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原　著

Effect of Predilatation Methods on Drug Coated Balloon Treatment in In-Stent Restenosis Lesions

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【Abstract】

Background: Even in the modern drug eluting stent (DES) era, in stent restenosis (ISR) is still the problem and existing treatment options are debatable. Among these, treatment with drug coated balloon (DCB) can be promising on long term outcomes. However the predilatation methods before DCB are controversial.

Objective: The aim of this study is to evaluate whether the methods of predilatation (lesion preparation) before DCB treatment can affect the outcomes in ISR cases.

Methods: Between 2014-2017, 101 patients were treated with DCB for ISR cases. Among these, 66 patients (65.3%) were followed up for CAG (coronary angiography) assessment. These patients were divided into two groups; scoring balloon group (n = 40) and non-scoring balloon group (n= 26). Primary endpoint was the target lesion revascularization (TLR) at follow up. We also compared QCA (quantitative coronary angiography) assessment for every procedure: before the procedure, after the procedure and during follow up. Then these QCA parameters were compared thoroughly between two groups.

Results: Total seventeen cases (25.8%) were found to have TLR. These TLR rates were 20.0% in Scoring balloon group and 34.6% in Non-scoring balloon group (p value = 0.18). In QCA analysis after the procedure and during follow up, minimal lumen diameter was higher, % diameter stenosis and % area stenosis were significantly lower in scoring balloon group than non-scoring balloon group. For the specific predilatation groups, TLR rates were 16.1% in cutting balloon group, 33.3% in non-slip element (NSE) balloon group and 45.0% in non-compliant (NC) balloon group respectively. In our subgroup analysis, TLR rates were 34.4% in hemodialysis patients and 17.6% in non-hemodialysis patients (p value = 0.03). RCA (right coronary artery) proximal segment had the highest TLR rate (53.8 %) compared with the other groups - RCA mid to distal, LCX (left circumflex) and LAD (left anterior descending) with 25.0%, 8.3% and 17.6% respectively (p value = 0.009).

Conclusions: Regarding the predilatation methods before DCB treatment in ISR cases, scoring balloon especially cutting balloon is more superior to the non-scoring balloon in terms of TLR and QCA assessment.

Key words：In stent restenosis, Drug coated balloon, Lesion preparation, Predilatation methods, Cutting balloon angioplasty

Abbreviations：

CABG：Coronary artery bypass graft
CAG：Coronary angiography
CBA：Cutting balloon angioplasty
CVD：Cardiovascular diseases
DCB：Drug coated balloon
DES：Drug eluting stent
IHDF：Intermittent haemodiafiltration
ISR：In stent restenosis
IVUS：Intravascular ultrasound
LAD：Left anterior descending
LCX：Left circumflex
LLL：Late lumen loss
MLD：Minimal lumen diameter
NC：Non-complaint
NSE：Non-slip element
PCI：Percutaneous coronary intervention
QCA：Quantitative coronary angiography
RCA：Right coronary artery
TLR：Target lesion revascularization

【Background】

The development of stent is the turning point for the field of percutaneous coronary intervention (PCI). The progressive improvement of the modern DES makes good clinical outcomes for the patients. But the penetration of DES is quite variable and patients with DES may also suffer from in-stent restenosis[1]. Revisiting to the historical background, in-stent restenosis were treated with conventional balloon angioplasty, stent in stent technique, brachytherapy, debulking devices (rotational arthrectomy, excimer laser coronary arthrectomy and directional coronary arthrectomy), cutting balloon angioplasty and DCB[1]. Among these treatments in ISR cases, DCB treatment is the most outstanding and guidelines also recommended to use in that situation[2]. Currently available DCB delivers Paclitaxel to the vessel wall during balloon inflation, where the lipophilic nature of Paclitaxel enable it to partitions into the vessel walls, upon which it exerts its anti-restenotic effect[3]. However we have no data regarding the predilatation methods before DCB treatment.

【Methods】

We retrospectively analyzed 101 cases, in which DCB treatments were used for ISR from 2014 to 2017. Out of these cases, 66 patients (study patient populations) were followed up for CAG (follow up rate was 65.3%). The average follow up period was 9.7 ± 5.8 months. All of these DCB treated cases were divided into two groups by predilatation methods: scoring balloon group (NSE balloon and cutting balloon, n = 40) and non-scoring balloon group (direct DCB, NC balloon and semi-compliance balloon, n = 26). During follow up, if the % stenosis was more than 75%, these cases were retreated as ISR cases. No special exclusion criteria were applied for this study. According to our usual standard procedure, informed consent was signed by the patient and one responsible family member.

