Efficacy of seal-wing paclitaxel-eluting balloon catheters in the treatment of drug-eluting stent restenosis

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Aim: Our study aimed to compare the efficacy of seal-wing paclitaxel-eluting balloon catheters (PEB) for treating drug eluting stent restenosis (DES-ISR).
Methods: We enrolled 17 patients with 19 DES-ISR lesions. The control group comprised of 64 patients with bare-metal stent restenosis (BMS-ISR) from the seal-wing PEB arm of a previous TIS study. The primary end-point was 12-month in-segment late lumen loss (LLL). Secondary end-points included incidence of binary in-stent restenosis, 12-month major adverse cardiac events (MACE) and target vessel revascularisation (TVR).
Results: Compared to BMS-ISR, seal-wing PEB used for DES-ISR treatment was associated with a significantly higher LLL (1.12 ± 0.83 mm vs. 0.47 ± 0.57 mm; p = 0.008), percent diameter stenosis (% DS; 62.6 ± 29.2 % vs. 42.4 ± 27.9 %; p = 0.020) and incidence of repeated binary restenosis (64.3 % vs. 28.1 %; p = 0.014). Differences at the 12-month clinical follow-up (MACE and TVR) did not reach statistical significance (50 % vs. 30 %; p = 0.077 and 43.7 % vs. 20.6 %; p = 0.103, respectively).
Conclusion: Treatment of DES-ISR using seal-wing PEB was associated with significantly worse 12-month angiographic outcomes. Differences at the 12-month clinical follow-up (MACE and TVR) did not reach statistical significance. (ClinicalTrials.gov; https://clinicaltrials.gov; NCT01735825.)

Klíčová slova: in-stent restenosis, paclitaxel-elution balloon, drug-eluting stent

Posouzení účinnosti seal-wing balonkových katétrů s paclitaxelem v léčbě restenóz v lékových stentech

Cíl: Cílem naší studie bylo srovnání účinnosti seal-wing balonkových katétrů s paclitaxelem (PEB) v léčbě restenóz v lékových (DES-ISR) a holých kovových stentech (BMS-ISR).
Metodika: Do studie bylo zahrnuto 17 pacientů s 19 DES-ISR lézemi. Kontrolní skupinu představovalo 64 pacientů s BMS-ISR ze seal-wing PEB větve předchozí studie TIS. Primárním end-pointem byl 12měsíční late lumen loss (LLL). Sekundární end-pointy zahrnovaly výskyt opakovaných in-stent restenóz, hlavních nežádoucích kardiovaskulárních příhod (MACE) a nutnosti opakované revaskularizace cílové tepny (TVR) po 12 měsících.
Výsledky: Ve srovnání s BMS-ISR, byla léčba DES-ISR pomocí seal-wing PEB spojena se signifikantně vyšším LLL (1,12 ± 0,83 mm vs. 0,47 ± 0,57 mm; p = 0,008), procentuálním diametrem stenózy (% DS; 62,6 ± 29,2 % vs. 42,4 ± 27,9 %; p = 0,020) a výskytem opakovaných binárních restenóz (64,3 % vs. 28,1%; p=0,014). Rozdíly ve 12měsíčních klinických výsledcích (MACE a TVR) nedosáhly statistické významnosti (50 % vs. 30 %; p = 0,077 a 43,7 % vs. 20,6 %; p = 0,103).
Závěr: Léčba DES-ISR pomocí seal-wing PEB je spojena se signifikantně horšími 12měsíčními angiografickými výsledky. Rozdíly ve 12 měsíčním klinickém sledování (MACE a TVR) nedosáhly statistické významnosti. (ClinicalTrials.gov; https://clinicaltrials.gov; NCT01735825.)

Klíčová slova: in-stent restenóza, paclitaxel-eluting balonkový katétr, drug-eluting stent.

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Table 1. *Baseline demographic, clinical and periprocedural parameters*

