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Angiographic, optical coherence tomography and histology findings from combination of a drug-coated balloon with an everolimus-eluting stent in a porcine model☆

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ABSTRACT

Background: We designed a porcine model to compare the angiographic, optical coherence tomography (OCT) and histological findings of implanting an everolimus-eluting stent (EES) in the same segment of the coronary artery pre-treated with a drug-coating balloon (DCB; paccocath as carrier) with EES alone and DCB plus a bare metal stent (BMS).

Methods: Seven female swine averaging 46.0 ± 2.4 kg were treated by random assignment as follows: DCB followed by EES; DCB followed by BMS; and EES alone. Quantitative coronary angiography (QCA) and OCT were carried out post-implantation and repeated after 28 ± 1 days.

Results: All arteries remained patent and demonstrated no sign of thrombus formation. There was no significant difference at 1 month between the treatment groups in lumen loss (0.64 ± 0.43, 0.44 ± 0.43 and 0.33 ± 0.28 mm for EES, DCB/EES and DCB/BMS respectively, p = 0.37) and binary restenosis (6.86 (2.91–9.12), 4.93 (−1.53–10.7) and 4.18 (3.27–10.2)% respectively, p = 0.87). OCT found mean neointimal thickness of 0.15 ± 0.09, 0.07 ± 0.03 and 0.08 ± 0.03 mm (p = 0.05) for EES, DCB/EES and DCB/BMS respectively. Endothelial strut coverage was 92.3 ± 5.5, 85.4 ± 8.6 and 89.1 ± 8.9% (p = 0.05) and mean neointimal area was 1.06 ± 0.42, 0.95 ± 0.24 and 1.20 ± 0.28 mm^2 (p = 0.09) respectively. Inflammation score was similar between the three groups: 0.20 (0.20–0.28), 0.30 (0.22–0.48), 0.30 (0.20–0.38) for EES, DCB/EES and DCB/BMS respectively (p = 0.14) and there were no differences in fibrin deposition.

Conclusions: The combination of DCB with EES appeared to be safe and effective. Using EES to bail out suboptimal DCB therapy appeared to be safe and effective in this porcine model.

1. Introduction

There is growing interest in the use of drug-coated balloon (DCB)-only angioplasty in de novo coronary lesions. DCB allows rapid and uniform antiproliferative drug transfer to the arterial wall, achieving inhibition of neointimal hyperplasia without implantation of a drug-eluting stent (DES) and thereby potentially avoiding the deleterious effect of stents on long-term vascular healing. In support of this concept, current evidence shows that a DCB-only strategy yields better late lumen loss compared to DES [1]. Unfortunately, the fragility of coronary vessels remains an important challenge as stent bailout due to dissection may be as high as 28% following DCB, whilst complex disease (e.g. bifurcations) or vessel recoil may also mandate stent implantation to maintain vessel patency or architecture [2].

Should a stent be required immediately following the use of a DCB, current expert consensus is to use a bare metal stent (BMS) [3]. This is to avoid combination of paclitaxel (DCB) with a limus agent (DES), the effects of which on coronary vasculature are largely unknown. However, this strategy may be questionable given the well-demonstrated superior efficacy of DES-containing limus analogues compared to paclitaxel-coated DES. We therefore sought to evaluate the safety and performance of EES following pre-treatment with a paclitaxel-based DCB compared to both isolated EES and to a Paccocath-based DCB plus BMS in a porcine model.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have approved the final article.

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2. Methods

2.1. Study design

Seven female swine were studied using quantitative coronary angiography (QCA), optical coherence tomography (OCT) and histology to assess the presence of microthrombus, neointimal hyperplasia, endothelial coverage, and inflammation.