Procedure: Interventional procedures were performed according to the usual standard of our catheterization laboratory either from femoral or radial approach. All patients were receiving dual antiplatelet therapy with aspirin and clopidogrel or prasugrel and other usual treatments for coronary artery disease. There was one case of Acute Coronary Syndrome in this study who was treated with DCB. In every PCI case, an intravenous unfractionated heparin 10000 units was used as soon as after the arterial puncture and sheath insertion. In some cases of Heparin Induced Thrombocytopenia (known during the previous procedure), we used Argatroban (direct thrombin inhibitors). In all cases, the anticoagulant (either heparin or Argatroban) dose was controlled according to the activated clotting time between 250 and 350 seconds. In renal impairment cases (without under regular haemodialysis), we used the intermittent haemodiafiltration (IHDF) method during the procedure as previously reported[4]. In every case, in which we decided to treat with DCB, predilatation methods (direct DCB, NC balloon, Scoring balloon and Cutting balloon) were decided by the operator's decision. Intravascular ultrasound (IVUS) was performed for every procedure of PCI cases. In follow up CAG checkup, we used IVUS only in TLR cases.

The DCB that we used in every procedure was SeQuent Please (NIPRO). This is a second generation DCB and has more efficient delivery of paclitaxel to the vessel wall, which results in a longer persistence of the drug. It has the concentration of paclitaxel of 3.0 $\mu g/mm^2$ on the balloon surface. After the lesion modification, if there was no significant dissection which was approved by IVUS, we used the DCB. Inflation time was variable from 30 seconds to 90 seconds. In every PCI procedure, after DCB treatment we checked IVUS again.

Angiographic analysis: Quantitative coronary angiography (QCA) was performed for every PCI case before and after the procedure and also during follow up (both CAG and PCI cases). We measured percent (%) area stenosis, percent (%) diameter stenosis, minimal lumen

diameter (MLD) and lesion length for every procedure. The calcification and tortuosity of the vessels were also classified angiographically.

Definition: Restenosis was defined as more than 75% stenosis of the luminal diameter compared to the reference vessels. In-stent restenosis was defined as the restenosis in stent (focal or diffuse) and stent edge restenosis (in segment restenosis). Lesion length was defined as the distance from proximal edge of the lesion to the distal shoulder edge of the lesion.

Statistical analysis: Continuous variables were mentioned as mean ± standard deviation and categorical variables were expressed as numbers with percentage. Continuous variables were compared using the paired Student's t-test. Categorical variables were compared using the chi-square test. Regarding the p value, < 0.05 was considered significant.

【Results】

Patient characteristics are shown in Table (1). Average age distribution of the study population was 70.5 years. Regarding the cardiovascular risk factors, hypertension was common; 89.4 % of the study population. The prevalence of other risk factors, dyslipidemia and diabetes mellitus, were also very high; 75.8% and 69.7% respectively. Smoking was 31.8%, family history of CVD was 16.7% and previous history of CABG was found in 4.5% of the population. Chronic kidney disease under routine haemodialysis patient population, was also high in this study and it was 48.5%. Haemodialysis population was higher in non-scoring balloon group in this study. It was because of the higher calcification burden in these patients and scoring balloons were slightly difficult to use due to its low crossing profile. The other patient characteristics between scoring and non-scoring groups were not significantly different.

The total involvement of the coronary vessels were LAD 24.2%, LCX 18.1%, RCA proximal 19.6% and RCA mid to distal 36.3% and no significant difference between 2 groups. In this study, one case was the SVG graft ISR. Regarding the lesion characteristics, scoring balloon group and non-scoring balloon group were not different significantly. In procedural characteristics, the balloon length used in scoring balloon group was shorter than non-

