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In-stent restenosis treatment with seal-wing paclitaxel-eluting balloon catheters

Leoš Pleva[a,b], Pavel Kukla[a], Jana Zapletalová[c], Ota Hlinomaz[d,e]

[a] *Department of Cardiovascular Diseases, Clinic of Internal Medicine and Cardiology, University Hospital Ostrava, Ostrava*
[b] *Medical Faculty, University of Ostrava, Ostrava*
[c] *Department of Medical Biophysics, Palacky University, Olomouc*
[d] *Department of Cardioangiology, St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno*
[e] *International Clinical Research Center, St. Anne's University Hospital, Brno*

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SOUHRN

Cíl: Cílem této studie je srovnání dlouhodobých klinických výsledků léčby restenóz v holých kovových stentech (BMS-ISR) pomocí seal-wing a iopromidových lékových balonkových katétrů s paclitaxelem (PEB).
Metodika: Celkem bylo po dobu tří let roky klinicky sledováno 132 pacientů s BMS-ISR, z nichž 64 bylo léčeno pomocí seal-wing PEB; kontrolní skupinu tvořilo 68 pacientů z iopromidové PEB větve předchozí studie TIS. Primárním cílovým ukazatelem byla četnost výskytu závažných nežádoucích kardiovaskulárních příhod (MACE; úmrtí z kardiovaskulárních příčin, infarkt myokardu [IM] nebo nutnost opakované revaskularizace cílové tepny [TVR])
Výsledky: Výskyt MACE byl po třech letech signifikantně vyšší ve skupině pacientů léčených seal-wing PEB oproti skupině iopromidových PEB (40,6 % vs. 19,1%; $p = 0{,}008$); obdobného rozdílu bylo dosaženo ve srovnání nutnosti TVR (26,9 % vs. 8,8 %; $p = 0{,}011$). Doba přežití bez klinické příhody byla ve skupině iopromidových PEB signifikantně delší ($p = 0{,}021$). Mezi oběma skupinami nebyly zaznamenány rozdíly v mortalitě z kardiovaskulárních příčin (4,7 % vs. 5,9 %; $p = 1{,}000$), výskytu IM (6,3 % vs. 4,4 %; $p = 0{,}712$), potvrzené trombózy stentů (0 % vs. 2,9 %; $p = 0{,}497$) nebo opakovaných MACE (4,7 % vs. 1,5 %; $p = 0{,}354$).
Závěr: Ve srovnání s iopromidovými PEB je použití seal-wing PEB v léčbě BMS-ISR spojeno se signifikantně vyšším tříletým výskytem MACE a TVR (ClinicalTrials.gov; https://clinicaltrials.gov; NCT01735825).

ABSTRACT

Objectives: We aimed to compare the long-term clinical outcomes of seal-wing and iopromide-coated paclitaxel eluting balloon catheters (PEB) in the treatment of bare-metal stent restenosis (BMS-ISR).
Methods: A 3-year clinical follow-up of 132 patients with BMS-ISR was performed, of whom 64 were treated with seal-wing PEB; the control group consisted of 68 patients from iopromide-coated PEB branch of the previous TIS study. The primary endpoint was the occurrence of major adverse cardiac events (MACE; cardiovascular [CV] death, myocardial infarction [MI], or target vessel revascularization [TVR]).
Results: Compared to iopromide-coated PEB, the incidence of 3-year MACE was significantly higher (40.6% vs. 19.1%; $p = 0.008$) in the seal-wing PEB group; a similar difference was achieved when comparing the need for TVR (26.9% vs. 8.8%; $p = 0.011$). The event-free survival in the iopromide-coated PEB group was significantly longer ($p = 0.021$). There were no differences in cardiovascular mortality (4.7% vs. 5.9%; $p = 1.000$), occurrence of MI (6.3% vs. 4.4%; $p = 0.712$), definite ST (0% vs. 2.9%; $p = 0.497$) or repeated MACE (4.7% vs. 1.5%; $p = 0.354$) between the two groups.
Conclusion: Compared to iopromide-coated PEB, the use of seal-wing PEB in the treatment of BMS-ISR is associated with a significantly higher 3-year incidence of MACE and TVR (ClinicalTrials.gov; https://clinicaltrials.gov; NCT01735825).

