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# A Randomized Comparison of Paclitaxel-Eluting Balloon Versus Drug Eluting Stent for the treatment of any In-Stent Restenosis

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**Abstract: Background:** In-stent restenosis (ISR) is when the inner diameter gets much smaller in the area that has a stent in it after a successful percutaneous coronary intervention (PCI).

**Aim:** To assess the safety and efficacy of a drug-eluting balloon (DEB) with paclitaxel (PEB) as compared with the implantation of a 2nd-generation drug-eluting stent (DES) for the treatment of ISR.

**Patients and methods:** This research included 60 patients admitted to King Abdullah Medical Complex Hospital in Jeddah who presented with angina or objective evidence of ischemia & revealed ISR on angiography (fifty percent stenosis on visual evaluation) in the period from 2018 to 2021. Individuals were separated into 2 groups: Group I, which involved thirty cases managed by DES, & Group II, which involved thirty cases managed by DEB.

**Results:** 6-month mortality was equally recorded in either group; the variance statistically was not significant. 6-month myocardial infarction recorded only in Drug-Eluting Balloon, but the variance statistically was not significant; & 6-month cerebrovascular accidents recorded only in Drug-Eluting Stent, but the variance statistically was not significant. 6-month need for revascularization (target lesion & target vessel) was more frequent in DEB, but the differences statistically were not significant.

**Conclusion:** DEB therapy was shown to be noninferior to DES treatment in cases with ISR throughout a six-month follow-up period. There were no statistically significant variances in clinical outcomes, such as target vessel revascularization. Thus, employing a drug-eluting balloon is an appealing therapy choice for ISR.

**Keywords:** ISR, DES, PEB

**Introduction**

After a successful PCI, ISR—which manifests as a significant decline in the inner diameter within the stented area—is the main cause of stent failure [1]. The occurrence of ISR has decreased compared to BMS generation because of advancements in DES technology [2]. ISR therapy accounts for five to ten percent of all PCI procedures conducted in clinical practice [3].

In order to avoid arterial recoil and restenosis following balloon dilatation, coronary stents were created. BMS, DES, & BRS are the three main kinds of stents [4].

Neo-intimal hyperplasia was shown to be the primary reason for stent restenosis (ISR), & the use of anti-proliferative drugs was the obvious therapy. Stents were developed into effective local drug delivery platforms in addition to serving as permanent vascular scaffolds. Sousa installed the first DES in Brazil in 1999, ushering in the third dramatic paradigm shift in intervention cardiology history [5].

Drugs for DES must have a selective mode of action, which includes: being able to inhibit platelet aggregation, inflammation, smooth muscle cell proliferation, & migration, all of which ultimately lead to ISR; and facilitating adequate healing and rapid endothelialization [6].

DCBs are a new therapeutic approach for CAD. They work by quickly & evenly delivering anti-proliferative medications into the arterial wall using a lipophilic matrix throughout a single balloon inflation, without the need for permanent implants [7].

The idea behind using DCB in PCI for stenosis is to avoid putting permanent or semi-permanent implants in places where they are more likely to cause an acute arterial closure or have bad long-term results [8].

The objective of the current work was to evaluate the safety & efficiency of DEB with paclitaxel (PEB) as compared with the implantation of a 2nd-generation DES for the treatment of ISR.

**Patient and methods**

This research included 60 patients admitted to King Abdullah Medical Complex Hospital in Jeddah who presented with angina or objective evidence of ischemia & showed ISR on angiography (fifty percent stenosis on visual evaluation) in the period from 2018 to 2021. The cases were separated into two groups: **Group I, which** involved thirty cases managed by DES, & **Group II, which** involved thirty cases managed by DEB. A written consent was obtained in all cases.

**Inclusion criteria:** ISR is indicated for bare-metal stents or DES with a reference vessel diameter between 2.5 & 3.5 mm & lesion length below thirty mm.

**Exclusion criteria:** thrombus in the target vessel, clinically substantial calcification of the target lesion, complete blockage of the coronary artery, & contraindication to dual antiplatelet treatment.

**Methods:**

**All cases were subjected to the following:** history-taking, examination, electrocardiography (ECG), and echocardiography.

**Percutaneous coronary intervention with the following interventional data and recording of:**

**Lesion characteristics:** site & number of vessels affected; site: ostial, proximal, mid- or distal segment; and type of the lesion.

