Anticoagulation in severe sepsis and the multiple organ dysfunction syndrome

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Chapter 8

Treatment with recombinant human activated protein C obviates additional anticoagulation during continuous venovenous hemofiltration in patients with severe sepsis

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Abstract

Background
Recombinant human activated protein C (rhAPC) is the first drug for which a reduction of mortality in severe sepsis has been demonstrated. In expectance of registration, more information regarding efficacy and safety was gathered in the ENHANCE study. Several patients participating in this study needed renal replacement therapy. Aim of this study was to evaluate whether continuous venovenous hemofiltration can be performed without the addition of another anticoagulant in patients treated with rhAPC.

Methods and Results
Three severely septic patients with acute renal failure were treated with rhAPC and hemofiltration. Within 48 h after the onset of organ failure, rhAPC was administered intravenously at a constant rate of 24 μg/kg/h for a total of 96 h. Predilutional hemofiltration with a blood flow rate of 150 ml/min and an ultrafiltrate rate of 2000 ml/h was performed using a cellulose triacetate membrane. After termination of the treatment with rhAPC, hemofiltration was performed using unfractionated heparin (UFH) as an anticoagulant. The hemofiltration runs during rhAPC were compared with those during UFH, each patient being his own control. Mean filter survival time during rhAPC was 55 ± 13 h compared with 66 ± 19 h for those during UFH (p=0.62). Filter survival time in both groups was limited by filter pore obstruction.

Conclusions
In these three severely septic patients treated with rhAPC and hemofiltration, circuit survival times during rhAPC and UFH were similar. This preliminary finding suggests that when rhAPC is administered, no additional anticoagulant therapy may be needed to prevent thrombosis in the extracorporeal circuit.
Introduction

During severe sepsis, activation of the inflammatory cascade leads to cell damage and organ failure. In these circumstances, renal failure necessitating renal replacement therapy often occurs. Continuous intravenous anticoagulation is usually necessary to keep the extracorporeal circuit open [1]. For decades, strategies to reverse the inflammatory cascade were limited. During recent years, the important role of the cross-talk between coagulation and inflammation in the pathogenesis of severe sepsis has been well defined [2]. Recombinant human activated protein C (rhAPC, drotrecogin alfa (activated) Xigris®) is the first drug for which a reduction of mortality in severe sepsis has been demonstrated. In the PROWESS study, comparing rhAPC to placebo in 1690 patients, mortality was 24.7% in the rhAPC group as compared to 30.8% in the control group (p=0.005) [3]. In expectance of approval by the FDA and other regulatory agencies, more information regarding the efficacy and safety of rhAPC needed to be gathered. For this purpose, an open-label study was designed: the ENHANCE study. During the ENHANCE study at this site, several participating patients needed renal replacement therapy. Activated protein C (APC) proteolytically degrades activated factors V and VIII, thereby decreasing the formation of thrombin [4]. Based on this knowledge, one could argue that during the administration of rhAPC, no additional antithrombotic agent is needed to prevent thrombosis in the extracorporeal circuit. The present study was conducted to test this hypothesis.

Materials and Methods

Patients

The ENHANCE study was approved by the institutional review board and written informed consent was obtained from all participants or their authorized representatives. Patients were eligible for the study if they had a known or suspected infection on the basis of clinical data at the time of screening and if they met the following criteria within a 48 h period: three or more signs of systemic inflammation and sepsis-induced dysfunction of at least one organ system that lasted no longer than 48 h. Patients had to begin rhAPC treatment within 48 hours after they met the inclusion criteria. Continuous venovenous hemofiltration (CVVH) was performed in patients with renal failure, associated with volume overload or uremia.

Treatment with rhAPC

Drotrecogin alfa (activated) was administered intravenously at a constant rate of 24 μg/kg body weight per hour for a total duration of 96 h. The infusion was interrupted for 1 h
before any percutaneous procedure and was resumed 1 h later. During the infusion of rhAPC, no other anticoagulant was administered.