Keywords:
In-stent restenosis
Paclitaxel-eluting balloon
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Address: Doc. MUDr. Leoš Pleva, Ph.D., Department of Cardiovascular Diseases, Clinic of Internal Medicine and Cardiology, Medical Faculty, University of Ostrava and University Hospital of Ostrava, 17. listopadu 1790, 708 52 Ostrava-Poruba, e-mail: leos.pleva@volny.cz
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Introduction

The effectiveness of paclitaxel-eluting balloon catheters (PEB) is affected by the way paclitaxel is attached to the surface of the balloon catheter. In a previous study, we demonstrated that treatment of in-stent restenosis in bare-metal stents (BMS-ISR) with iopromide-coated PEB leads to a significantly lower 12-month late lumen loss (LLL), reducing the incidence of recurrent binary restenosis and major adverse cardiac events (MACE; cardiovascular [CV] death, myocardial infarction [MI], or target vessel revascularization [TVR]) compared to seal-wing PEB.[1]

The aim of our current study is to compare the long-term clinical results of BMS-ISR therapy using these PEBs with different binding of the active substance on their surface.

Materials and methods

The study methodology has been described previously.[1,2] Our study group consisted of patients with BMS-ISR (≥50% diameter stenosis [DS]), who were treated with seal-wing PEB (Protége) at the Department of Cardiovascular Diseases, University Hospital Ostrava in the period of 2013–2015. The control group consisted of patients with BMS-ISR treated with iopromide-coated PEB (SeQuent Please) in a previous randomized TIS study.[2]

The main exclusion criteria were: associated disease with an expected survival time <12 months or limiting the possibility of control coronary angiography and the inability to use long-term dual antiplatelet therapy.

The primary endpoint of the original study was the 12-month in-segment LLL, and the secondary endpoints were: the frequency of binary restenosis, stent thrombosis (ST), and the overall incidence of MACE after 12 months.[1]

In this study, we extended the clinical follow-up (incidence of MACE) to 3 years. The occurrence of repeated MACE was also monitored.

Prior to enrolment in the study, written Informed Consent was obtained from each patient. 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).

The PCI itself was performed under standard conditions using a radial or femoral approach, 6F guiding catheters and Axiom X-ray system (Siemens AG, Forchheim, Germany). A shorter semicompliant or scoring balloon catheter was used to predilate the lesion to prevent possible edge dissection. Subsequently, PEB was insufflated to nominal pressure for 30 seconds. For seal-wing PEB Protége (Blue Medical, Helmond, the Netherlands), paclitaxel at a concentration of 3 µg/mm^2 is applied directly to the surface of the balloon catheter between the "wings" and the hydrophilic coating before folding. This application is intended to prevent premature release of the active ingredient during insertion of the balloon catheter. Only paclitaxel, not the coating, is released into the vessel wall during balloon insufflation.[3,4] In the case of iopromide-coated PEB SeQuent Please (B. Braun AG, Melsungen, Germany), paclitaxel is bound to the surface of the balloon catheter at the same concentration using the hydrophilic contrast agent iopromide (Paccocath®), which increases its solubility and improves tissue penetration. In the case of a suboptimal angiographic result, postdilatation was performed using a non-compliant balloon catheter, and in the case of edge dissection, the implantation of another bailout stent was allowed. All patients subsequently received dual antiplatelet therapy for 6 months.