Pre-procedural aspirin and clopidogrel were given to the patients, with a loading dosage (300 to 600 mg) being given to those who had never taken clopidogrel before. During the operation, an initial bolus of 100 mg/kg of unfractionated heparin was given, followed by further boluses as needed, to keep the active clotting time above 250 s. The operation necessitated cautious pre-dilation of the lesion. Lesions were initially dilated using shorter balloons at lower pressures to avoid damaging neighboring coronary segments. From then on, high pressures were suggested as the rule. If under-expanded stents were discovered, it was suggested to use short, noncompliant balloons at very high pressures. After adequate pre-dilation of the lesion, patients followed the suggested therapy with special attention paid to avoiding "geographic miss" complications. cases randomized to DEB (SeQuent Please, B. Braun Surgical, Melsungen, Germany) had balloon angioplasty at minimal pressures (8 to 10 atm) for 60 seconds with a balloon-to-artery ratio of 1.1:1. Patients assigned to the EES group had their

stents chosen so that they would be fully expanded to the same diameter as the final predilation balloon. The stent length was decided upon to cover the original stent length plus an additional 2-3 mm on either end. The choice to employ a post-dilation balloon was left to the operator. Serum creatine kinase levels (with MB analyses for values over the regional upper normal limits) & troponin levels were among the cardiac enzymes that were collected in a systematic fashion in the laboratory. Similar 12-lead ECGs were taken every 8 hours on the first day [9]. Following the technique, all cases were given a 12-month course of DAPT and then continued on lifelong aspirin, independent of their randomized treatment assignment.

**Follow up after 6 months:**

Every individual was recommended to undergo a follow-up angiography at six months (+3 months). The incidence of binary ISR (=50% DS) detected by follow-up coronary angiography was the main endpoint. Clinical follow-up occurred through a telephone interview or an in-person clinic visit six months after the index operation. Cardiac death, target vessel revascularization (percutaneous coronary intervention or coronary artery bypass grafting), stent thrombosis (definite or probable In accordance with Academic Research Consortium criteria, myocardial infarction (unless originating from an untreated vessel) and death from any cause were all considered clinical outcomes (all deaths were considered cardiac unless a certain non-cardiac cause could be determined). The Academic Research Consortium's definition of myocardial infarction, derived from the Global Task Force definitions, may be located in "the myocardial infarction classification and criteria for diagnosis." Pathological indicators of an acute heart attack include the distinct increase and decrease of biomarkers indicating heart tissue damage, together with symptoms of reduced blood flow. Additionally, the development of abnormal Q waves on a subsequent ECG without testing for heart damage during the first episode [10]. Major adverse outcomes were characterised as death, a heart attack related to the specific blood vessel, or surgical restoration of the specific blood vessel.

**Results**

Table 1 shows that: No statistical significant variances among the studied groups concerning baseline demographic characteristics and comorbidities; age, gender, smoking, hypertension, DM & dyslipidemia.

**Table (1):** Baseline demographic characteristics and comorbidities among the studied groups

| **Variables** | **Measures** | **Drug-Eluting Stent (N=30)** | **Drug-Eluting Balloon (N=30)** | **p-value** |
|---|---|---|---|---|
| **Age (years)** | **Mean±SD** | 60.1±9.5 | 62.1±8.4 | ^0.398 |
| | **Range** | 45.0–78.0 | 42.0–76.0 | |
| **Sex, (n, %)** | **Male** | 29 (96.7%) | 28 (93.3%) | §0.999 |
| | **Female** | 1 (3.3%) | 2 (6.7%) | |
| **Smoking, (n, %)** | | 13 (43.3%) | 15 (50.0%) | #0.605 |
| **Hypertension, (n, %)** | | 18 (60.0%) | 22 (73.3%) | #0.273 |
| **Diabetes mellitus, (n, %)** | | 21 (70.0%) | 20 (66.7%) | #0.781 |
| **Dyslipidemia, (n, %)** | | 8 (26.7%) | 11 (36.7%) | #0.405 |

^Independent t-test. §Fisher's Exact test. #Chi square test.

Table (2) show that: No statistical significant variances among the studied groups concerning baseline clinical characteristics; presentation, affected artery and ejection fraction

**Table (2):** Baseline clinical characteristics among the studied groups

| Variables | Measures | Drug-Eluting Stent (N=30) | Drug-Eluting Balloon (N=30) | p-value |
|---|---|---|---|---|
| **Presentation, (n, %)** | **UA** | 16 (53.3%) | 20 (66.7%) | §0.614 |
| | **NSTEMI** | 11 (36.7%) | 8 (26.7%) | |
| | **STEMI** | 3 (10.0%) | 2 (6.7%) | |
| **Affected artery, (n, %)** | **RCA** | 15 (50.0%) | 11 (36.7%) | §0.226 |
| | **LAD** | 10 (33.3%) | 8 (26.7%) | |
| | **LCx** | 2 (6.7%) | 8 (26.7%) | |
| | **Others** | 3 (10.0%) | 3 (10.0%) | |
| **Ejection fraction (%)** | **Mean±SD** | 46.9±9.6 | 47.0±9.2 | ^0.978 |
| | **Range** | 30.0–60.0 | 30.0–60.0 | |

UA: Unstable angina. NSTEMI: Non-ST-elevation myocardial infarction. STEMI: ST-elevation myocardial infarction. RCA: Right coronary artery. LAD: Left anterior descending. LCx: Left circumflex.

