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Long-Term Outcomes of Drug-Coated Balloon Angioplasty in The Treatment of Small Vessel Coronary Artery Disease

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ABSTRACT

Objectives: To determine the outcomes in patients with small-vessel disease (SVD) who underwent percutaneous coronary intervention (PCI) with a drug-coated balloon (DCB) and correlate these adverse outcomes with various risk factors.

Methodology: The prospective cohort study was conducted at the Rawalpindi Institute of Cardiology (RIC) from January 2020 to December 2022. After being approved by the Hospital Ethics Committee, fifty-four patients who presented with SVD were enrolled using non-probability consecutive sampling. Written informed consent was obtained from the patients. They were treated with DCB and observed clinically on follow-ups at 15, 30, 60, and 90 days, & later after every 6 months for up to 2 years. Only those patients who presented with symptoms underwent repeat angiography. The outcomes assessed were cardiovascular mortality, myocardial infarction (MI), and target lesion revascularization (TLR).

Results: Cardiovascular mortality occurred in 2(3.7%), MI in 3(5.6%) and TLR in 2(3.7%) patients. There was a significant association between cardiovascular mortality, MI, and TLR with diabetes mellitus and BMI. Age was only significantly related to cardiovascular mortality.

Conclusion: A drug-coated balloon is an effective and feasible treatment modality for small vessel disease. The incidence of outcomes of cardiovascular mortality, MI, and TLR after DCB is low, making it a safe modality. Advanced age, obesity, and diabetes mellitus alone or with hypertension are the predicting factors of adverse outcomes after DCB in patients with SVD.

Keywords: Drug-coated balloon, DCB, Small vessel coronary artery disease, SVD

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Introduction

Coronary artery disease (CAD) is the most frequent cardiovascular disease in both developing and developed nations. In addition to genetic and environmental factors, lifestyle changes also play a major role in disease pathogenesis. These predisposing factors are diabetes mellitus (DM), hyperlipidemia, smoking, hypertension (HTN), and obesity.[1] The management of CAD includes percutaneous coronary intervention (PCI) as the main treatment modality.[2] Re-stenosis is a well-known complication occurring in 15-30% of the patients following the PCI procedure.[3] It results from the pathological response of the vascular endothelium to injury, leading to abnormal vascular smooth muscle proliferation. Its management involves either coronary artery bypass graft (CABG) or repeat PCI.[4] Diabetes mellitus, smoking, and small vessel disease (SVD) are linked with higher chances of re-stenosis.[2]

The advances in the field of interventional cardiology have led to the development of new technologies, drugs, and devices in PCI with their clinical indications based on the results of randomized controlled trials.[5]

Historically, the management of CAD had been limited to balloon angioplasty. But acute vessel closure, elastic recoil, less durability, and re-stenosis were common. To overcome these complications, bare metal stents (BMS) were developed.[6] The invention of BMS solved the problem of elastic recoil that occurred with balloon angioplasty. However, they also caused in-stent restenosis (ISR) and thrombosis.[7] With further advancements, drug-eluting stents (DES) were introduced with lesser rates of ISR, target lesion revascularization (TLR), and good prognosis. The use of DES in SVD is still a major challenge due to three main causes. First, the small vessel size makes the device delivery difficult. Secondly, DES is correlated with higher frequency of ISR and major adverse cardiovascular events (MACE) in SVD.[8] Lastly, SVD is very common, constituting 30% of cases of coronary artery disease.[9]

Drug-coated balloon (DCB), a semi-compliant angioplasty balloon, is comparatively a newer technology to treat CAD. The advantages of DCB are rapid delivery of an anti-proliferative drug into the vessel wall during balloon inflation in 30-60 seconds and no need for a stent scaffold implant with no inflammation & delayed healing. In addition, it also overcomes the side effects of vascular recoil caused by traditional balloons and the long-term use of antiplatelet drugs.[10] The effectiveness and safety of DCB is proven in the management of ISR. Many clinical trials have supported DCB as the treatment of choice in SVD.[11] They cause lesser ISR, and TLR.[12] Some other studies have shown that MACE in DCB is comparable to DES.[13] A study has also reported higher efficacy and safety of DCB in SVD in diabetic patients.[14]

Small vessel disease is a frequent presentation of CAD. The development of DES has revolutionized the efficacy and safety of PCI but its use in small vessel disease is challenging, linked with higher chances of ISR. The drug-coated balloon is an appropriate alternative in such cases with a reduced incidence of ISR, MACE and TLR. It rapidly delivers the anti-proliferative drug into the vessel wall during inflation and does not need a stent scaffold with no inflammation. This study was planned to determine the effectiveness of DCB in patients with SVD in terms of cardiovascular mortality, MI, and TLR. In addition, the correlation of these outcomes was also seen with age, body mass index (BMI), HTN, and DM in these patients.