Clinical examinations were planned after 6 and 12 months and angiographic follow-up (quantitative coronary angiography [QCA]) after 12 months in the range of ±2 months.[1,2] Subsequently, patients were followed every 12 months, and after 3 years (±6 months) a final clinical examination was performed, during which all MACE were recorded. The evaluation of the events was blinded and performed by an independent researcher. Any death for which a non-cardiac cause could not be clearly ruled out was considered cardiac. Acute myocardial infarction was defined according to the 3rd universal definition of the European Society of Cardiology[5] and stent thrombosis was assessed according to criteria of the Academic Research Consortium.[6]

Statistical analysis

Continuous variables with normal distribution are reported as mean and standard deviation (SD) and were assessed using Student's t-test. Continuous variables with abnormal distribution are reported as median and 25th to 75th percentile and were assessed using Mann–Whitney U test. Categorical variables are given as number and percentage and were evaluated using χ^2 or Fisher's exact test. A p-value <0.05 is considered significant. Kaplan–Meier analysis with Log-rank test was used to analyse time-to-event data. Cox proportional hazard regression analysis was performed to assess hazard ratio with or without adjustment to significantly different input variables. IBM SPSS Statistics version 22 software was used for statistical analysis.

Results

We evaluated 3-year clinical data of 132 patients with BMS-ISR. Sixty-four of them were treated with seal-wing PEB and the control group consisted of 68 patients from iopromide-coated PEB branch of the previous TIS study. Table 1 shows the input demographic, clinical, angiographic and ISR parameters of both groups.

Three-year clinical data were obtained from all patients. The follow-up period was 1170 days (±176; median 1260) in the seal-wing PEB group and 1210 days (±167; median 1270) in the iopromide-coated PEB group (p = 0.089).

Table 2 presents the frequency of MACE after 12 months, in the interval of 13–36 months and in total after 3 years. In a 3-year clinical follow-up, the use of seal-wing PEB was associated with a significantly higher incidence of MACE (p = 0.008) and TVR (p = 0.011) compared to iopromide-coated PEB. This statistically significant difference occurred mainly in the first year of follow-up. Differences in the incidence of individual adverse events: CV deaths (p = 1.000),

Table 1 – Baseline parameters

	Seal-wing PEB	Iopromide-coated PEB	*p*
Demographic parameters			
Patients/ISR lesions, n	64/69	68/74	
Male/female	49 (76.6%) / 15 (23.4%)	43 (63.2%) / 25 (36.7%)	0.288[c]
Age, years	65.25±11.01[a]	65.6±10.9[a]	1.000[d]
Body mass index, kg/m^2	28.38±4.93[a]/21.19[b]	28.7±4.0[a]/19.23[b]	1.000[e]
Ejection fraction, %	52.31±10.01[a]/55.00[b]	49.74±11.95[a]/50.0[b]	0.732[e]
Diabetes mellitus	18 (28.1%)	17 (25.0%)	1.000[c]
Renal insufficiency	2 (3.1%)	2 (2.9%)	1.000[f]
CABG	6 (9.4%)	3 (4.4%)	1.000[f]
Ever smoked	31 (48.4%)	31 (45.6%)	1.000[f]
Previous MI	31 (48.4%)	43 (63.2%)	0.117[c]
2VD/3VD	43 (67.2%)	38 (55.9%)	1.000[c]
Multi ISR	5 (7.8%)	4 (5.9%)	1.000[f]
Baseline PCI			
ACSy (STEMI/NSTEMI)	37 (57.8%)	45 (66.2%)	0.966[c]
Stable AP	27 (42.2%)	23 (33.8%)	
Type of lesion			
B2/C	47 (68.1%)	51 (68.9%)	1.000[c]
Lesion localization			
LAD/RD	34 (49.3%)	35 (47.3%)	1.000[f]
RCx/OM	15 (21.7%)	16 (21.6%)	
RCA	18 (26.1%)	22 (29.7%)	
SVG	2 (2.9%)	1 (1.4%)	
Diameter of the previous stent, mm	3.09±0.48[a]/3.00[b]	3.18±0.43[a]/3.0[b]	0.390[e]
Length of the previous stent, mm	25.67±15.48[a]/20.00[b]	22.65±11.70[a]/19.0[b]	0.720[e]
In-stent restenosis			
ACSy, STEMI/NSTEMI	19 (29.7%)	24 (35.3%)	1.000[f]
Stable AP	42 (65.6%)	41 (60.3%)	
Other, silent ischemia	4 (6.2%)	3 (4.4%)	
Time to ISR, months	12.49±11.06[a]/7.00[b]	12.10±8.47[a]/9.0[b]	1.000[e]
Type of ISR			
I (focal; all)	25 (36.2%)	30 (40.5%)	1.000[f]
II (diffuse)	33 (47.8%)	34 (46.0%)	
III (proliferative)	6 (8.7%)	5 (6.8%)	
IV (occlusion)	5 (7.2%)	5 (6.8%)	
Periprocedural parameters			
Cutting predilatation	20 (29.0%)	16 (21.6%)	0.933[c]
ISR; PEB/EES diameter, mm	3.27±0.47[a]/3.17[b]	3.32±0.39[a]/3.5[b]	1.000[e]
ISR; PEB/EES length, mm	23.19±12.98[a]/20.00[b]	22.53±8.13[a]/20.0[b]	1.000[e]
Postdilatation, atm	13.48±2.34[a]/12.00[b]	14.84±2.77[a]/16.0[b]	**0.009**[e]
Second stent implantation	8 (11.6%)	11 (14.9%)	1.000[c]
Crossover to DES	2 (3.0%)	2 (2.7%)	1.000[c]