2.2. Subject preparation

Clopidogrel (75 mg, PO, s.i.d) was administered daily for 3 ± 1 days prior to the index procedure and continued throughout the study. Analgesia (tramadol, 2–4 mg/kg, IM) and antibiotics (enrofloxacin, 5 mg/kg, IM) were administered to the animal prior to induction. Anaesthesia was maintained using 1–3% isoflurane. A 6 Fr vascular sheath was placed in the right femoral artery and immediately a single bolus of heparin (80–120 IU/kg body weight) was administered intra-arterially. Electrocardiogram and blood pressure were continuously monitored during the procedure.

2.3. Coronary angiography

After administration of 100 mcg IC nitroglycerine, coronary angiography was performed in orthogonal planes using an Innova 520 digital imaging system (GE Medical System, Buc Cedex, France) and QCA analysis performed using CAAS version 7.2 (Pie Medical Imaging B.V., Maastricht, The Netherlands) to determine the baseline mean vessel diameters of each coronary artery for test article deployment. Mid-arterial segments, without major side branches of all three coronary arteries (RCA, LAD, LCX), and with appropriate diameters to permit a 110% overstretch, were identified.

2.4. Percutaneous coronary intervention procedure

Individual coronary arteries were treated by random assignment as follows: DCB followed by EES; DCB followed by BMS; and EES alone. Test articles were SeQuent® Please 3 × 15 mm DCB (BBraun, Melsungen, Germany), Xience Pro 3 × 8 mm EES (Abbott Vascular, Illinois, USA) and Coroflex Blue Neo 3 × 8 mm BMS (BBraun, Melsungen, Germany). All devices were inflated to nominal pressure, maintained for 30 s. Immediately following device deployment, additional 100 mcg IC nitroglycerine was administered, QCA repeated and OCT assessment performed using a Dragonfly catheter, C7 system (St. Jude Medical, St. Paul, Minnesota).

2.5. OCT analysis

OCT image analysis was performed using a dedicated off-line review system with semi-automated contour-detection software (St. Jude Medical). All cross-sectional images within the stent segment were initially screened for quality assessment. Frames with inadequate definition were excluded from analysis. Qualitative OCT analysis was performed at 1 mm intervals detect intra-stent thrombus and neoatherosclerosis. Neointimal coverage was assessed on each individual strut and where observed, thickness was measured from the lumen border to the center of the strut blooming.

2.6. Follow-up assessment

At 28 days, coronary angiography, QCA and OCT assessment were repeated in the same manner as before. The swine were subsequently sacrificed using intravenous pentobarbitol. Coronary arteries were harvested for pathological and histological analysis.

2.7. Histological analysis

Treated segments of the coronary arteries were fixed in 10% formalin, dehydrated in a graded series of ethanol and embedded in methylmethacrylate plastic. After polymerization, approximately 200-micrometer sections were sliced from the proximal, mid and distal portions of each treated artery. Sections were stained with methylene blue and eosin and examined by light microscopy to assess fibrin presence, inflammation extent, percentage stenosis and stent endothelialization. Inflammation was quantified using an established system: 0 = no lymphocytes on strut surface, 1 = light lymphohistiocytic infiltrate on strut surface, 2 = moderate, localized aggregate of histiocytes/lymphocytes on strut surface, and 3 = mixed lympho-histiocytic cell infiltrates surrounding the struts [4].

2.8. Ethical considerations

The study was approved by the local ethics committee for animal research. All procedures were conducted according to the Singapore laws for animal care [5].

2.9. Statistical analysis

Following a test of statistical normality (Kolmogorov–Smirnov test), data is expressed as mean with standard deviation (mean ± SD) or as median with inter-quartile range (IQR) for the normally distributed data and non-parametrically distributed data respectively. Comparisons between groups were analysed by two-way repeated ANOVA or Kruskal–Wallis test, as appropriate. A value of $p < 0.05$ was considered statistically significant. All statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 17.0 for Windows (SPSS Inc. (IBM) Chicago, IL, USA).

