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DRUG-COATED BALLOONS (DCB) FOR THE TREATMENT OF IN-STENT RESTENOSIS (ISR) IN POST-PCI PATIENTS: A SHORT-TERM CLINICAL OUTCOMES STUDY

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ABSTRACT

Objective: To assess the short-term clinical outcomes of treating in-stent restenosis (ISR) in patients who have had PCI at monthly and three-month follow-ups using drug-coated balloons (DCB).

Methodology: This prospective observational study, conducted at Department of Interventional Cardiology AFIC/ NIHD Rawalpindi, Pakistan from January, 2023 to January, 2024 involved 121 patients. Participants were selected using consecutive sampling, including adults treated with a paclitaxel-coated balloon, presenting with acute coronary syndrome (ACS) or worsening angina, and showing angiographic luminal narrowing of 50% or more in the diameter of a pre-deployed stent or within 4-5 mm of the stent. Ethical approval and informed consent were obtained. Data collection involved a structured questionnaire covering baseline clinical variables, procedural information (ISR type, target vessel, therapies, complications, outcomes), and angiographic data (lesion diameter, TIMI flow grade). SPSS version 20.0 was used for data analysis. The Chi-square test ($p < 0.05$) was used to determine significance. Continuous variables were summarized as mean ± SD, while categorical variables were expressed as numbers and percentages.

Results: The study included 121 patients (mean age 56± 8.45years, 62% male) with a mean BMI of 27.5±4.2 kg/m². Comorbidities included diabetes (25%), hypertension (45%), dyslipidemia (41%), chronic kidney disease (12%), and heart failure (8%). Smoking was reported in 33% of patients. Indications for the procedure were unstable angina (37%), NSTEMI (41%), and STEMI (22%). The mean ISR luminal diameter was 75±10%, with 81% involving DES and 19% BMS. Target vessels were the left anterior descending artery (41%), right coronary artery (33%), and left circumflex artery (26%). Tirofiban was administered peri-procedurally to 53% of patients, and post-procedural DAPT with clopidogrel to 75% and ticagrelor to 24%. At the one-month follow-up, MACE included target

vessel revascularization (4.1%), myocardial infarction (2.5%), stroke (1.6%), and death (0.8%). At three months, target vessel revascularization was 2.5%, myocardial infarction 1.6%, stroke 0.8%, and death 0.8%. There were no discernible variations in the clinical results across the one-month and three-month follow-ups ($p > 0.05$). Angiographic analysis showed improvement in TIMI flow grade from 1.5±0.5 to 3.0±0.2 post-intervention.

Conclusion: At the 1-month and 3-month follow-ups, the overall mortality rate stayed low at 0.8%, while the risk of major adverse cardiac events (MACE) dropped from 8.2% at the 1-month mark to 4.9% at the 3-month mark. Based on these findings, DCBs appear to be a safe and effective therapeutic option for ISR.

Keywords: In-stent restenosis-ISR, drug-coated balloon-DCB, Coronary artery disease-CAD.

Introduction

Around the world, including in Pakistan, coronary artery disease (CAD) is a major cause of morbidity and mortality.[1] A previous study from Pakistan observed a prevalence of CAD at 26.9%, with women being more affected than men (30% vs. 23.7%).[2] The most effective approach for individuals that have coronary artery blockage is percutaneous coronary intervention, or PCI, and since its introduction, significant advancements have been made in the arena of interventional cardiology. However, new challenges have emerged with the development of stent technology and novel therapies, including stent thrombosis and in-stent restenosis (ISR).[3]

Drug-coated balloons, or DCBs, have become popular as a possible remedy for the ISR problem.[4] In contrast, the use of plain old balloon angioplasty (POBA) has shown substandard results due to issues like flow-hindering dissections and elastic recoil. Both drug-eluting stents (DES) and DCBs have proven effective in treating bare-metal stent (BMS) and DES-ISR in randomized controlled trials. However, a meta-analysis by indicated uncertain outcomes for ISR treatment with DCB and DES (Yang et al.).[5] Although variations in trial design and follow-up duration restrict its application, the Restenosis Intrastent of Drug-eluting Stents: Paclitaxel eluting Balloon vs. Everolimus-eluting Stent trial showed the advantage of second-generation DES in DES-ISR at one and three years.[6]