**Continuous venovenous hemofiltration**
Vascular access was obtained by insertion of a 14 F double lumen catheter (Duo-Flow 400 XL, Medcomp, Harleysville PA, USA) into a large vein (femoral, subclavian, or internal jugular vein). Renal replacement therapy was performed by continuous venovenous hemofiltration using a Diapact hemofiltration machine (Braun AG, Melsungen, Germany). The standard blood flow rate was 150 ml/min and substitution fluid was added in predilution mode at a flow rate of 2000 ml/h. We used a cellulose triacetate filter with a surface of 1.9 m² and a cut off point of 50 kDa (CT190G, Baxter, Deerfield IL, USA). The hemofiltration run was stopped when clotting in the hemofilter had occurred.

**Anticoagulant administration**
The extracorporeal circuit was primed with heparinized saline (25000 IU unfractionated heparin (UFH) in 2000 ml NaCl 0.9%). Before being connected to the patient, the circuit was rinsed with plain saline in order to prevent the intravenous administration of heparin to the patient. During the treatment with rhAPC, no other anticoagulant was administered. If additional hemofiltration treatment was needed after termination of the infusion of rhAPC, UFH by continuous intravenous infusion was used as an anticoagulant, aiming at a prolongation of the activated partial thromboplastin time (APTT) of 1.5 times normal.

**Evaluation of patients**
Patients were followed for 28 days after the start of the rhAPC infusion or until death. Baseline characteristics including demographic information and information on preexisting conditions, organ function, markers of disease severity, infection, and hematologic and other laboratory tests were assessed within 24 h prior to rhAPC infusion. Hemoglobin, leukocyte and platelet counts, prothrombin time (PT) and APTT were measured twice daily.

The hemofiltration runs during rhAPC were compared to those during UFH, using the patient as his own control. Hemofiltration runs terminated because of a procedure (e.g. CT-scan) or because hemofiltration therapy was no longer deemed necessary, were excluded from the study. Parameters studied were filter survival time, extracorporeal circuit pressures, APTT and platelet count.
Statistical analysis
Values are given as mean ± SD. Differences in results between rhAPC and heparin were analyzed by a paired Student’s t-test. p<0.05 was considered significant.

Results

Patient characteristics
In our hospital, 9 patients with severe sepsis were enrolled in the ENHANCE study. Three of these patients needed renal replacement therapy. Their characteristics are shown in Table 1. After completion of rhAPC treatment, all patients needed additional hemofiltration therapy.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>No</th>
<th>Gender</th>
<th>Age (y)</th>
<th>APACHE</th>
<th>TSLS</th>
<th>Filter survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>40</td>
<td>76</td>
<td>19</td>
<td>55 ± 13 h</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>55</td>
<td>93</td>
<td>21</td>
<td>66 ± 19 h</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>60</td>
<td>70</td>
<td>32</td>
<td>60 ± 19 h</td>
</tr>
</tbody>
</table>

APACHE, Acute Physiology and Chronic Health Evaluation; TSLS, toxic shock like syndrome.

Filter survival
Mean filter survival time of the hemofilters during rhAPC was 55 ± 13 h compared with 66 ± 19 h for the hemofilters during UFH (p=0.62). The reason for stopping the hemofiltration runs in both groups was filter pore obstruction, as reflected by a 6-fold rise in transmembrane pressure (TMP). TMP rose from 34 ± 12 to 227 ± 108 mmHg in the rhAPC group (p=0.22) and from 36 ± 13 to 196 ± 103 mmHg in the UFH group (p=0.13) (Table 2). Because of the small number of patients, the rise in TMP was not statistically significant. We also evaluated coagulation parameters that might have influenced filter survival time, such as APTT and platelet count. In the rhAPC group, the APTT tended to be higher and the platelet count was lower, but again because of the small number, this difference did not reach statistical significance.