Table (3) shows that: No statistical significant variances among the studied groups concerning device characteristics; diameter & length.

**Table (3):** Device characteristics among the studied groups

| Variables | Measures | Drug-Eluting Stent (N=30) | Drug-Eluting Balloon (N=30) | p-value |
|---|---|---|---|---|
| **Diameter (mm)** | **Mean±SD** | 3.2±0.5 | 3.0±0.4 | ^0.206 |
| | **Range** | 2.0–4.0 | 2.5–4.0 | |
| **Length (mm)** | **Mean±SD** | 23.6±8.2 | 21.0±6.5 | ^0.169 |
| | **Range** | 8.0–38.0 | 12.0–35.0 | |

Table (4) shows that: 6-Month mortality was equally recorded in either group; the variance statistically was not significant, 6-Month myocardial infarction recorded only in Drug-Eluting Balloon, but the variance statistically was not significant & 6-Month cerebrovascular accidents recorded only in Drug-Eluting Stent, but the variance statistically was not significant.

**Table (4):** 6-Month mortality, myocardial infarction and cerebrovascular accidents among the studied groups

| Findings | | Drug-Eluting Stent (N=30) | Drug-Eluting Balloon (N=30) | p-value |
|---|---|---|---|---|
| **Mortality** | | 1 (3.3%) | 1 (3.3%) | §0.999 |
| **Survival** | | 29 (96.7%) | 29 (96.7%) | |
| **Myocardial infarction** | **Occurred** | 0 (0.0%) | 1 (3.3%) | §0.999 |
| | **Not** | 30 (100.0%) | 29 (96.7%) | |
| **Cerebrovascular** | **Occurred** | 1 (3.3%) | 0 (0.0%) | §0.999 |

| | | | | |
|---|---|---|---|---|
| **accidents** | **Not** | 29 (96.7%) | 30 (100.0%) | |

§Fisher's Exact test

Table (5) shows that: 6-Month binary ISR ≥50.0% was more frequent in Drug-Eluting Balloon, but the variance statistically was not significant.

**Table (5):** 6-Month binary ISR ≥50.0% among the studied groups

| **Findings** | **Drug-Eluting Stent (N=30)** | **Drug-Eluting Balloon (N=30)** | **p-value** |
|---|---|---|---|
| **Occurred** | 5 (16.7%) | 6 (20.0%) | #0.738 |
| **Not** | 25 (83.3%) | 24 (80.0%) | |

#Chi square test

Table (6) shows that: 6-Month need to revascularization (target lesion and target vessel) was more frequent in Drug-Eluting Balloon, but the differences statistically were not significant.

**Table (6):** 6-Month target lesion & vessel revascularization among the studied groups

| **Revascularization** | **Drug-Eluting Stent (N=30)** | **Drug-Eluting Balloon (N=30)** | **p-value** |
|---|---|---|---|
| **Target lesion** | 4 (13.3%) | 6 (20.0%) | #0.488 |
| **Target vessel** | 5 (16.7%) | 6 (20.0%) | #0.739 |

**Discussion**

Our results showed that no statistically significant variances were noted among the studied groups regarding baseline demographic characteristics and comorbidities (age, gender, smoking, hypertension, DM, & dyslipidemia), regarding baseline clinical characteristics (presentation, affected artery, and ejection fraction), and regarding device characteristics (diameter and length).

Also, our results showed that 6-month mortality was equally recorded in either group; the variance statistically was not significant; 6-month myocardial infarction was recorded only in drug-eluting balloons, but the variance statistically was not significant; & 6-month cerebrovascular accidents were recorded only in drug-eluting stents, but the variance statistically was not significant. 6-Month binary ISR ≥50.0% was more frequent in Drug-Eluting Balloon, but the difference statistically was not significant, & 6-Month need for revascularization (target lesion and target vessel) was more frequent in Drug-Eluting Balloon, but the variances statistically were not significant.

The outcomes of our study were in accordance with the results of several other studies.

DEB & DES performance in cases with any (bare-metal or DES) ISR was evaluated in the DARE study, a multicenter randomised noninferiority research study. The in-segment MLD at six-month angiographic follow-up served as the study's primary goal. The secondary outcomes were angiographic follow-up at six months & clinical follow-up at twelve months. 278 patients were involved in the trial; 56% of them had DES-ISR and were randomly identified to receive management with DEB (n = 141) or DES (n = 137) at 8 different centers. Instantly after the procedure, DES was linked to higher MLD and lower-diameter stenosis than DEB. In 79% of patients, the angiographic follow-up was finished at 196± 53 days. DEB was noninferior to DES in terms of the main endpoint of in-segment MLD at six months (DEB 1.71 0.51 mm vs. DES 1.74 0.61 mm; p for noninferiority 0.0001). Target vessel revascularization was comparable in two groups at the 12-month follow-up (DES 7.1 percent vs. DEB 8.8 percent; p = 0.65) [11].

