paclitaxel-coated SeQuent Please balloon, while patients who used DES were treated with the everolimus-eluting firebird stent. PCI with a DCB was performed according to the current guidelines [7]. The DCB was 2 to 3 mm longer on each side than the predilatation balloon to avoid geographic mismatch and inflation at nominal pressure for at least 30 s. (Residual stenosis ≤30%, TIMI 3 flow, no dissection at the lesion or type A or B dissection, or type C dissection without blood flow restriction, In the case of flow-limiting dissections after DCB treatment, PCI using DES was recommended.) The DCB length must be 2 to 3 mm beyond the lesion at both ends, with a diameter-to-target lesion reference vessel diameter ratio of 1:1. After removal of the balloon, the procedure is successful if the coronary angiogram confirms that there is no type C or higher entrapment and TIMI flow ≥ grade III. Preoperative clopidogrel loading dose 0.3g or ticagrelor 0.18g, after PCI, a dual antiplatelet therapy (DAPT) was prescribed using acetylsalicylic acid (100 mg/d) and either clopidogrel (75 mg/d) or ticagrelor (90 mg twice per day). DAPT was continued for 4 weeks after DCB or 6 months after DES in CCS and in patients with ACS for 12 months irrespective of treatment randomization. 9 months (±3 months) after surgery, patients are recommended to undergo coronary angiography review and follow-up to date. Both groups were given secondary prevention medications for coronary heart diseases, such as statins, ACEI/ARB drugs and β-blockers, according to the patients' conditions.

2.4. Outcomes

We collected multiple indicators such as gender, age, smoking history, BMI, history of hypertension and diabetes, blood creatinine, serum potassium and troponin, and LVEF as baseline data. The primary clinical endpoint was the LLL of the target lesion 9 months postoperatively, and the secondary clinical endpoint included the incidence of the TLR (target lesion reconstruction), MACE (major adverse cardiovascular event rate), all-cause mortality, all myocardial infarctions, and major bleeding.

2.5. Statistical analysis

SPSS 26.0 software (BM SPSS, Chicago, IL) was used for data analysis. Data were expressed as mean ± SD. Inter-group comparisons were performed using the unpaired Student's t-test and the Mann–Whitney U test for continuous variables and the $\chi 2$ test for categorical variables. The influencing factors of clinical endpoint events were analyzed by the Kaplan-Meier method, and the comparison was performed using the log-rank method. The risk factors of the second recurrence were analyzed by univariate and multivariate analyses using the Cox proportional hazard regression. $P<0.05$ was considered as a statistically significant difference.

3. Result

3.1. Comparison of basic characteristics between DCB and DES group patients

A total of 88 patients (33 DCB-treated patients and 55 DES-treated patients) were followed up with coronary angiography results at an average of 9 months after the procedure. 1 DES-treated patient was not followed up with coronary angiography because of death. Baseline characteristics are depicted in Table 1. All of the baseline parameters were balanced between groups.

Procedural characteristics are shown in Table 2. In comparison with DCB patients, DES patients whose treating blood vessels account for the highest proportion in LAD (63.6% versus 39.4%), followed by RCA (21.8% versus 27.3%), and LCX (14.5% versus 33.3%) accounts for the least. The distribution of clinical typing was comparable between groups.

Table 1. Baseline characteristics according to clinical presentation between DCB and DES group patients.

	DCB (n=33)	DES (n=55)	P value
Age (years)	63.33±14.14	61.95±13.18	0.676
BMI (kg/m^2)	25.87±3.83	24.56±3.21	0.138
Male (n, %)	22(66.7)	39(70.9)	0.676
Smoke (n, %)	19(57.6)	27(49.1)	0.440
Hypertension (n, %)	28(84.4)	40(72.7)	0.189
Diabetes (n, %)	14(42.4)	19(34.5)	0.460
Cr (μmol/L)	85.11±52.84	71.37±21.93	0.223
K (mmol/L)	3.8±0.43	3.83±0.5	0.779
pro-BNP (pg/mL)	32.03±13.34	27.47±16.89	0.054
CRP (mg/L)	10.35±27.21	6.35±7.91	0.077
LVEF (%)	0.59±0.08	0.61±0.08	0.374
TC (mmol/L)	4.39±1.5	4.49±1.06	0.246
TG (mmol/L)	1.55±0.7	1.87±1.01	0.175
LDL-C (mmol/L)	2.72±1.26	2.79±0.83	0.243
HDL (mmol/L)	1.12±0.28	1.04±0.23	0.343

BMI (Body Mass Index); BNP (B-type natriuretic peptide); CRP (C-reactive protein); LVEF (Left Ventricular Ejection Fractions); TC (Total Cholesterol); TG (Triglyceride); LDL-C (Low-Density Lipoprotein Cholesterol); HDL (High-Density Lipoprotein).

Table 2. Procedural data according to clinical presentation.