Table (1). Patient characteristics of the study

Patient Characteristics	All ISR cases (n = 66)	Scoring balloon group (n = 40)	Non-scoring balloon group (n = 26)	p value
Male	84.8 %	90.0 %	76.9 %	0.15
Age	70.5 ± 11.0	71.1 ± 10.7	69.6 ± 11.2	0.56
Hypertension	89.4 %	85.0 %	96.1 %	0.15
Dyslipidaemia	75.8 %	75.0 %	76.9 %	0.86
Diabetes Mellitus	69.7 %	67.5 %	73.0 %	0.63
Haemodialysis	48.5 %	32.5 %	73.0 %	0.001
Smoking	31.8 %	45.0 %	11.5 %	0.004
Family History	16.7 %	12.5 %	23.0 %	0.26
Prior CABG	4.5 %	2.5 %	7.6 %	0.32
ACS	1.5 %	2.5 %	0 %	0.42

scoring balloon group (10.7 ± 1.3 v.s 14.5 ± 5.7, p =0.003). It was because scoring balloons we used were Flextome and NSE, their maximal length was only up to 13 mm. There was no difference between DCB size, length, inflation pressure and inflation duration between 2 groups (Table 2). Before we retreated the ISR lesions with DCB, we decided the predilatation methods – non-scoring or scoring balloon.

【Clinical outcomes】

Out of these 66 ISR cases with DCB treatment 17 cases had TLR during follow up (5 cases for CBA, 3 cases for NSE balloon and 9 cases for NC balloon). TLR rate in scoring balloon was 20.0% and non-scoring balloon was 34.6 % (p value = 0.18) (Table 3). For specific predilatation sub-groups, TLR rate in cutting balloon group was significantly lower than NC balloon (16.1% v.s 45.0%, p value = 0.02). There was no TLR rate in cases in which direct DCB (n = 2) and semi-compliance balloon (n = 4) were used, but these sub-groups were only small numbers in the study. Concerning about the clinical outcomes in terms of TLR, predilatation methods by using cutting balloon had significantly better than NC balloon group in DCB treatment. (Figure 1).

Another finding with this study was that TLR rates in haemodialysis group and non-haemodialysis group were 34.4% and 17.6% respectively and it was statistically

Table (2). Coronary artery involvement, lesion and procedural characteristics of the study

		Scoring balloon	Non-scoring balloon	p value
Coronary Artery Involvement				
LAD	16 (24.2 %)	10 (25.0 %)	6 (23.1 %)	0.85
LCX	12 (18.1 %)	7 (17.5 %)	5 (19.2 %)	0.85
RCA proximal	13 (19.6 %)	7 (17.5%)	6 (23.1 %)	0.57
RCA mid to distal	24 (36.3 %)	15 (37.5 %)	9 (34.6 %)	0.81
SVG	1 (1.5 %)	1 (2.5 %)	0 (0%)	0.41
Lesion Characteristics				
Lesion Length (mm)		10.6 ± 5.0	11.9 ± 5.6	0.36
Reference Vessel Diameter (mm)		3.3 ± 0.6	3.3 ± 0.8	0.97
% Diameter Stenosis		72.2 ± 19.3	79.4 ± 21.8	0.18
	Mild	47.5%	38.5%	0.47
Calcification	Moderate	15.0%	30.8%	0.13
	Severe	12.5%	19.2%	0.46
Tortuosity		7.5%	23.1%	0.07
Procedural Characteristics				
Predilatation Balloon Size (mm)		2.9 ± 0.5	2.6 ± 0.7	0.06
Predilatation Balloon Length (mm)		10.7 ± 1.3	14.5 ± 5.7	0.003
DCB Size (mm)		3.2 ± 0.6	3.1 ± 0.6	0.65
DCB Length (mm)		20.1 ± 4.4	22.0 ± 5.4	0.15
DCB Inflation Pressure (atm)		13.2 ± 3.1	13.8 ± 3.4	0.44
DCB Inflation Duration (seconds)		51.3 ± 14.3	52.3 ± 10.2	0.73

significant (p value = 0.03). The underlying pathological mechanism of calciphylaxis in chronic kidney disease make heavily calcified lesion in coronary arteries and these patients had higher chance of restenosis in comparison with the other patients although the interventional procedures were relatively same. So we sub-analyzed the predilatation methods in haemodialysis patient (n = 32) between scoring and non-scoring balloon groups. Although the TLR rate was higher in non-scoring balloon group (42.1% in non-scoring and 30.8% in scoring group), it was statistically non-significant. It might be due to small number of population in the study.