A meta-analysis on the clinical and angiographic results of RCTs & observational research comparing 2nd generation DES to DCB for the management of ISR was carried out by **Kokkinidis** et al., comprising ten studies

and 2,173 participants. In both randomised and observational investigations, it was shown that the two treatment approaches were equivalent in terms of TLR, MI, stent thrombosis, & cardiac mortality. In observational research, individuals treated with second-generation DES had a decreased mortality compared to DCB (OR: 0.47; 95 percent CI: 0.27–0.83), although no difference in all-cause mortality was reported among RCTs. Additionally, in the pooled analysis (RCTs & observational research), DES was linked to decreased all-cause mortality compared to DCB. Patients who received DES also had a better MLD. They found that the two ways of treating ISR are about the same, and that any difference in overall mortality might be due to differences between the two groups at the start of the real-world trials [12].

Fifty patients with BMS ISR participated in SEDUCE research, & they were randomly identified to receive either a paclitaxel-eluting balloon or EES. The proportion of exposed struts at nine months was used as the main endpoint to assess the success of the healing process in the vessel wall. For each patient in the DEB and EES groups, researchers analysed an average of 366±35 and 636±84 struts. DEB had a statistically significant decrease in the number of exposed struts per patient compared to EES (1.4% vs. 3.1%, p = 0.025). While the proportion of malapposed struts per case was rather low in both groups (0.2 percent vs. 0.3 percent, p = 0.699), the mean area of neointimal hyperplasia was larger in DEB (2.41.08 mm) than in EES (1.920.67 mm). At nine months, the angiographic in-stent MLD (minimum lumen diameter) was smaller after DEB than after EES (2.13 vs. 2.54 mm, p = 0.006), whereas diameter stenosis was greater after DEB than after EES (26.4 vs. 11.4 percent, p = 0.002), & the LLL was smaller after DEB than after EES (0.28 vs. 0.07 mm, p = 0.1). Death, TLR, & stent thrombosis rates were similar across groups after a single year of follow-up. The outcomes of the research indicated that, compared to EES, DEB had a slightly lower efficacy rate, but was linked with improved healing qualities as measured by stent strut coverage using OCT. These results provide credence to the efficacy of DEB and EES in treating ISR [13].

On the other hand, several other trials agreed partially with our results and differed only in terms of TLR in cases with ISR in previously deployed DES.

In their meta-analysis comparing DCB with EES for the management of ISR, **Ping et al.** used data from six randomised controlled trials (RCTs) with a total of 1134 individuals. Data showed that DCB had different results in DES-ISR & BMS-ISR than it did in EES. The angiographic and clinical results for DES-ISR were worse with DCB compared to EES. In cases with DES-ISR, DCB was associated with a lesser MLD, a greater percentage of diameter stenosis, a higher rate of binary restenosis, & a higher risk of thromboembolic events, including TVR and TLR, compared to EES. However, EES and DCB were similarly efficacious in terms of angiographic outcomes & clinical events in individuals with BMS-ISR [14].

The DAEDALUS research analysed data from 10 randomised controlled investigations to compare the efficiency of DES vs. DCB angioplasty in preventing coronary ISR. cases were categorised into 2 groups depending on whether they had BMS-ISR or DES-ISR, and their corresponding therapies were recorded. The main objective regarding effectiveness was TLR after three years. The key safety outcome was a combination of mortality, MI, & clotting in the target artery occurring within three years [15].

**Study Limitations: A small** number of cases or a larger number of cases is required for better outcomes of the research. Short duration of follow-up: cases were followed for 6 months; only longer periods of follow-up are required. Assessment of restenosis was done only by visual assessment; using other modalities like IVUS or OCT could help with a better assessment of the restenosis percentage, nature, and pathology. In our study, we depended on the Paclitaxel drug balloon. Newer balloons are now available using Sirolimus instead of Paclitaxel; further studies may be required using these balloons and comparing them with the newer generation of DES. Good preparation of the lesions prior to intervention using scoring or cutting balloons may have better results.

**Conclusion**

DEB therapy was shown to be noninferior to DES treatment in cases with ISR throughout the six-month follow-up period. No statistically significant variances in clinical outcomes were noted, such as target vessel revascularization. Thus, employing a drug-eluting balloon is an appealing therapy choice for in-stent restenosis. Future randomised controlled trials (RCTs) & meticulously planned prospective observational studies are expected to provide more definitive outcomes

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