	DES-ISR	BMS-ISR	p
Demographic parameters			
Patients/ ISR lesions, n	17/19	64/69	
Male	13 (76.5 %)	49 (76.6 %)	1.000#
Age, years	63.6 ± 10.5† / 63‡	65.25 ± 11.01† / 67‡	0.417#
Body mass index, kg/m^2	29.9 ± 3.7† / 29.7‡	28.38 ± 4.93† / 27.8‡	0.085#
Ejection fraction, %	54.7 ± 39.9† / 55‡	52.31 ± 10.01† / 55.00‡	0.344#
Diabetes mellitus	8 (47.1 %)	18 (28.1 %)	0.137#
2VD/3VD	10 (58.8 %)	43 (67.2 %)	0.519#
Multi ISR	2 (11.8 %)	5 (7.8 %)	0.633§
Baseline PCI			
ACSy (STEMI/NSTEMI)	12 (70.6 %)	37 (57.8 %)	0.338#
Type of lesion			
B2/C	17 (89.5 %)	47 (68.1 %)	0.064#
Length of the previous stent, mm	#24.7 ± 9.2† / 22.0‡	25.67 ± 15.48† / 20.0‡	0.548#
In-stent restenosis			
ACSy, STEMI/NSTEMI	8 (47.1 %)	19 (29.7 %)	0.318§
Time to ISR, months	13.3 ± 7.7† / 11.0‡	12.49 ± 11.06† / 7.0‡	0.155#
Type of ISR			
I (focal; all)	10 (52.6 %)	25 (36.2 %)	0.576§
II (diffuse)	8 (42.1 %)	33 (47.8 %)	
III (proliferative)	1 (5.3 %)	6 (8.7 %)	
IV (occlusion)	0	5 (7.2 %)	
Cutting predilatation	11 (57.9 %)	20 (29 %)	0.019*
ISR; PEB diameter, mm	3.61 ± 0.54† / 4.0‡	3.27 ± 0.47† / 3.17‡	0.009#
ISR; PEB length, mm	18.9 ± 5.7† / 20.0‡	23.19 ± 12.98† / 20.0‡	0.192#
Postdilatation, atm	15.0 ± 2.9† / 16.0	13.48 ± 2.34† / 12.0‡	0.049#
Second stent implantation	1 (5.3 %)	8 (11.6 %)	0.677*

*Qualitative data are given as n (%); quantitative data as † mean (± standard deviation) and ‡ median; * chi-square test; § Fisher's exact test; # Mann–Whitney U test*

Introduction

Current treatments for in-stent restenosis utilize drug-eluting stents (DES) or drug-eluting balloon catheters (DEB) with locally released antiproliferative drugs. In contrast to DES, DEB allow short-term passage of the active substance (paclitaxel) into the vascular wall, preventing hyperproliferation of smooth muscle cells (1, 2). The main factor that influences PEB efficacy is the method used to bind paclitaxel to the balloon catheter surface. Therefore, this is not considered a "class effect".

We demonstated, that BMS-ISR treatment using seal-wing PEB led to significantly higher 12-month late lumen loss (LLL), repeated binary restenosis, major adverse cardiac events (MACE) and tagret vessel revascularisation (TVR) compared to iopromide-coated PEB (3). In our present study, we aimed to compare the effects of seal-wing PEB for treating DES-ISR.

Patients and methods

Our study included consecutive adult patients (>18 years of age) with DES-ISR (≥ 50 % diameter stenosis; DS) who were treated with seal-wing PEB (Protége) in the Cathlab of University Hospital Ostrava in 2013–2015. The control group comprised patients with BMS-ISR who were treated using seal-wing PEB in the corresponding part of previous the TIS study (3). The main exclusion criteria were concomitant diseases carrying expected survival times of <12 months or limiting the possibility of control coronary angiography.

The primary end-point was in-segment LLL at 12 months as measured by quantitative control angiography (QCA) (4). Secondary end-points were the incidence of binary ISR (≥ 50 % DS) and the overall incidence of 12-month MACE, including cardiovascular death, non-fatal acute myocardial infarction (MI), and target vessel revascularization (TVR).

Written informed consent was obtained from each patient before enrollment in the study. The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of University Hospital Ostrava, Czech Republic. The study was registered at ClinicalTrials.gov (NCT01735825).

PCI was performed under standard conditions using a 6F guiding catheter and an Axiom X-ray system (Siemens AG, Forchheim, Germany). Following predilatation, the PEB Protége (Blue Medical, Helmond, the Netherlands) was inflated for 30s at the recommended pressure.The seal-wing PEB Protége has paclitaxel (3 µg/mm2) tightly bound directly to the balloon catheter surface between the wings and hydrophilic coating prior to folding. This coating prevents releasing particles during bending of the balloon or transition to the stenosis. Paclitaxel, not coating, is only released when the balloon touches the vessel wall (5, 6). Dual antiplatelet therapy with aspirin (100 mg) and clopidogrel (75 mg) was administered daily for three months following PEB dilatation.

Clinical follow-up was performed at 6 and 12 months. Angiographic follow-up was performed at 12 months (± 2 months) unless needed earlier.

