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Corn trypsin inhibitor coating attenuates the prothrombotic properties of catheters in vitro and in vivo

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ABSTRACT

Catheters initiate coagulation by activating factor (f) XII, which can lead to catheter thrombosis. Fondaparinux, which only targets activated fX (fXa), is associated with more catheter thrombosis than heparin, which targets fXa and thrombin. To render catheters less thrombogenic and fondaparinux more effective, we examined whether coating catheters with corn trypsin inhibitor (CTI), which blocks fXIIa, attenuates catheter-induced clotting and promotes fondaparinux activity. Compared with unmodified catheters, CTI-coated catheters demonstrated (a) decreased adsorption of fibrinogen and fXII, (b) greater inhibition of fXIIa generated by catheter-induced autoactivation, (c) attenuated fXIIa-mediated activation of fXI and (d) longer plasma clotting times in the absence or presence of fondaparinux. In an accelerated catheter thrombosis model in rabbits, (a) the time to catheter occlusion was longer with CTI-coated catheters than with unmodified catheters and (b) an intravenous dose of fondaparinux that had no effect on the time to occlusion of unmodified catheters extended the time to occlusion of CTI-coated catheters. These findings support the concept that the prothrombotic activity of catheters reflects their capacity to activate fXII and identify CTI immobilization as a novel approach for rendering catheters and other blood-contacting medical devices less thrombogenic.

1. Introduction

Percutaneous coronary intervention (PCI) is a mainstay of treatment for patients with acute coronary syndromes (ACS). Guide catheter thrombosis, a peri-procedural complication of PCI, can lead to myocardial infarction [1,2]. Although heparin abrogates catheter thrombosis, its use in conjunction with potent antiplatelet drugs can lead to serious bleeding complications [3]. This is problematic because there is mounting evidence that bleeding in ACS patients is associated with adverse outcomes, including increased mortality [4–7]. To reduce the risk of bleeding, attention has focused on anticoagulants that are safer than heparin in the ACS setting. One such agent is fondaparinux, a synthetic analog of the unique pentasaccharide sequence that mediates the interaction of heparin with antithrombin. Whereas heparin and low-molecular-weight heparin (LMWH) promote the inhibition of activated factor X (fXa) and thrombin by antithrombin, fondaparinux only enhances fXa inhibition because it is too short to bridge antithrombin to thrombin [8].

When compared with LMWH for treatment of non-ST-segment elevation ACS, fondaparinux was associated with a 50% reduction in major bleeding, which resulted in a 17% decrease in mortality at 30 days [9]. There also was an overall reduction in 30-day mortality and reinfarction when fondaparinux was compared with heparin or placebo in patients with ST-segment elevation myocardial infarction [10]. However, the risk of catheter thrombosis was higher with fondaparinux than with LMWH or heparin in ACS patients who underwent PCI [11], and because of this problem, fondaparinux was of no benefit in patients undergoing urgent PCI [10]. These findings highlight the need for new strategies to eliminate the requirement for potent systemic anticoagulants during PCI, or to render agents such as fondaparinux more effective. One approach to this problem is to modify the surface of PCI catheters so as to make them less thrombogenic.

Blood coagulation is initiated by two distinct pathways, the tissue factor pathway and the contact factor pathway, which are triggered by activation of factor (f) VII or fXII, respectively. FVII is activated when tissue factor is exposed at sites of atherosclerotic

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