	DCB (n=33)	DES (n=55)	P value
Target vessel			0.054
LAD (%)	13(39.4)	35(63.6)	
LCX (%)	11(33.3)	8(14.5)	
RCA (%)	9(27.3)	12(21.8)	
Type of CAD			0.332
Stable angina pectoris (%)	3(9.10)	11(20.00)	
Unstable angina pectoris (%)	18(54.50)	23(41.80)	
NSTEMI (%)	7(21.20)	16(29.10)	
STEMI (%)	5(15.20)	5(9.10)	

DCB, drug-coated balloon; DES, drug-eluting stents; LAD Left Anterior descending artery; LCX Left circumflex artery; RCA Right Coronary Artery; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; CAD, coronary artery disease.

Table 3. Comparison of pre- and post-operative data between the two groups.

	DCB (n=33)	DES (n=54)	P value
lesion length pre-PCI (mm)	8.32±4.75	8.28±3.97	0.645
RFD pre-PCI (mm)	3.8±0.74	3.82±0.67	0.890
MLD pre-PCI (mm)	0.48±0.4	0.41±0.39	0.506
Percentage of DS pre-PCI	87.73±9.44	89.07±9.89	0.513
DS post pre-intervention (mm)	2.77±0.7	2.74±0.62	0.928
Percentage of DS post pre-intervention	26.06±6.09	28.72±8.01	0.212
MLD final in-lesion (mm)	3.54±0.74	3.76±0.65	0.195
Percentage of MLD final in-lesion	6.81±0.07	1.48±0.03	0.001
MLD FU in-lesion, (mm)	3.63±0.9	3.54±1.06	0.958
Percentage of DS FU	5.61(0.00,5.00)	7.11(0.00,5.00)	0.005
LLL (mm)	-0.07(-0.13,0.00)	0.19(0.00,0.23)	0.001

RFD: reference diameter; MLD: minimal lumen diameter; FU: follow up; LLL: late lumen loss; DS: diameter stenosis.

As shown in Table 3, there was no significant difference in the length and lumen diameter of the lesioned vessels between the two groups before surgery (p value>0.05). The minimum lumen diameter, and percentage of diameter stenosis were (0.48±0.4) mm, (87.73±9.44) % in the DCB group and (0.41±0.39) mm, (89.07±9.89) % in the DES group. There was no significant difference in the degree of stenosis (2.77±0.7 versus 2.74±0.62 mm, p value = 0.928) and percentage of stenosis (26.06%±6.09 % versus 28.72%±8.01%, p value=0.212) between the two groups after pre-dilation. The degree of minimal lumen diameter final in-lesion was (3.54±0.74) mm in the DCB group and (3.76±0.65) mm in the DES group.

In terms of follow-up results after 9 months, the DCB group had a larger diameter (3.63±0.9 versus 3.54±1.06mm, p-value = 0.958) and the same percentage of stenosis (5.61 versus 7.11, p-value = 0.005) than the DES group, and as for LLL, the DCB group was smaller than the DES group (-0.07 versus 0.19 mm, p value<0.001) (Figure 1).

3.2. Clinical follow-up at 12 months in the DCB and DES groups

Outcomes according to clinical presentation and treatment stratum at 1-year follow-up are summarized in Table 4. During the follow-up period, rates of TLR (1 patient [3.03%] for the DCB group vs 4 patients [7.23%] for the DES group; p=0.519), MACE (1 patient [3.03%] for the

Fig. 1. Comparison of pre-and post-operative data between the two groups. DCB=drug-coated balloons; DES=drug-eluting stents; RFD: reference diameter; MLD: minimal lumen diameter; FU: follow up; LLL: late lumen loss; DS: diameter stenosis.

Table 4. Outcomes at 1-year follow-up according to clinical presentation.

	DCB (n=33)	DES (n=55)	P value
TLR (%)	1(3.03)	4(7.23)	0.519
MACE (%)	1(3.03)	4(7.23)	0.519
Cardiac death (%)	0(0)	1(1.82)	0.446
Major bleeding (%)	1(3.03)	3(5.45)	0.580
Myocardial infarction	0	0	-
Acute vessel closure	0	0	-

TLR: target lesion reconstruction; MACE: major adverse cardiovascular event.

DCB group vs 4 patients [7.23%] for the DES group; p=0.519), Cardiac death (0 patients for the DCB group vs 1 patient [1.82%] for the DES group; p=0.446), Major bleeding (1 patient [3.03%] for the DCB group vs 3 patients [5.45%] for the DES group; p=0.580). There was no significant difference in the incidence of those secondary clinical endpoints. There was also no acute vessel closure and myocardial infarction in DCB and DES lesions. Figure 2 shows the K-M curves plotted for the secondary clinical endpoint and used for comparison of survival analysis without endpoint events.