Angiographic imagings were performed using appropriate orthogonal projections to best avoid potential shortening or overlap of the reporting segment. Lesions were evaluated in an in-segment section ±5 mm from the proximal and distal edges of the stent. Angiographic parameters were evaluated off-line using syngo Quantification software version 2007 (Siemens AG, Forchheim, Germany). The following parameters were measured: minimum lumen diameter (MLD), reference lumen diameter (RefD = ½ proximal + distal diameter), acute gain, lesion length, diameter of the stenosis (% DS), and late lumen loss (LLL = MLD post-intervention – MLD control). Binary ISR was defined as DS ≥ 50 % in the stented segment.

Normally distributed continuous variables are presented as mean and standard deviation; continuous variables with non-normal distribution are presented as median and range, and were compared using the non-parametric Mann–Whitney U test. Categorical variables are presented as count and percentage, and were compared using the chi-square or Fisher's exact test. Multiple logistic regression (stepwise forward method) was used to identify the most significant predictive factors for repeated binary restenosis, with adjustment for diabetes mellitus and other possible confounding factors. Each odds ratio (OR) is expressed with a 95 % confidence interval (CI). A P value of < 0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics version 22.

Table 2. *Baseline, postprocedural, 12-month QCA parameters and 12-month clinical follow-up*

	DES-ISR	BMS-ISR	p
Lesions, n	17	64	
Baseline			
Minimal lumen diameter, mm	0.93 ± 0.53/0.92	0.86 ± 0.46/0.93	0.653§
Reference diameter, mm	2.83 ± 0.54/2.78	2.50 ± 0.43/2.45	0.011§
% Diameter stenosis	75.1 ± 11.9/77.5	74.3 ± 14.5/73.0	0.830§
Post-PCI			
Minimal lumen diameter, mm	2.35 ± 0.48/2.37	2.09 ± 0.45/1.99	0.021§
Reference diameter, mm	3.12 ± 0.64/3.18	2.72 ± 0.42/2.63	0.031§
Acute gain, mm	1.42 ± 0.54/1.41	1.23 ± 0.53/1.19	0.277§
% Diameter residual stenosis	21.5 ± 8.0/24.5	21.5 ± 7.9/23.5	0.948§
12-month QCA parameters			
Minimal lumen diameter, mm	1.23 ± 1.03/1.05	1.63 ± 0.78/1.68	0.139§
Reference diameter, mm	3.06 ± 0.76/3.42	2.62 ± 0.53/2.56	0.060§
% Diameter stenosis	62.6 ± 29.2/72.0	42.4 ± 27.9/33.5	0.020§
Late lumen loss, mm	1.12 ± 0.83/1.03	0.47 ± 0.57/0.30	0.008§
Binary restenosis (% DS > 50 %)	9 (64.3 %)	18 (28.1 %)	0.014#
12-month clinical follow-up			
Patients, n	16	63	
MACE all	8 (50 %)	17 (30 %)	0.077*
MI	1 (6,2 %)	4 (6,4 %)	1.000#
TVR	7 (43,8 %)	13 (20,6 %)	0.103#
Event-free survivors	8 (50 %)	46 (73 %)	0.077*

*§ Mann-Whitney U test; # Fisher's exact test; * chi-square test;*

Table 3. *Logistic (separately for each parametrs) and multivariate logistic regression analysis (stepwise forward method)*

Logistic regression analysis			
	p	**Unadjusted OR**	**95 % CI**
Diabetes mellitus (1 = yes, 0 = no)	0.029	3.018	1.117–8.156
Type B2/C lesion (1 = yes, 0 = no)	0.172	2.200	0.709–6.825
DES-ISR = 1 / BMS-ISR = 0	0.014	4.600	1.356–15.604
Vessel diameter < 3 mm (1 = yes,0 = no)	0.611	1.354	0.422–4.348
ISR length > 10 mm (1 = yes, 0 = no)	0.245	1.778	0.673–4.694
Multivariate logistic regression analysis			
	p	**Adjusted OR**	**95 % CI**
DES-ISR = 1 / BMS-ISR = 0	0.004	8.064	1,921–33.858
ISR length > 10 mm (1 = yes, 0 = no)	0.048	3.375	1,011–11.270

Results

Our study included 17 patients with 19 DES-ISR lesions, all of whom were treated with seal-wing PEB. The course of the study is shown in the study flow diagram (Fig. 1). We obtained 12-month clinical data for 16 patients with DES-ISR (94.1 %; 95 % CI: 71.3–99.8 %) and 12-month QCA was performed in 17 DES-ISR lesions (89.5 %; 95 % CI: 66.9–98.7 %).