Methodology

This was a prospective cohort study done at the Rawalpindi Institute of Cardiology (RIC), Rawalpindi from January 2020 to December 2022 after being approved by the Hospital Ethics Committee. Fifty-four patients who presented with SVD were enrolled using non-probability consecutive sampling after taking written informed consent. The inclusion criteria were patients of either gender with the age ranging from 18 to 85 years, SVD with vessel diameter >2mm but < 3mm, lesions considered suitable for treatment with DCB at the discretion of the operator, stable angina, bifurcation lesions, both main and/or side branches only, finding a small caliber native vessel after opening CTO and critical lesions adjacent to ectatic or aneurysmal coronaries. Patients with acute coronary syndrome (ACS), residual stenosis of >30% or flow-limiting dissection after pre-dilatation, serum creatinine > 2.0 mg/dL, ISR, or contraindication to anti-platelet therapy were excluded. Detailed patient history was noted on the Proforma.

The DCB placement criteria were followed by using a semi-compliant balloon for pre-dilating the lesion. DCB to vessel size ratio was kept at 0.8:1. Diameter of SeQuent® Please NEO (B. Braun) DCB was the same as the pre-dilatation balloon size and was not allowed to exceed the pre-dilatation balloon size. After pre-dilatation DCB was used in lesions with residual stenosis of less than 30%, and no flow-limiting dissection occurred. Anticoagulation during the procedure was done with unfractionated heparin at a dose of 100 units/kg, maintaining activated clotting time between 250-300 seconds throughout the procedure. Patients were loaded with 300mg aspirin and 300mg Plavix on the day of the intervention. A dual anti-platelet drug regime consisting of 75mg aspirin and 75mg clopidogrel daily was advised for one month, after which clopidogrel was discontinued. A lifelong prescription of aspirin 75mg was advised to be taken once daily. The rest of the medication was given per international and hospital policies, considering the patient's co-morbidities. This procedure's angiographic success rate was 100%, so no bail-out stenting was needed. Clinical follow-ups per the defined protocol were carried out at 15, 30, 60, and 90 days and later after every 6 months for up to 2 years. Only those patients who presented with symptoms underwent repeat angiography. The outcomes assessed were cardiovascular mortality, MI, and TLR.

The data was compiled with the Statistical Package for the Social Sciences (SPSS) version 25. The mean and standard deviation were used for quantitative variables such as age, BMI, and DCB diameter. Frequencies and percentages were calculated for categorical variables such as DM, HTN, MI, etc. A Pearson Chi-square test was applied to determine the correlation between outcomes (cardiovascular mortality, MI & TLR) and study variables including patient's age, gender, BMI, diabetes mellitus, and hypertension). The significant p-value was ≤0.05.

Results

Patients had a mean age of 54.41+10.09 years, with minimum and maximum ages of 32 and 79 years, respectively. The mean BMI was 25.39+2.58 kg/m^2 ranging from 20-31 kg/ m^2. Drug-coated balloons had a mean diameter of 2.35+0.25 mm ranging from 2-2.75 mm.

The majority of the patients had ages ranging from 41-60 years and were males (70.4%). Most of the patients (64.8%) were obese with BMI ranging from 25-29.9 kg/m^2. Out of the total 54 cases, 24(44.4%) cases were neither hypertensive nor diabetic whereas; 17(31.5%) were hypertensive only, 9(16.7%) were diabetic only, 4(7.4%) were both hypertensive and diabetic as shown in Table I.

Table I: Demographic Profile of the Patients	
Parameter	**N (%)**
Age Groups	
31-40 years	3(5.6%)
41-50 years	18(33.3%)
51-60 years	18(33.3%)
61-70 years	12(22.2%)
71-80 years	3(5.6%)
Total	**54(100%)**
Gender	
Male	38(70.4%)
Female	16(29.6%)
Total	**54(100%)**
BMI Groups	
<18.5 kg/m^2	0(0%)
18.5-24.9	17(31.5%)
25-29.9	35(64.8%)
>30	2(3.7%)
Total	**54(100%)**
Diabetic & Hypertensive	
Diabetic only	9(16.7%)
Hypertensive only	17(31.5%)
Both Diabetic & Hypertensive	4(7.4%)
Neither Diabetic nor Hypertensive	24(44.4%)
Total	**54(100%)**

Out of 54 patients, cardiovascular mortality occurred in only 2(3.7%) patients, MI in 3(5.6%) and target lesion revascularization in 2(3.7%) patients (Figure 1).

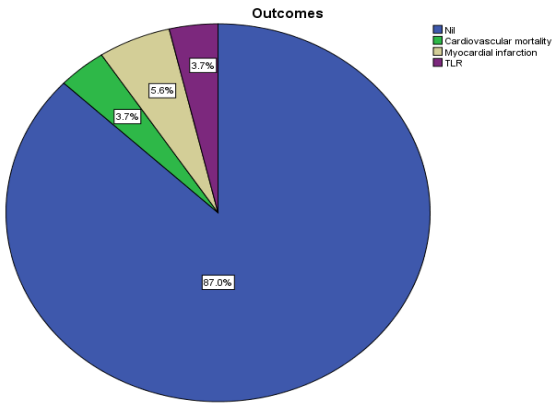

Figure 1. Outcomes of the Patients after Angioplasty with DCB.