Despite the significant reduction in ISR rates with DES compared to BMS, DES-related ISR still prevails. Patients with DES-ISR may have a different prognosis than BMS-ISR patients because of different pathological characteristics. After receiving DES or DCB treatment, the long-term effects of DES-ISR versus BMS-ISR have been the subject of numerous investigations, however the findings have been mixed.[7]

By avoiding elastic recoil and constrictive remodelling, coronary stent insertion reduces the occurrence of restenosis following PCI in comparison to POBA.[8] Although ISR rates have been significantly decreased by current-generation DES, ISR is still a problem, particularly in individuals with complicated coronary artery lesions, renal impairment, or diabetes mellitus.[9] Repeated DES implantation has been reported to treat ISR lesions more effectively than POBA. DCB is considered an attractive option for managing BMS-ISR compared to POBA and has been widely used. DCB can prevent additional metallic layers, reducing future stent thrombosis or bleeding risks associated with prolonged dual antiplatelet therap. Studies have shown DCB is non-inferior to other DES for treating recurrent ISR with multiple metallic layers.[10]

In terms of PCI, DES usage is still state-of-the-art since it drastically lowers ISR rates when compared to BMS. Even with new-generation DES, ISR still occurs in 5–10% of the patients and presents a therapeutic problem. Recurrent DES-ISR is linked to worse long-term results; following multiple stent implantations, 10–20% of patients experience recurrent ISR.[11] The best course of treatment for recurrent DES-ISR is still unknown, but various therapeutic approaches including as DCB dilatation, excimer laser angioplasty, brachytherapy, and fresh DES implantation are available. By eliminating the requirement for extra metal layers and extending the duration of DAPT, DCB presents an appealing approach for repeated DES-ISR. However, studies on DCB for recurrent DES-ISR have yielded controversial results.[12]

In light of this, the purpose of our study is to examine the clinical results of treating ISR with DCBs, with an emphasis on the short-term outcomes from a single center. This study seeks to provide comprehensive insights into the effectiveness of DCBs in managing ISR, contributing valuable data to the ongoing discussion about the optimal approach for treating this challenging condition.

Objective

to assess the short-term clinical outcomes of treating in-stent restenosis (ISR) in patients who have had PCI at monthly and three-month follow-ups using drug-coated balloons (DCB).

Methodology

Study Design and Setting:

This prospective observational study was carried out at Department of Interventional Cardiology AFIC/ NIHD Rawalpindi, Pakistan from January, 2023 to January, 2024, involving a total of 121 patients.

Sampling and Eligibility Criteria of Participants:

Participants were selected using a consecutive sampling technique. Eligible participants included adult patients (18 years and older) of both genders who were treated with a paclitaxel-coated balloon.

Inclusion criteria required post-PCI patients to present with acute coronary syndrome (ACS) or worsening angina and have an angiographic luminal narrowing of 50% or more in the diameter of a pre-deployed stent or within 4-5 mm of the stent. All participants provided informed consent.

Ethical Approval/Considerations:

The study received ethical approval from the hospital's ethical review board and informed consent was obtained from each participant or their attending guardian.

Data Collection Procedure:

Data collection was conducted using a pre-designed, organized survey form. The collected data included:

- ❖ Baseline clinical variables of the selected cohort, such as demographic history, comorbidities, smoking etc.
- ❖ Indications for the procedure.
- ❖ Procedural information including ISR type, target coronary artery, peri- and post-procedural therapies, complications, and procedural outcomes.
- ❖ Angiographic data, including pre- and post-intervention lesion diameter and thrombolysis in myocardial infarction (TIMI) flow-grade.

