Basic Science, Animal Models, and Cell Therapy

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TCT-793

Metformin Impairs Endothelialization After Placement of Newer Generation Drug Eluting Stents

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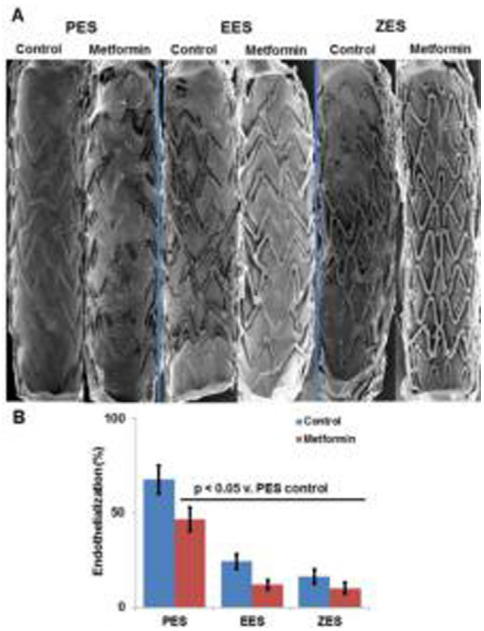
Background: Metformin may delay endothelialization of drug eluting stents (DES) due to convergent signaling at the mammalian target of rapamycin (mTOR) pathway. We aim to assess whether metformin will continue to adversely affect stent endothelialization despite improvements in newer generation DES.

Methods: Rabbit iliac artery stenting with newer generation DES was performed followed by 14 days of oral metformin or placebo treatment. Scanning electron microscopy was used to assess stent endothelialization after sacrifice.

Results: In the metformin-treated group there was significantly less endothelialization compared to the placebo-treated group. Paclitaxel-eluting stents in placebo-treated group had the least delay in endothelialization with significantly greater delay in both its metformin-treated counterpart and all –limus eluting stent groups (figure 1). Representative scanning electron micrographs (15x) of 14-day paclitaxel eluting stents (PES), everolimus- and zotarolimus-eluting stents (EES, ZES) in the presence or absence of oral Metformin (100 mg/kg/day) treatment (figure 1A) with quantification shown (Figure 1B, groups under the line representing $p < 0.05$ compared with PES-control with at least 4 animals per group).



Conclusions: Metformin inhibited stent endothelialization in newer generation DES likely through convergent and divergent mechanisms. By delaying stent endothelialization, metformin may increase the risk for thrombotic complications after DES placement.

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Intracoronary Infusion of Bone Marrow Mesenchymal Stem Cells in Acute Myocardial Infarction- A Critical Challenge for Dosage-Related Efficacy and Safety

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Background: To date, there have been debates on the risk and efficacy of bone marrow mesenchymal stem cell (BMSC) therapy in patients with acute myocardial infarction (AMI). This study aimed at testing whether BMSC intracoronary infusion following revascularization has a beneficial effect on the myocardium of AMI patients. This study is registered with ChiCTR, number ChiCTR-TRC-08000080.

Methods: A single-blind, randomized multicenter trial was conducted in patients with ST-elevation MI (STEMI, n=43), (2008-2009). All the patients who had been successfully reperfused within 12 hours were randomly assigned to receive an intracoronary infusion of BMSCs or optimum medical therapy after PCI. The primary endpoint was the change in myocardial viability and perfusion within the infarcted territory by 18-FDG/99mTc-sestamibi SPECT, and the change in global left ventricular ejection fraction by 2D echocardiography.

Results: A mean of (3.08±0.52) x106 2nd passage MSCs were obtained from 80 ml bone marrow after an average of 14.6±0.7 days in culture. BMSCs were transplanted at an average of 17.1±0.6 days. Six months after cell transfer, myocardial viability within the infarct area was improved in both groups compared with baseline, but 18-FDG SPECT showed no significant difference between the BMSC and control groups (4.0 ± 0.4% 95%CI 3.1-4.9 vs. 3.2 ± 0.5% 95%CI 2.1-4.3, P=0.237). Moreover, 99mTc-sestamibi SPECT demonstrated that myocardial perfusion within the infarct area in patients receiving BMSCs did not differ from the control group (4.4±0.5% 95%CI 3.2-5.5 vs. 3.9±0.6% 95%CI 2.6-5.2, P=0.594). Similarly, LVEF after 12, 24 months of followup also did not show any difference between the two groups (12mon' LVEF: 4.5±0.7% 95%CI 3.0-6.1 vs. 3.2±0.7% 95%CI 1.7-4.6, P=0.182). In the BMSC group, one patient suffered a serious complication involving coronary artery occlusion during the MSC injection procedure.

Conclusions: The clinical benefits and the safety of intracoronary injection of autologous BMSCs in acute STEMI patients need further investigation and reevaluation.

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Pre-clinical analysis of safety and efficacy of a new sirolimus eluting stent compared with bare metal, everolimus and sirolimus eluting controls

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Background: As requested by the regulatory agencies, new drug-eluting stents (DES) must be tested in animal models before conducting clinical trials. This study analyzes the antiproliferative efficacy and the safety profile (vascular healing) of new sirolimus eluting stents (SES) as compared with their bare metallic backbone, bare metal stents (BMS) and 2 different commercial DES, one SES and one everolimus-eluting stent (EES).

Methods: In 12 young domestic pigs (25±3 kg), 36 stents were implanted: 11 SES Test1, 10 SES Test2 (iVascular, Spain), 5 SES Cypher® (J&J, USA), 5 EES Xience® (Abbott, USA) and 5 control BMS Architect® (iVascular, Spain). The achieved stent:artery ratio was 1.39±0.13. The efficacy and safety results were analyzed at 28 days. We measured the angiographic % diameter stenosis and histologic % area stenosis, as well as neointimal area. The vascular healing process was evaluated through the semi-quantitative scores of vascular injury, inflammation, fibrin, and the rate of endothelialized luminal surface.

Results: The tested SES (Test1, Test2) and the control SES and EES showed similar restenosis results, while the control BMS showed significantly higher restenosis values. All the stents showed low values of vascular injury, as demonstrated by low global injury (0.9±0.5) and inflammation (1±0.5) scores, without differences between groups. On the contrary, some signs of delayed vascular healing (directly related to the pharmacological effect) as lower endothelialization rate and persistent fibrin deposition, are significantly worse in DES (no differences between groups) than in BMS.