Table (3). TLR rates of scoring balloon and non-scoring balloon group

TLR rate	Scoring balloon	Non-scoring balloon	P value
	20.0 %	34.6 %	0.18

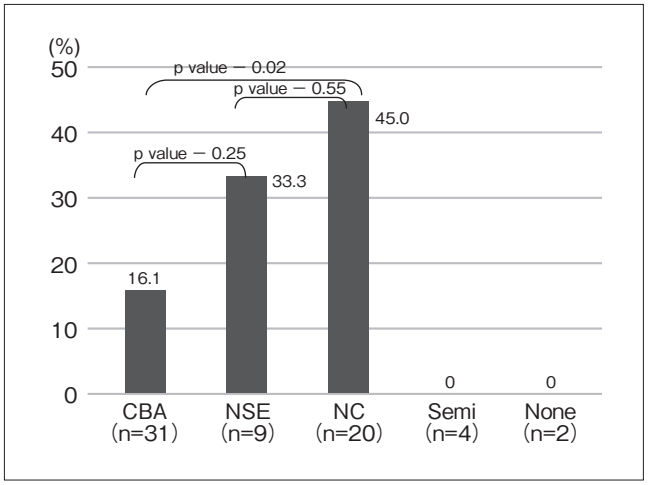

Figure (1). TLR rates of specific predilatation groups

Angiographic results: QCA was performed totally 3 times for every procedure – before and immediately after the procedure and at follow up (Figure 2 - 4). Although there were no significant differences in baseline and post procedure between 2 groups, the % diameter stenosis, % area stenosis were significantly reduced (30.2 ± 25.5 % v.s 47.1 ± 30.8 %, p value = 0.02; 44.8 ± 26.2 % v.s 63.1 ± 27.5 %, p value = 0.01) and minimal lumen diameter was significantly higher (2.3 ± 1.0 v.s 1.8 ± 1.2, p value < 0.05) in scoring balloon group compared with the non-scoring balloon group at follow up. There was no difference in acute gain (2.0 ± 0.8 mm v.s 1.9 ± 0.7 mm, p value = 0.59) and late lumen loss (0.7 ± 0.8 mm v.s 0.9 ± 1.0 mm, p value = 0.22) between scoring balloon group and non-scoring balloon group.

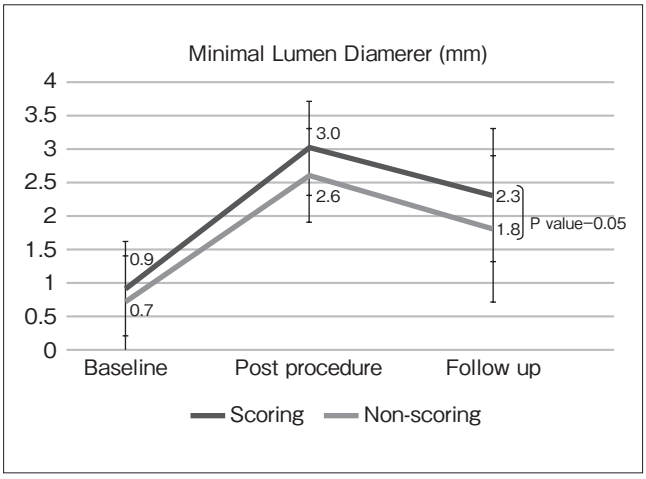

Figure (2). Comparison of the minimal lumen diameter between scoring balloon group and non-scoring balloon group

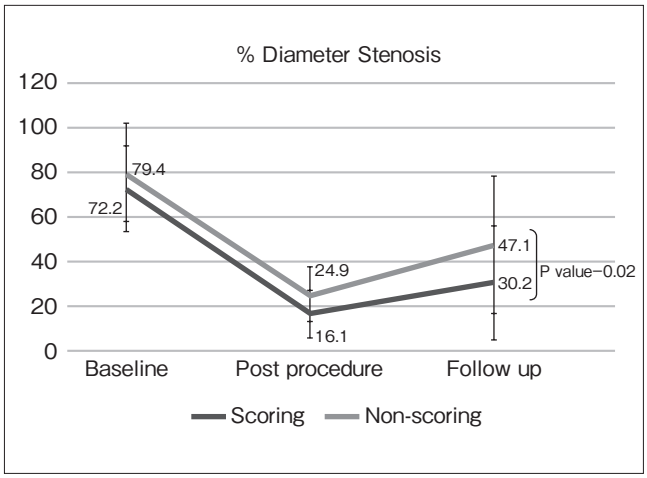

Figure (3). Comparison of the % diameter stenosis between scoring balloon group and non-scoring balloon group