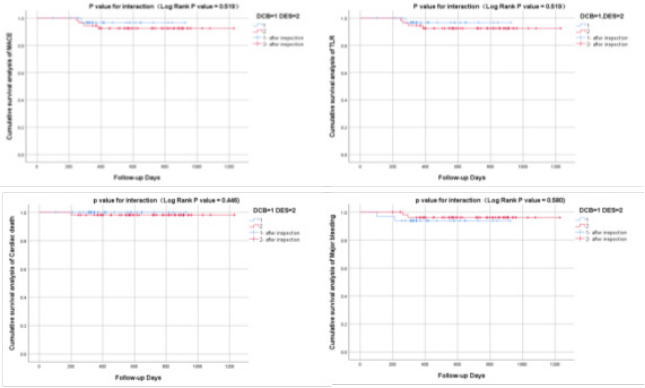

Fig. 2. Major adverse cardiac events and their components according to clinical presentation in the DCB and DES groups.

4. Discussion

The results of the 9-month angiography showed that for LLL, the DCB-only strategy was non-inferior to DES in treating de novo lesions in the coronary arteries. Furthermore, the efficacy of DCB was comparable to DES at 1 year of follow-up for secondary clinical endpoints (major adverse cardiovascular events, cardiac death, targeted vessel revascularization, major bleeding). In addition, it is worth mentioning that in terms of MACE and major bleeding, incidence tended to be lower in the DCB group than in the DES group, but did not reach significance. TLR and cardiac death did not differ significantly in the two groups.

Coronary heart disease, a highly prevalent cardiovascular disease, has one of the highest mortality rates in the world, and DES, the standard means of PCI, requires long-term DAPT to avoid stenosis and increased risk of thrombosis in late stenting. Since 2006, when the treatment of coronary heart disease entered the era of DCB, an increasingly used treatment option for various clinical situations in coronary artery disease. By delivering the drug to the vessel wall through highly lipophilic drugs, DCBs have the advantage of an implant-free treatment of coronary artery disease without the risk of late or very late implant-associated complications such as stent thrombosis or neoatherosclerosis. Yu *et al*. [17]. Conducted a non-inferiority randomized controlled trial that included 170 patients with vessel diameters of 2.25-4 mm. The 9-month angiographic follow-up showed that LLL of the target lesions was -0.19±0.49mm versus 0.03±0.64 mm, and conducted that the DCB for de novo lesion was non-inferior to the DES in terms of 9-month late lumen loss. However, the study did not limit the diameter of the vessels, which may have an impact on the results of the experiment because of the definite efficacy of DCB in small vessels. A retrospective analysis by Cortese *et al*. [16]. included 122 large vessel cases with up to 6 months of follow-up, but the study covered both single and multiple lesions, and the efficacy at long-term follow-up may be biased by multiple lesions, while the follow-up period of the study was too short and its long-term efficacy is unclear. A coronary macrovascular study by Cortese *et al*. [16], also demonstrated the safety and efficacy of DCB, but it was only confirmed by follow-up of adverse events and not by coronary angiographic results.

In this retrospective analysis, we screened out large coronary vessels(reference vessel diameter (RVD) >2.75 mm) as well as de novo coronary vessels, and compared their late lumen loss by following up the coronary angiographic results of both groups at 9 months after surgery, and assessed the TLR rate, MACE rate, etc. in both groups by following up at least 1 year after surgery, taking into account single vessel lesions as well as postoperative vascular and clinical assessments while ensuring their follow-up time, fully controlling the variables of the trial and ensuring the accuracy of the trial results as much as possible. The present study is a retrospective study that screened patients who had their first coronary treatment and whose duration of DAPT was strictly controlled according to the guidelines [7], it also allows for greater control of coronary artery disease in patients and can further reduce bias due to the number of vascular lesions, so that the safety and efficacy of DCB for de novo vascular treatment could be better evaluated. Similar to the results of our study, all of these aforementioned studies suggest that DCB is not inferior to DES in terms of LLL. It has been shown that DCB protects the endothelial function of coronary vessels better than newer-generation DES and may have better long-term benefits for patients [20]. We will continue to follow patients to further evaluate the long-term efficacy of DCB treatment.

The use of sirolimus as an antiproliferative agent in drug-coated balloons has been initiated and its efficacy in small vessels [19] and in de novo vessels [21] has been encouraging. However, studies in large vessels are still very limited, and there are no large multicenter studies for large vessels. Although this study and the single-center or retrospective analyses mentioned above have positive findings for drug-coated balloons in large vessels, they are not sufficient evidence to recommend their general use in large-vessel studies but may provide a viable idea for subsequent investigators to pave the way for large multicenter randomized controlled trials.

5. Conclusion

This retrospective single-center controlled variable study demonstrated that DCB was non-inferior to DES in

controlling LLL at 9 months, and it was comparable to DES in terms of safety and efficacy of clinical outcomes at 1 year for secondary clinical endpoints.

Conflict of interests
The author has no conflicts with any step of the article preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate
No humans or animals were used in the present research.

Informed consent
The authors declare not used any patients in this research.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
CX and HX conducted the experiments and wrote the paper; WY and LY analyzed and organized the data; XG conceived, designed the study and revised the manuscript.

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