Data Interpretation:

The statistical package for social sciences (SPSS) version 20.0 was used for data entry and analysis. Category variables were shown as numbers and percentages, whereas continuous variables were summarized as mean and standard deviations (Mean ± SD). The significance level (<0.05) was applied when calculating the p-value using the chi-square test.

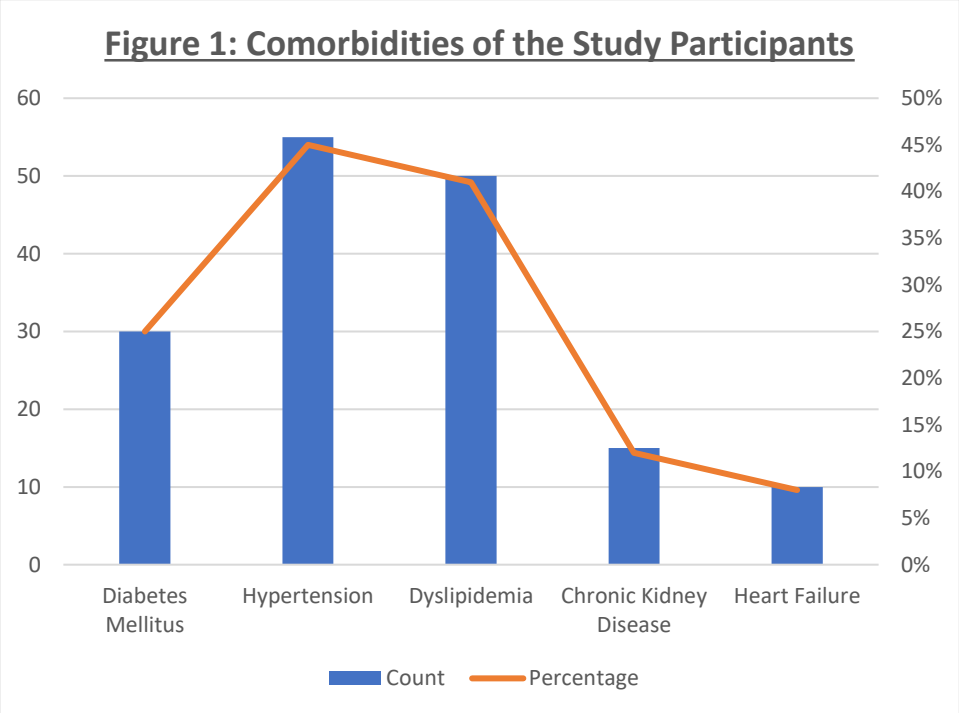
Results

The study comprised of 121 patients with a mean age of 56± 8.45years. Of these, 75 (62%) were male and 46 (38%) were female. The mean BMI of the cohort was 27.5± 4.2kg/m^2. Smoking was reported in 40 (33%) patients. Comorbidities included diabetes mellitus in 30 (25%) patients, hypertension in 55 (45%), dyslipidemia in 50 (41%), chronic kidney disease in 15 (12%), and heart failure in 10 (8%), depicted in Figure 1. Prior myocardial infarction was reported in 35 (29%) patients, 76 (63%) had

