



Synergistic effect of anti-platelet and anti-inflammation of drug-coated Co–Cr substrates for prevention of initial in-stent restenosis



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ABSTRACT

Antiplatelet and antithrombotic therapies are systematically considered to prevent restenosis following coronary stent implantation. Currently, patients receiving medicated stents are prescribed to orally take anticoagulants and antiplatelet drugs such as aspirin (ASP) and prasugrel (PRAS). Propolis (PROP) known as a natural organic compound was recently evaluated for its antiplatelet activity, antibiotics and immunomodulatory activities. In this study, antiplatelet drug-coated Co–Cr substrates were prepared with biodegradable poly(D,L-lactide) (PDLLA) containing ASP, PRA, or PROP using electrospray and the blood compatibility of the different substrates was investigated by measuring protein adsorption and platelet adhesion. In addition, the anti-inflammatory properties of the modified Co–Cr surfaces were assessed by measuring IL-8 and IL-6 expression levels in human endothelial cell cultures. Drug-coated surfaces were found to resist the adsorption of fibrinogen when compared to bare Co–Cr or PDLLA-coated Co–Cr. Interestingly, ASP- and PROP-containing substrates not only showed reduced adhesion of platelets and delayed coagulation time, but also drastically reduced the expression level of IL-8 and IL-6. Such results are supported that ASP- or PROP-coated Co–Cr can be potentially used as a stent material to mitigate early stage of restenosis. The developed coating materials might be an interesting alternative to systemic anticoagulant therapies prescribed after stent implantation.

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1. Introduction

Coronary vascular disease is one of the leading causes of death globally, killing nearly 17.5 million people in 2012, representing 31% of all deaths [1]. This is caused mainly by the increasing level of cholesterol plaques in the blood that in turn narrows the luminal diameter and restricts the blood flow [2,3]. Metallic stent implantation is used extensively to restore the normal blood flow [4]. As a material for metallic stents, cobalt–chromium (Co–Cr) alloys have received considerable attention because of their superior properties, such as high abrasion resistance and fatigue strength along with good ductility [5,6]. In addition, stents made of Co–Cr

enable the construction of more flexible and thinner struts [7]. Although Co–Cr has excellent physico-mechanical properties, the blood compatibility is always an issue as with other blood contacting materials [8,9]. In particular, the platelets interaction with biomaterial surfaces leads to significant platelet adhesion and consequently to risk of early thrombosis or in-stent restenosis [10].

Restenosis after coronary stent implantation is a complex process that an arterial injury induces triggers increasing platelet deposition and inflammatory response within the vessel wall that lead to the release of growth factors and cytokines activating smooth muscle cells and to neointimal hyperplasia [11,12]. It is necessary in most patients undergoing coronary stenting to continue the combination therapy of oral anticoagulation and antiplatelet drugs [13]. Aspirin (ASP), the most common antiplatelet medication, has been extensively evaluated for prevention of platelet aggregation through the inhibition of thromboxane production [14]. However, the lacking clinical outcomes with

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