3. Results

The swine had a mean weight of 46.0 ± 2.4 kg. Baseline coronary angiography and QCA identified appropriate segments of each coronary artery for study. Treatment articles were randomly assigned to each coronary artery. The reference vessel diameter was 2.65 ± 0.27, 2.90 ± 0.24 and 2.89 ± 0.10 mm ($p = 0.06$) for EES, DCB/EES and DCB/BMS (Table 1) respectively. In all cases a >110% overstretch was achieved following balloon and stent inflation.

Follow-up coronary angiography was performed at a mean 28 ± 1 days. All arteries remained widely patent with TIMI (thrombolysis in myocardial infarction) grade III flow. None of the treated arteries exhibited evidence of thrombus on either angiography or OCT. Following QCA analysis, there were no significant inter-group differences in reference vessel diameter or minimal luminal diameter (Table 1). Lumen loss was similar between the three treatment groups (0.64 ± 0.43, 0.44 ± 0.43 and 0.33 ± 0.28 mm for EES, DCB/EES and DCB/BMS respectively, $p = 0.37$). Similarly there was no difference in binary restenosis (6.86 (2.91–9.12), 4.93 (−1.53–10.7) and 4.18 (3.27–10.2)% for EES, DCB/EES and DCB/BMS respectively, $p = 0.87$).

OCT analysis recorded mean neointimal thickness of 0.15 ± 0.09, 0.07 ± 0.03 and 0.08 ± 0.03 mm ($p = 0.05$), and mean neointimal volume 10.8 ± 7.5, 4.1 ± 1.7 and 5.4 ± 2.8 mm^3 ($p = 0.04$) for EES, DCB/EES and DCB/BMS respectively. Endothelial strut coverage was 98.5 ± 4.0, 95.3 ± 5.2 and 91.8 ± 9.2% respectively ($p = 0.19$). The mean endothelial area was 1.58 ± 0.83, 0.95 ± 0.19 and 0.97 ± 0.23 mm^2 for EES, DCB/EES and DCB/BMS respectively ($p = 0.06$).

Mean neointimal area on histology was 1.06 ± 0.42, 0.95 ± 0.24 and 1.20 ± 0.28 mm^2 ($p = 0.09$) for EES, DCB/EES and DCB/BMS respectively (Table 2; Fig. 1). Endothelial strut coverage was 92.3 ± 5.5, 85.4 ± 8.6 and 89.1 ± 8.9% ($p = 0.05$). Median inflammation scores were 0.20 (0.20–0.28), 0.30 (0.22–0.48) and 0.30 (0.20–0.38) ($p = 0.22$) respectively. There were no significant differences in fibrin deposition. No neointimal macrophages or lipids were seen in any samples.

4. Discussion

We believe that this is the first study which has systematically examined the effect of using an EES after DCB in an established and validated porcine pre-clinical model [6]. At 28 days, the DCB/EES combination showed good neointimal suppression and endothelial strut coverage as evidenced by angiography and OCT. Histologically, no neointimal macrophages were observed and no thrombus was detected in any of the stents, whilst inflammation scores were similar in all three treatment groups. Importantly the EES/DCB combination did not seem to excessively suppress neo-endothelialization.

The era of balloon-only angioplasty in the early 1980s was marred by high rates of elastic recoil and abrupt vessel closure mandating emergency coronary artery bypass and re-intervention respectively. The introduction of (bare metal) stents improved the safety of percutaneous coronary intervention (PCI) procedures, although it was clear from the outset that these devices generated significant localized inflammation resulting in dramatic neo-intimal hyperplasia and restenosis. DES, introduced in 2001 dramatically reduced the occurrence of neo-intimal hyperplasia allowing PCI to evolve into both a safe and efficacious procedure. Progressive improvements in DES technology have allowed operators to undertake PCI in challenging anatomy, such that PCI has become the primary mode of coronary revascularization.

However, despite marked progress in DES technology, fundamental limitations include variable occurrence of restenosis (especially amongst diabetics and diffuse disease) and also late stent thrombosis, which may be due to incomplete endothelialization from persisting presence of polymer/antiproliferative drug. This has led to growing