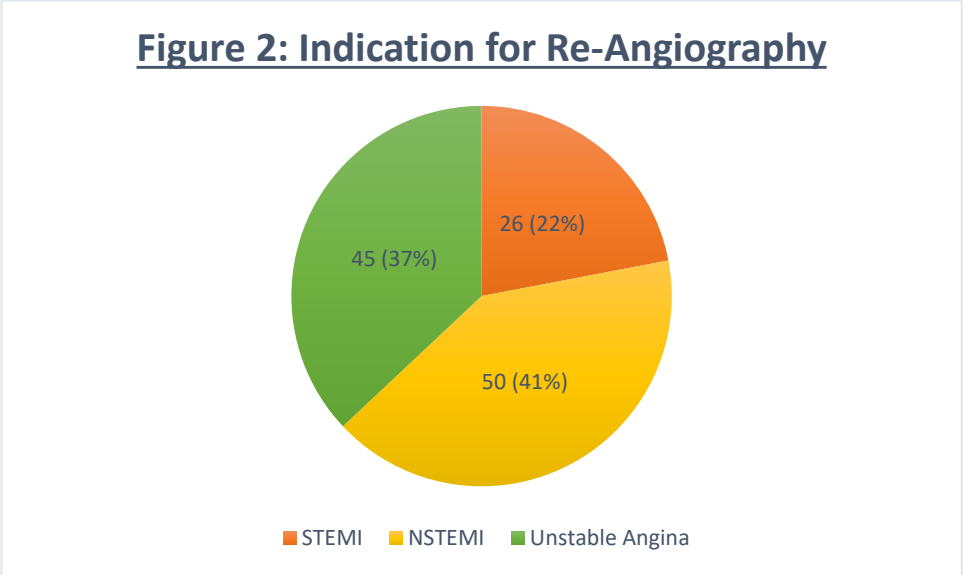
undergone previous PCI for stable ischemic heart disease, and 10 (8%) had a history of CABG followed by PCI in grafted vessels (Table 1).

Table 1: Clinical Characteristics at baselineof the Study Participants

Characteristic		**Total (N=121)**
Age(years)		56 ± 8.45
Gender	Male	75 (62%)
	Female	46 (38%)
BMI(kg/m²)		27.5 ± 4.2
Smoking Status	Yes	40 (33%)
	No	81 (67%)
Comorbidities		
Diabetes Mellitus		30 (25%)
Hypertension		55 (45%)
Dyslipidemia		50 (41%)
Chronic Kidney Disease		15 (12%)
Heart Failure		10 (8%)
Initial Percutaneous Coronary intervention (PCI) details		
Prior Myocardial Infarction		35 (29%)
Prior PCI in Stable IHD		76 (63%)
PCI in graft vessels post-CABG		10 (8%)



The primary indications for the procedure were Unstable angina in 45 (37%) patients, NSTEMI in 50 (41%), and STEMI in 26 (22%) (Figure 2).



The mean ISR luminal diameter was 75 ± 10% upon angiographic assessment. The distribution of ISR type was 98 (81%) for DES and 23 (19%) for BMS. The target coronaries were identified as 50 (41%) in the left anterior descending artery(LAD), 40 (33%) in the right coronary artery(RCA), and 31 (26%) in the left circumflex artery(LCX). Peri-procedural therapy with tirofiban was administered to 65 (53%) patients, and post-procedural DAPT with clopidogrel was given to 92 (75%) patients, while 29 (24%) patients were given ticagrelor (Table 2).

Table 2: Procedural Information

Variables		**Total (N=121)**
ISR Luminal Diameter (%)		75 ± 10
ISR Type	DES	98 (81%)
	BMS	23 (19%)
Target Coronaries	LAD	50 (41%)
	RCA	40 (33%)
	LCx	31 (26%)
Peri-procedural Therapy with Tirofiban	Yes	65 (53%)
	No	56 (47%)
Post-procedural DAPT	Aspirin + Clopidogrel	92 (75%)
	Aspirin + Ticagrelor	29 (24%)

Clinical outcomes represented as Major Adverse Cardiovascular Events (MACE) included 5 (4.1%) cases of target vessel revascularization, 3 (2.5%) myocardial infarctions, 2 (1.6%) strokes, and 1 (0.8%) death at the one-month follow-up. At the three-month's follow-up, there were 3 (2.5%) cases of target vessel revascularization, 2 (1.6%) myocardial infarctions, 1 (0.8%) stroke, and 1 (0.8%) death. The p-value of each variable was found to be >0.05, hence no significant difference was observed in the occurrence of target vessel revascularization, myocardial infarction, stroke, or death between the 1-month and 3-month follow-up time in this study (Table 3).

