Comparison of endothelialization and neointimal formation with stents coated with antibodies against CD34 and vascular endothelial-cadherin

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ABSTRACT
Vascular endothelial-cadherin (VE-cadherin) is exclusively expressed on the late endothelial progenitor cells (EPC). Therefore, VE-cadherin could be an ideal target surface molecule to capture circulating late EPC. In the present study, we evaluated whether anti-VE-cadherin antibody-coated stents (VE-cad stents) might accelerate endothelial recovery and reduce neointimal formation more than anti-CD34 antibody-coated stents (CD34 stents) through the superior ability to capture the late EPC. The stainless steel stents were coated with anti-human VE-cadherin antibodies or anti-human CD34 antibodies under the same condition. In vitro, VE-cad stents showed higher number of adhering EPC (823.6 ± 397.2 cells per HPF, p < 0.001). VE-cad stents also demonstrated better specific capturing of cells with endothelial lineage markers than CD34 stents did in flow cytometric analysis. VE-cad stents showed more effective re-endothelialization after 1 h, 24 h, and 3 days in vivo. At 42 days, VE-cad stents demonstrated significantly smaller neointima area (0.92 ± 0.38 versus 1.24 ± 0.41 mm², p = 0.002) and significantly lower PCNA positive cells in neointima (1684.8 ± 658.8/mm² versus 2681.7 ± 375.1/mm², p = 0.008), compared with CD34 stents. In conclusion, VE-cad stents captured EPC and endothelial cells more selectively in vitro, accelerated re-endothelialization over stents, and reduced neointimal formation in vivo, compared with CD34 stents.

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1. Introduction

In the era of drug eluting stents (DES), angiographic and clinical measures of restenosis have been substantially reduced. However, analyses of long-term clinical outcome have raised concerns about the serious safety problem of DES like stent thrombosis, which has been known to be associated with allergic and inflammatory reactions to polymers and incomplete endothelialization over stent struts [1−3]. Stenting with DES interferes with the natural vascular healing process by preventing or delaying the formation of a functional endothelial layer over the stent [4]. The lack of a functional endothelial layer after vascular injury is a crucial factor for stent thrombosis as well as neointimal proliferation [5−7]. To deal with the substantial pitfall of former DES, new generation DES with biocompatible or biodegradable polymer are developed and widely used in clinical practice. However, such newer generation stents also need to be re-endothelialized to minimize the risk of stent thrombosis; therefore, rapid restoration of functional endothelium might be more feasible way to overcome these pitfalls.

Recruitment of endothelial progenitor cell (EPC) to the site of vascular injury has been proposed to promote vascular healing and has been shown to inhibit neointimal proliferation and restenosis associated with percutaneous coronary intervention [6−9]. Recently, the Genous™ Bio-engineered R™ stent (OrbusNeich Medical BV, Hoelvelaken, The Netherlands) has been developed to enhance the capture of circulating EPCs to the stent surface using an immobilized anti-human CD34 monoclonal antibody [10]. However, CD34 is not a specific marker of EPC, rather pluripotent stem cell marker. CD34-positive cells are able to differentiate into...