Commentary

Anticoagulant properties of drotrecogin alfa (activated) during hemofiltration in patients with severe sepsis

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Abstract

In a retrospective study among 35 severely septic patients treated with drotrecogin alfa (activated) (DrotAA) and renal replacement therapy (RRT), Camporota and colleagues demonstrated that the addition of heparin, epoprostenol, or both to DrotAA during RRT did not improve filter survival. Furthermore, in a multivariate logistic regression analysis, they identified the minimum value in platelet count as the only predictive factor of filter clotting during DrotAA infusion. These findings are in line with the previously formulated suggestion that DrotAA alone is as effective as heparin in the prevention of coagulation in the extracorporeal circuit. They also confirm the importance of baseline platelet count in the pathogenesis of extracorporeal circuit thrombosis. In the study by Camporata and colleagues, DrotAA treatment was not associated with an increase in red blood cell requirements. The results of this study supply a background to clinical decision making when choosing an anticoagulant for RRT in septic patients.

As DrotAA is an anticoagulant itself, the risk of bleeding during its use might be increased by the addition of other anticoagulants during RRT. Until now, only one report of three cases has been published on this topic. This report suggested that DrotAA alone is as effective as heparin in the prevention of coagulation in the extracorporeal circuit [7].

The current study demonstrates that the addition of heparin, epoprostenol, or both to DrotAA during RRT does not prolong filter survival. The lack of an additional effect of heparin on filter survival is not surprising since the antithrombotic effect of DrotAA is not enhanced by the addition of heparin [8]. However, since epoprostenol is a potent inhibitor of platelet function and DrotAA does not seem to have a direct inhibitory effect on platelet aggregation [9], one might have expected prolongation of filter survival during treatment with both DrotAA and epoprostenol.

Notably, multivariate logistic regression analysis identified the minimum value in platelet count as the only predictive factor of filter clotting during DrotAA infusion. Several studies have demonstrated the association between baseline platelet count and circuit clotting, especially during postdilution [10,11]. It is hypothesized that, due to an increase in local viscosity and shear stress, a higher baseline platelet count facilitates platelet cohesion along the hollow fiber wall [11]. Increased platelet cohesion may cause enhanced thrombin generation in the hemofilter, leading to filter clotting. During sepsis, however, coagulation is initiated by inflammatory mediators, such as endotoxin and cytokines, capable of inducing tissue factor expression on monocytes and macrophages [12]. DrotAA can completely inhibit tissue factor-induced platelet activation [13]. Since epoprostenol inhibits platelet function by decreasing the synthesis of cyclic adenosine monophosphate, its effect may be insufficient to

ARF = acute renal failure; DrotAA = drotrecogin alfa (activated); RRT = renal replacement therapy.
add to the effect of coagulation-induced platelet consumption in combination with complete inhibition of tissue factor-induced platelet activation by DrotAA.

In the current study, no difference in red blood cell requirements, either between DrotAA episodes and post-DrotAA episodes or between medical and surgical patients, was found. This is surprising given that, among the 4,459 patients included in INDEPTH (International Integrated Database for the Evaluation of Severe Sepsis and Drotrecogin alfa [activated] Therapy), the bleeding incidence in surgical patients was about 10 times higher in the DrotAA group than in the placebo group (4.9% versus 0.5%) and in medical patients it was about 2.5 times higher (2.6% versus 1%) [14]. The lack of a difference in the current study might be due to the relatively small number of patients.

**Conclusion**

In summary, the results of the current study add to the understanding of the effect of Drot AA on coagulation in the extracorporeal circuit and supply a background to clinical decision making when choosing an anticoagulant for RRT in septic patients.

**Competing interests**

The authors declare that they have no competing interests.

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