When the correlation of outcomes was seen with the study variables, a significant association was seen between cardiovascular mortality, MI, & TLR and diabetes mellitus and BMI. Age was only significantly related to cardiovascular mortality (Table II).

Discussion

Drug-coated balloons are being extensively used in interventional cardiology for restenotic as well as de-novo lesions. The delivery of anti-re-stenotic drug directly into the vessel wall on balloon inflation without the need for metal or polymer is their interesting feature.

The European Society of Cardiology has given class IA recommendations for the use of DCB in re-stenotic lesions, but no such recommendations exist for de-novo lesions. However, literature has supported their use in de-novo lesions.[15] Regardless of the strategy used, PCI in SVD is associated with an increased rate of both short-term and long-term MACE. Bare metal stents cause ISR in a significant number of patients.[16,17] The risk of TLR is less with DES, but still, patients report worse outcomes, especially those with diabetes mellitus.[18] To minimize these complications, DCBs were introduced with a decreased incidence of target lesion thrombosis and re-stenosis.[16,17]

Our results showed cardiovascular mortality in only 3.7% of the patients. Similar results were reported in a study with 4.4% cardiovascular deaths in DCB patients.[19] Cortese et al. reported cardiovascular deaths in 1% of the patients with DCB.[20] Another study reported better outcomes with DCB with no cardiovascular mortality.[21]

Table II: Association of Outcomes with the Study Variables.

Parameter	Frequency								
	Yes	No	P value	Yes	No	P value	Yes	No	P value
	Cardiovascular Mortality			Myocardial Infarction			TLR		
Age Groups									
31-40 years	0	3		0	3		0	3	
41-50 years	0	18		1	17		0	18	
51-60 years	0	18	**0.048***	1	17	0.258	1	17	0.066
61-70 years	1	11		0	12		0	12	
71-80 years	1	2		1	2		1	2	
Total	2	52		3	51		2	52	
Gender									
Male	1	37		2	36		1	37	
Female	1	15	0.520	1	15	0.885	1	15	0.520
Total	2	52					2	52	
BMI Groups									
<18.5 kg/m^2	0	0		0	0		0	0	
18.5-24.9	0	17		1	16		0	17	
25-29.9	1	34	**0.002***	1	34	**0.018***	1	34	**0.002***
>30	1	1		1	1		1	1	
Total	2	52		3	51		2	52	
Diabetic & Hypertensive									
DM only	1	8		2	7		2	7	
HTN only	0	17		0	17		0	17	
Both DM & HTN	1	3	**0.045***	1	3	**0.018***	0	4	**0.016***
Neither DM nor HTN	0	24		0	24		0	24	
Total	2	52		4	50		2	52	

The results of a meta-analysis revealed no cardiovascular mortality in patients who underwent DCB.[22] Our study revealed the occurrence of MI in 5.6% of the patients. In a study, MI occurred in 3.6% of the patients after DCB.[22] A study done in China revealed that MI occurred in only 0.9% of the patients.[19] Another study reported that none of the patients developed MI after DCB.[23] On the other hand, the PICCOLETTO study revealed a higher incidence of major adverse cardiovascular events, including myocardial infarction, with DCB (35.7%) than DES (13.8%). It was concluded that it might be attributed to defects in balloon design used or inadequate preparation for balloon pre-dilatation.[24]

In our study, 3.7% of patients developed TLR. Another study reported TLR in only 3.6% of the patients who underwent DCB.[21] Funatsu et al. reported TLR in 3.4% of the patients with DCB.[25] The results of the PEPCAD I trial showed a significant decrease in the rate of re-stenosis with DCB as compared to DES.[26] A study reported the superiority of DCB over DES in terms of less late lumen loss in patients who underwent DCB.[17] In a study conducted in China, the rate of TLR was equal in patients who underwent PCI with DCB and DES.[27] In another study, it was reported that DCB was correlated with fewer chances of target vessel restenosis and thrombosis as compared to DES and BMS, hence, was superior to other treatment modalities.[28] Our study reported a significant association between cardiovascular mortality, MI, and TLR with diabetes mellitus. In another study, the frequency of cardiovascular mortality, MACE, and TLR was higher in diabetic patients as compared to non-diabetic patients.[29]

Conclusion

A drug-coated balloon is an effective and feasible treatment modality for small-vessel disease. The incidence of outcomes of cardiovascular mortality, MI, and target lesion revascularization after DCB is low, making it a safe modality. Advanced age, obesity, and diabetes mellitus alone or with hypertension are the predicting factors of adverse outcomes after DCB in patients with SVD.

Limitations of the study: The study was carried out on a small number of patients. Repeat angiography of only those patients was done who presented with symptoms.

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