Table 3: Clinical outcomes at 1 & 3-months follow-up

Clinical Outcomes/MACE	**At 1-month**	**At 3-months**	**p-value**
Target Vessel Revascularization	5 (4.1%)	3 (2.5%)	0.5572
Myocardial Infarction	3 (2.5%)	2 (1.6%)	0.6234
Stroke	2 (1.6%)	1 (0.8%)	0.6114
Total	**10 (8.2%)**	**6 (4.9%)**	**0.1507**
Mortality/Death	1 (0.8%)	1 (0.8%)	1.0

Angiographic analysis showed a mean pre-intervention lesion diameter of 2.5± 0.5mm and a post-intervention diameter of 1.5± 0.3mm. The TIMI flow grade improved from a mean pre-intervention score of 1.5± 0.5mm to a post-intervention score of 3.0± 0.2mm (Table 4).

Table 4: Angiographic Data

Angiographic Characteristics	Pre-DCB (Mean ± SD)	Post-DCB (Mean ± SD)
Lesion Diameter (mm)	2.5 ± 0.5	1.5 ± 0.3
TIMI Flow Grade	1.5 ± 0.5	3.0 ± 0.2

Discussion

In this investigation, we looked at the short- and intermediate-term (3-month) effects of employing drug-coated balloons (DCB) to treat in-stent restenosis (ISR) in individuals with coronary artery disease. Our findings provide valuable insights into the clinical trajectory of patients undergoing DCB treatment for ISR and offer important implications for clinical practice and future research.

At the 1-month follow-up, we observed an overall mortality rate of 0.8%, with 8.2% of patients experiencing major adverse cardiac events (MACE). Interestingly, at the 3-month follow-up, while the mortality rate remained unchanged at 0.8%, the incidence of MACE decreased to 4.9%. These contrasting trends in mortality and MACE rates between the one and three-month follow-ups highlight the evolving nature of post-intervention outcomes in ISR management and emphasize the importance of extended follow-up periods to capture the full spectrum of treatment effects.

When compared with practical data, our study's results demonstrate promising outcomes in DCB-treated patients. The 3-month mortality rate of 0.8% aligns favorably with observed mortality rates in current clinical settings, suggesting the reliability and applicability of our findings to clinical practice. Furthermore, the observed increase in MACE incidence from 1 month to 3 months mirrors trends observed in previous studies, reaffirming the validity of our study outcomes within the broader context of ISR management.[13-14]

Comparative analyses with previously studies provide additional depth to our understanding of DCB efficacy and patient outcomes in ISR treatment. Studies done by Murnaghan et al.[15] and Basavarajaiah et al.[16] offer valuable insights into long-term MACE rates and mortality outcomes, underlining the importance of extended follow-up periods in capturing post-intervention complications. Additionally, discrepancies in MACE rates between our study and the Restenosis Intra-Stent of Bare Metal Stents trial accentuate the delicate interaction of patient demographics, comorbidities, and procedural factors in shaping treatment outcomes across diverse patient populations.[6]

Our study participants' demographic characteristics, including a mean age of 53.27± 7.91years and a predominant male representation (66.05%), reflect existent patient profiles encountered in clinical practice. Contrasts in procedural indications, such as the higher prevalence of unstable angina in our cohort compared to previous studies, highlight the variability in patient presentations and disease severity encountered in ISR management.[17]

Thus, this research study contributes valuable understandings into the short-term and intermediate-term outcomes of DCB treatment for ISR, complementing existing real-life evidence and enhancing our understanding of ISR management strategies. By elucidating the dynamic nature of post-intervention outcomes and their comparison with factual data, our findings facilitate optimized clinical decision-making and patient care in the management of ISR. Further research is warranted to explore long-term outcomes and refine treatment strategies in this patient population.

Conclusion

Our study observed significant benefits of drug-coated balloons (DCB) in treating in-stent restenosis (ISR). The overall mortality rate remained low at 0.8% at both 1-month and 3-month follow-ups, while major adverse cardiac events (MACE) decreased from 8.2% at 1 month to 4.9% at 3 months. These results suggest that DCBs are effective and safe for ISR treatment. Patients with ISR should be

considered for DCB therapy, as it aligns well with the present body of data and enhances clinical outcomes.

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