Qualitative data are given as n (%); quantitative data as [a] mean (± standard deviation) and [b] median; [c] chi-square test; [d] Student T-test; [e] Mann–Whitney U test; [f] Fisher's exact test.

Table 2 – Incidence of MACE within 12 months, 1 to 3 years, and for the entire follow-up period

	Seal-wing PEB	Iopromide PEB	
	n (%)	n (%)	*p*[a]
Patients, n	64	68	
0–12 months			
MACE all	17 (26.9%)	7 (10.3%)	**0.003**
CV death	0 (0%)	1 (1.5%)	1.000
MI	4 (6.3%)	1 (1.5%)	0.468
TVR	13 (20.6%)	5 (7.4%)	**0.009**
Definite ST	0 (0%)	1 (1.4 %)	1
1–3 years			
MACE all	9 (14.1%)	6 (8.8%)	0.343
CV death	3 (4.7%)	3 (4.4%)	1.000
MI	0 (0%)	2 (2.9%)	0.497
TVR	4 (6.3%)	1 (1.5%)	0.198
Definite ST	0 (0%)	1 (1.5%)	1.000
2nd MACE/TVR	3 (4.7%)	1 (1.5%)	0.354
Non CV death	6 (9.4%)	2 (2.9%)	0.156
All causes of death	9 (14.1%)	5 (7.4%)	0.264
0–3 years			
MACE all	26 (40.6%)	13 (19.1%)	**0.008**
CV death	3 (4.7%)	4 (5.9%)	1.000
MI	4 (6.3%)	3 (4.4%)	0.712
TVR	17 (26.9%)	6 (8.8%)	**0.011**
Definite ST	0 (0%)	2 (2.9%)	0.497
2nd MACE/TVR	3 (4.7%)	1 (1.5%)	0.354
Non CV death	6 (9.4%)	2 (2.9%)	0.156
All causes of death	9 (14.1%)	6 (8.8%)	0.416
Event-free survivals	43 (67.2%)	57 (83.2%)	**0.026**

[a] Fisher's exact test.

MI (p = 0.712), definite ST (p = 0.497) or repeated MACE (p = 0.354) were not significant between the two groups.

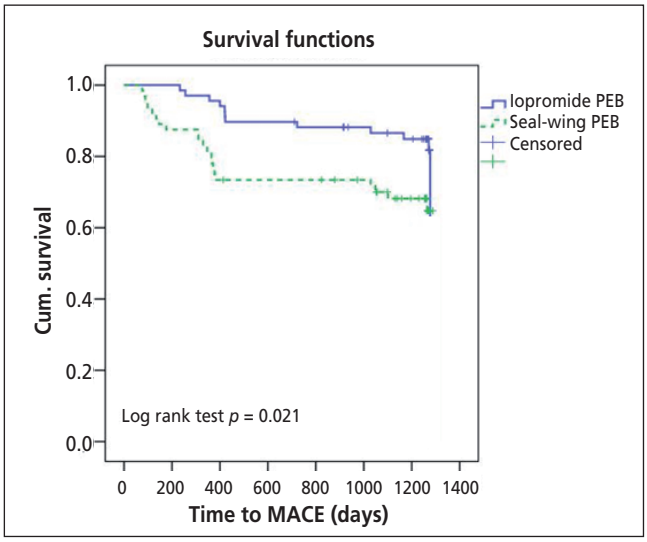

Fig. 1 – Event-free survival – time to MACE.