Table 1 presents the baseline demographic, clinical, angiographic, and ISR characteristics of the study group, with comparison to the control BMS-ISR groups from the seal-wing PEB arm of previous TIS study (3). In the DES-ISR group, 79 % of the lesions (n = 15) were originally treated with everolimus-eluting stent, 10.5 % (n = 2) with sirolimus-eluting stent and 10.5 % (n = 2) with paclitaxel-eluting stent. Compared to BMS-ISR, patients with DES-ISR had significantly higher pre-procedure and early postprocedural RefD values (p values: 0.011 and 0.031, respectively), as well as early postprocedural MLD (p = 0.021).

The 12-month follow-up showed no between-group difference in MLD (p = 0.139), while the DES-ISR group showed a significantly higher LLL, % DS, and incidence of repeated binary restenosis (p value: 0.008, 0.020, and 0.014, respectively). Differences at the 12-month clinical follow-up (MACE and TVR) did not reach statistical significance (p values: 0.077 and 0.103, respectively) (table 2).

Logistic regression analysis was performed to assess the impact of various risk factors on the incidence of repeated binary restenosis after seal-wing PEB treatment of ISR, with correlations to individual parameters in the whole group taking the type of ISR (BMS or DES-ISR) as an independent factor (table 3). The following factors were found to be important predictors of repeated binary restenosis: diabetes mellitus (unadjusted OR: 3.018; 95 %CI: 1.117–8.156; p = 0.029) and DES-ISR (unadjusted OR: 4.600; 95 %CI: 1.356–15.604; p = 014). Patients with DES-ISR (adjusted OR: 8.064; 95 % CI: 1.921–33.858; p = 0.004) and lesion length >10 mm (adjusted OR: 3.375; 95 % CI: 1.011–11.27; p = 0.048) who were treated with seal-wing PEB had significantly higher chances of repeated binary restenosis, even with adjustment for other confounding risk factors.

Discussion

Paclitaxel is commonly used as an antiproliferative agent in cases of DEB. This drug is highly lipophilic and rapidly penetrates into the tissues, with the utilized concentrations stabilizing at 3 µg/mm (7). In the original concept described by Scheller et al., paclitaxel was bound via the hydrophilic contrast agent iopromide (Paccocath®), which increased its solubility and vascular wall penetration (7).

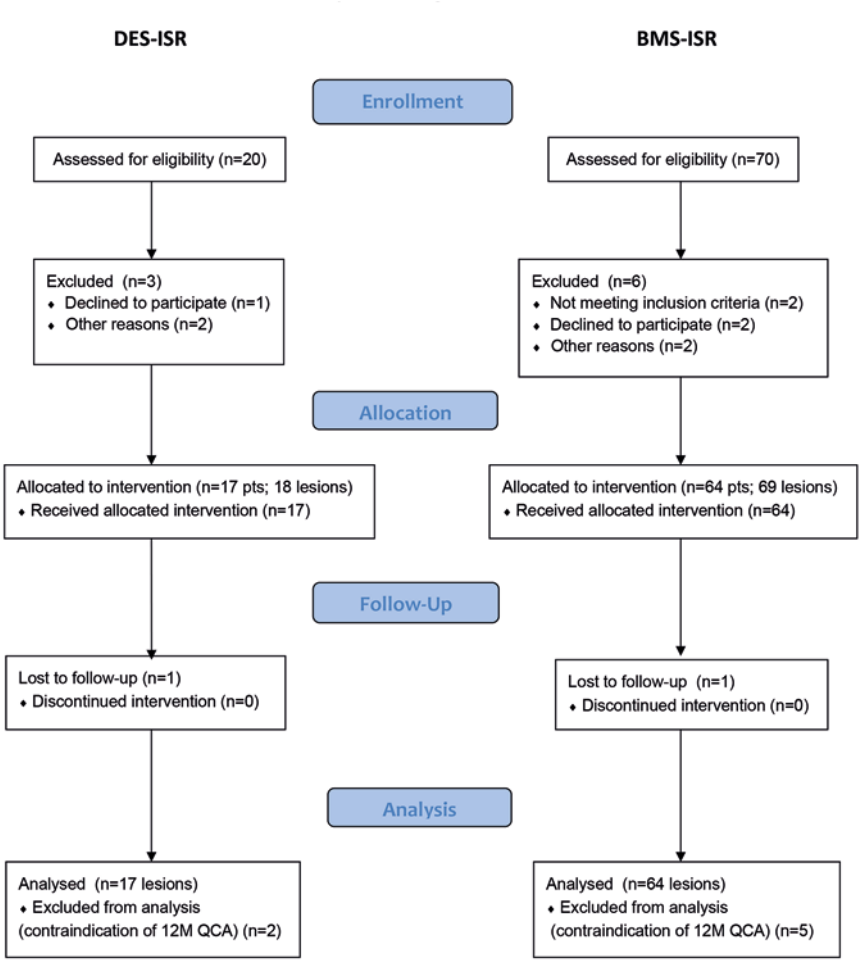
The efficacy of BMS-ISR treatment using iopromide-coated PEB has been demonstrated in comparison with POBA or paclitaxel-eluting stents (PES) (8, 9).