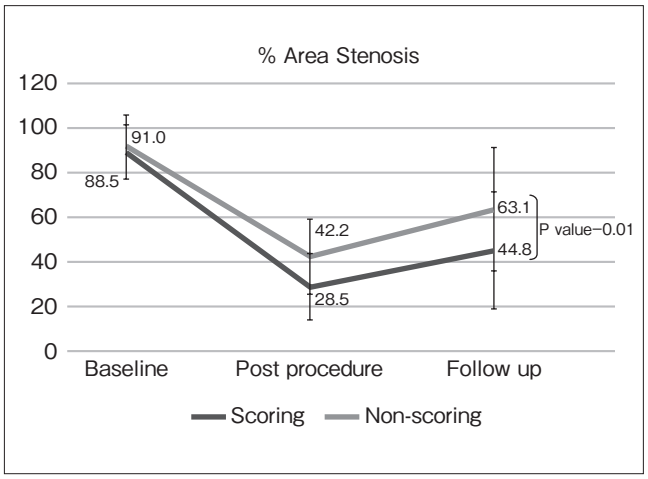

Figure (4). Comparison of the % area stenosis between scoring balloon group and non-scoring balloon group

Another important point from this study was the anatomical site of ISR. In our study of 66 ISR patients, one case was the vein graft ISR and the other 65 cases were native coronary ISR cases. By comparison of the QCA measurement, % diameter stenosis, % area stenosis, MLD and acute gain were not relatively different between segment 1(RCA proximal) and other segments of coronary arteries, but late lumen loss was more in segment 1 than other segments (1.3 ± 1.1 mm v.s 0.6 ± 0.8 mm, p value = 0.05). During the follow up period, the TLR rate in segment 1 (53.8%) was the highest, compared with the other segments (segment 2-4 was 25.0%, segment 5-10 was 17.6%, and segment 11-15 was 8.3%) and it was also statistically significant (p value – 0.009). While reanalysis of the segment 1 TLR cases, the comparison between the cutting balloon and NC balloon as predilatation methods were 42.9% and 80.1% respectively (p value = 0.19. TLR) rates seemed to be lower in cutting balloon group than in NC balloon group.

【Discussion】

In our single center retrospective study, we compared the different predilatation methods (lesion preparation) before DCB treatment in ISR cases. By using the scoring balloon for lesion preparation, QCA measurements (% diameter stenosis, % area stenosis, MLD) had better results than the non-scoring balloon and statistically significant. Furthermore, with the cutting balloon for predilatation before DCB, we were able to have the better clinical outcomes by reducing TLR rates although the expenses were approximately same as the other lesion preparation methods. Before the development of DCB, such ISR cases were treated with another stent implantation (stent in stent), but the two metallic layer of the stents make the further chances of restenosis and thrombosis higher. With the progressive development of DCB, we can have the stent like treatment without new metallic layer with good clinical outcome and also has the benefit for shorter duration of the dual antiplatelet therapy. But most of the ISR cases have many cardiovascular risk factors and their coronary arterial walls have high burden of calcification. To get the uniform delivery of the drug over the vessel wall, we must perform the plaque modification effectively. When treating in-stent restenosis with balloon angioplasty, luminal gain is achieved by a combination of additional stent expansion and neointimal tissue compression through the stent. Although satisfactory initial clinical and angiographic results were obtained with balloon angioplasty, a significant early late lumen loss was also observed shortly after in stent restenosis treatment due to recoil and re-intrusion of neointimal tissue in the lumen[6]. Cutting balloon has 3 or 4 longitudinal blades alongside the balloon and it makes the longitudinal focused force to effectively modify the atherosclerotic plaque. Cutting balloon present several advantages for the treatment of severe calcified lesions, allowing a larger luminal gain at lower pressure compared to balloon angioplasty alone and preventing late recoil due to the incisions created by the blades[7) 8)]. Furthermore cutting balloon anchors the lesion during inflation and reduce the risks of displacements and dissections at the stent margins[1)]. Scoring balloon also has the spiral shape blade over the balloon but the height of

the blade is shorter and the breaking power of the plaque is lower than the cutting balloon with similar crossing profile. NC balloons have the better crossing profile than the others but its plaque modification effect will be lower.
Although the study population in this study was small, the effectiveness of cutting balloon treatment prior to DCB was disclosed, may be due to such specific mechanism of cutting balloon angioplasty.

【Conclusions】

Although the treatments for in-stent restenosis are still challenging for the interventionists, drug coated balloon has the promising effect and also has the class IA recommendation in European Society of Cardiology guideline[2)] . Before the DCB treatment, lesion preparation by cutting balloon angioplasty has the satisfactory clinical and angiographic results in comparison with the other lesion preparation methods like NSE balloon and NC balloon.

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