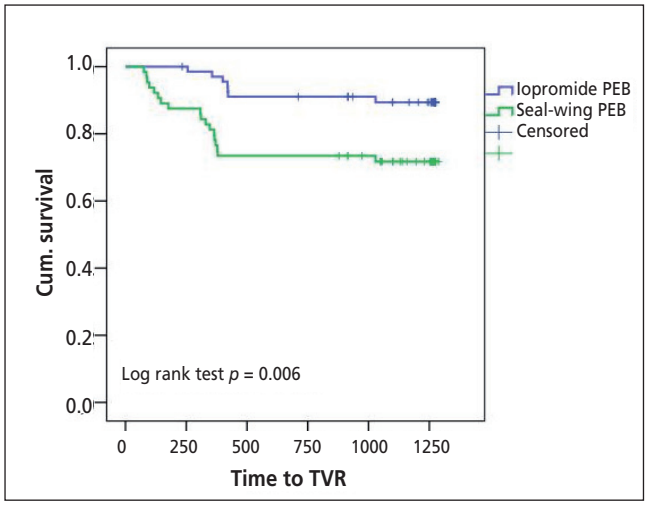

Fig. 2 – Event-free survival – time to TVR.

Figures 1 and 2 show the estimated times of event-free survivals (EFS). EFS (time to MACE and time to TVR) in the group of iopromide-coated PEB were significantly longer compared to seal-wing PEB.

Table 3 – Cox regression analysis

		Unadjusted estimates				Adjusted estimates			
				95% CI for HR				95% CI for HR	
Event	Predictor	Sig.	HR	Lower	Upper	Sig.	HR	Lower	Upper
MACE	Group (1 = Seal-wing PEB)	**0.025**	**2.265**	1.111	4.619	**0.026**	**2.325**	1.107	4.881
CV death	Group (1 = Seal-wing PEB)	0.981	0.982	0.215	4.477	0.848	0.856	0.174	4.209
Acute MI	Group (1 = Seal-wing PEB)	0.367	2.184	0.400	11.93	0.287	2.648	0.441	15.894
TVR	Group (1 = Seal-wing PEB)	**0.010**	**3.162**	1.320	7.573	**0.009**	**3.387**	1.363	8.420
All causes of death	Group (1 = Seal-wing PEB)	0.198	1.987	0.698	5.653	0.202	2.034	0.683	6.059
Definite ST	Group (1 = Seal-wing PEB)	0.475	0.016	0	1383	–	–	–	–
2nd MACE	Group (1 = Seal-wing PEB)	0.164	5.078	0.514	50.16	0.204	4.5781	0.439	47.84

Cox proportional hazards regression analysis proved a significantly higher risk of MACE (including TVR) in patients treated with seal-wing PEB, even after correction for different input parameters (e.g. postdilatation) (Table 3).

Discussion

In clinical practice, paclitaxel is used as an effective antiproliferative agent in DEB, which is highly lipophilic and rapidly penetrates tissues, most often at a concentration of 3 μg/mm^2,[7] as was the case with both PEB evaluated by us. The main factor that affects the effectiveness of PEB is the way it binds to the surface of the balloon catheter. In the original concept of the team of Scheller et al., paclitaxel was bound via the hydrophilic contrast agent iopromide, which increased its solubility and permeability (Paccocath®).[7]

In preclinical studies, iopromide-coated PEB showed a significant reduction in LLL (p = 0.001) compared to uncoated-PEB, as well as a significant reduction in maximal thickening and area of neointimal hyperplasia (p = 0.002 and <0.001).[8]