In the RIBS V trial, patients with BMS-ISR were treated with iopromide-coated PEB or everolimus-eluting stents (EES). The EES group showed significantly higher 9-month MLD (p < 0.001) and lower % DS (p < 0.001). However, both groups did not differ in LLL (p = 0.14), incidence of binary restenosis (p = 0.22),12-month MACE (p = 0.6), or TVR (p = 0.22) (10).

Contrary to the RIBS V, in our TIS study the use of iopromide-coated PEB for treatment of BMS-ISR was associated with significantly reduced 12-month LLL compared to implantation of EES (p = 0,0004). However, between-group differences in the incidence of repeated binary restenosis (p = 0.078) and 12-month MACE (p = 0.213) were non-significant (11).

The main factor influencing the PEB efficacy is the method used to bind paclitaxel to the balloon catheter surface. In the previous study we found, that BMS-ISR treatment using seal-wing PEB led to significantly higher 12-month LLL (p < 0.0001), repeated binary restenosis (p = 0.012), MACE (p = 0.003), and TVR (p = 0.009) compared to iopromide-coated PEB (3).

Fig. 1. *Study flow diagram*



The PEPCAD-DES and PEPCAD ISR China trials demonstrated the efficacy of iorpomide--coated PEB for DES-ISR treatment in comparison with POBA or PES (12, 13, 14).

In the RIBS IV study, the use of iopromide--coated PEB for DES-ISR treatment led to significanly lower 9-month MLD ($p < 0.01$), higher % DS ($p < 0.01$) and binary restenosis rate ($p=0.06$) compared to EES (15).

A pooled analysis of RIBS IV and V studies compared the outcomes of iopromide-coated PEB for BMS – or DES-ISR treatment and found significantly lower 9-month MLD ($p = 0.001$), higher repeated binary restenosis rate ($p < 0.05$), 12-month MACE ($p = 0.03$) and TVR ($p = 0.02$) in patients with DES-ISR (16).

We also demonstrated that treatment with seal-wing PEB led to significantly higher 12-month LLL and repeated binary restenosis in the treatment of DES-ISR compared to BMS-ISR. These results confirm the assumption that DES-ISR treatment is considerably more difficult than BMS-ISR treatment. However, in the clinical follow-up, the differences in 12-month MACE and TVR did not reach significance, probably due to the small sample size. Multivariable regression analysis confirmed that DES-ISR was a significant risk factor for repeated binary restenosis, even with adjustment for other confounding risk factors.

According to the German consensus group, the DEB should be used as a device for drug delivery after optimal predilatation of an ISR lesion. To avoid balloon slippage a semi– or non-compliant balloon is recommended for predilatation. The use of cutting or scoring balloons is also suitable (17).

In our study, optimal lesion preparation was left to the operator´s decision. More frequent use of scoring balloons in DES-ISR group was not associated with better angiographic results. Non-compliant predilatation was performed in both groups, with relatively low pressures to avoid edge dissection. It seems to be a reason for higher residual stenosis in both groups, however, as acceptable angiographic results of lesion preparation for DEB treatment are considered no major dissection (> A-B class), TIMI flow of 3 and residual stenosis < 30 % (17). Intravascular imagines (IVUS or OCT) were not used routinely.

Limitations

Our study has several limitations. In particular, it was a non-randomized study, nevertheless, selection bias likely did not play a major role, since the patient cohorts did not differ with respect to main baseline parameters. Additionally, this study did not have sufficient statistical power to detect significant differences in the clinical end-points (i.e., MACE) between the BMS-ISR and DES-ISR groups.

Conclusions

Treatment of DES-ISR using seal-wing PEB was associated with significantly worse 12-month angiographic outcomes compared to treatment of BMS-ISR. Differences at the 12-month clinical follow-up (MACE and TVR) did not reach statistical significance.

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We hereby declare that we have no conflict of interest.

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