Subanalysis of the SCAAR registry showed that iopromide-coated PEB (paclitaxel 3 μg/mm^2) is associated with a significantly lower risk of recurrent binary ISR in the treatment of ISR (adjusted HR = 0.48; 95% CI 0.23–0.98) compared to uncoated PEB (paclitaxel 2 μg/mm^2).[9]

A number of studies have demonstrated the efficacy of PEB in the treatment of BMS-ISR at 9–12 months of follow-up. Their long-term results are now available. In Paccocath I and II studies, PEBs showed significantly lower 6-month LLL (p = 0.002), frequency of recurrent binary restenosis (p = 0.002) and 12-month MACE (p = 0.01) when compared to POBA.[10] The difference in the incidence of MACE persisted even after 5 years (p = 0.009), mainly due to a decrease in the need for TVR from 38.9% to 9.3% (p = 0.004).[11]

In the PEPCAD II study, treatment of BMS-ISR with PEB resulted in significantly lower LLL after 6 months (p = 0.03), with a trend towards a reduced incidence of binary restenosis (p = 0.06) and MACE (p = 0.08) after 12 months compared to paclitaxel-eluting stents.[12] However, even in the next 3-year clinical follow-up, the differences in the incidence of MACE (p = 0.14) and TVR (p = 0.10) did not reach statistical significance.[13]

Several studies have compared PEBs with different coatings. Nijhoff et al. achieved significantly better angiographic (lower LLL: p = 0.014) functional (higher value of fractional flow reserve distally: p = 0.029) and OCT (lower percentage volume of intimal hyperplasia: p = 0.006) results with urea-coated PEB compared to shellac-coated PEB in BMS or DES-ISR, however, clinically there was only a trend towards lower target lesion revascularization (TLR; p = 0.057).[14]

In a RESTORE ISR China study comparing shellac-ammonium and iopromide-coated PEB in predominantly DES-ISR therapy (98%), this new type of PEB demonstrated the non-inferiority of 9-month LLL compared to iopromide-coated PEB (p_{NI} = 0.02). No differences were found in the frequency of 12-month target vessel failure (TVF; cardiac death, target vessel MI or TLR; p = 0.87).[15]

Also in the AGENT-ISR study, PEB with acetyl-tributyl citrate and lower paclitaxel (2 μg/mm^2) concentrations achieved non-inferior 6-month angiographic results (LLL: p_{NI} = 0.046) compared to iopromide-coated PEB (3 μg/mm^2). No significant differences were observed in the 12-month clinical follow-up or in this study (TLR: p = 0.89 and TLF: p >0.99).[16]

Our results confirm that iopromide coating affects the effectiveness of PEB in the treatment of ISR. In a previous study, we demonstrated that the use of seal-wing PEB in the treatment of BMS-ISR leads to a significantly higher 12-month LLL (p <0.0001), the incidence of recurrent binary restenosis (p = 0.012), MACE (p = 0.003) and TVR (p = 0.009) compared to iopromide-coated PEB.[1] The difference in the overall incidence of MACE was mainly due to a significantly higher need for TVR in the seal-wing PEB group due to a higher incidence of recurrent binary restenosis. In the other individual adverse events, such as CV mortality, MI, definite ST, or recurrent MACE, the two groups did not differ. Differences in the incidence of MACE and TVR, which appeared mainly during the first year, persisted in the 3-year follow-up. The use of seal-wing PEB in the treatment of BMS-ISR was associated with a higher risk of MACE (including TVR) even after correlation to some different baseline parameters in both groups.

Limitation

Our study has several limitations. First of all, it is a non-randomized study comparing the study group with the control group consisting of patients from the iopromide-coated PEB branch of the previous TIS study. However, the two groups did not differ in the main risk factors, so the selection bias should not play a significant role. Also, the duration and manner of clinical follow-up and other pharmacotherapy, including the duration of dual anti-platelet therapy, were the same in both groups.

Conclusion

Treatment of BMS-ISR with seal-wing PEB results in a significantly higher incidence of TVR and pooled MACE compared to iopromide-coated PEB in a 3-year clinical follow-up.

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