Complications
One patient experienced serious bleeding after the accidental removal of a central venous line during the infusion of rhAPC. Transfusion of 6 units of packed red blood cells was necessary in the 48 h period following the event. No other bleeding complications or thromboembolic events were observed.
Table 2. Filter survival times, extracorporeal circuit pressures, APTT and platelets, comparing rhAPC and heparin

<table>
<thead>
<tr>
<th></th>
<th>rhAPC</th>
<th>UFH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter survival time (FST)</td>
<td>24 ± 12</td>
<td>24 ± 13</td>
<td>0.96</td>
</tr>
<tr>
<td>PA min (mmHg)</td>
<td>-25 ± 18</td>
<td>-24 ± 3</td>
<td>0.96</td>
</tr>
<tr>
<td>PA max (mmHg)</td>
<td>-67 ± 36</td>
<td>-69 ± 28</td>
<td>0.96</td>
</tr>
<tr>
<td>PBE min (mmHg)</td>
<td>102 ± 0</td>
<td>100 ± 3</td>
<td>0.96</td>
</tr>
<tr>
<td>PBE max (mmHg)</td>
<td>186 ± 16</td>
<td>184 ± 77</td>
<td>0.96</td>
</tr>
<tr>
<td>PV min (mmHg)</td>
<td>41 ± 6</td>
<td>39 ± 5</td>
<td>0.96</td>
</tr>
<tr>
<td>PV max (mmHg)</td>
<td>63 ± 38</td>
<td>112 ± 32</td>
<td>0.96</td>
</tr>
<tr>
<td>TMP min (mmHg)</td>
<td>34 ± 12</td>
<td>36 ± 13</td>
<td>0.96</td>
</tr>
<tr>
<td>TMP max (mmHg)</td>
<td>227 ± 108</td>
<td>196 ± 103</td>
<td>0.96</td>
</tr>
<tr>
<td>APTT min (sec)</td>
<td>40 ± 6</td>
<td>38 ± 15</td>
<td>0.96</td>
</tr>
<tr>
<td>APTT max (sec)</td>
<td>103 ± 47</td>
<td>49 ± 16</td>
<td>0.96</td>
</tr>
<tr>
<td>Platelets min (x10^9/l)</td>
<td>58 ± 40</td>
<td>119 ± 80</td>
<td>0.96</td>
</tr>
<tr>
<td>Platelets max (x10^9/l)</td>
<td>91 ± 25</td>
<td>157 ± 90</td>
<td>0.96</td>
</tr>
</tbody>
</table>

rhAPC, recombinant human activated protein C; FST, filter survival time; PA, arterial pressure; min, minimal; max, maximal; PBE, pre-filter pressure; PV, venous pressure; TMP, transmembrane pressure; APTT, activated partial thromboplastin time.

Discussion

Continuous venovenous hemofiltration (CVVH) is increasingly being used in the management of acute renal failure in critically ill patients because of its beneficial effects on haemodynamics [5]. However, thrombosis in the filtration circuit is a frequently encountered problem. Several studies have addressed the pathophysiology of circuit thrombosis, but the exact mechanism has not yet been elucidated. Cardigan et al. demonstrated an increase in tissue factor during hemofiltration, correlated with thrombin generation and inversely correlated with filter life span [6]. These findings suggest that tissue factor plays a role in the initiation of coagulation in the extracorporeal circuit. Activated protein C (APC) inhibits activated factors V and VIII, thereby impeding fibrin formation [4]. Moreover, APC decreases the synthesis and expression of tissue factor in vitro, which could in turn lead to decreased thrombin formation [7]. Based on this knowledge, it was hypothesized that during the administration of rhAPC, no additional anticoagulant would be needed to keep the extracorporeal circuit open.

In the present study, we evaluated the efficacy of rhAPC in the prevention of thrombosis of the extracorporeal circuit during CVVH. We demonstrated that filter survival times during rhAPC did not differ from filter survival times during UFH in the same patient. The
pressures measured in the CVVH circuit using rhAPC or UFH were also not different. It is important to note that, although the difference was not statistically significant, during the CVVH runs with rhAPC the platelet count was lower, which might have positively affected the filter survival time [8]. As the hemofiltration runs during rhAPC always preceded those with UFH, the lower platelet count could be attributed to the earlier phase of sepsis. However, at that time also a more severe procoagulant state might be expected, which apparently did not affect the rhAPC-mediated anticoagulant protection of the filter.

Our findings add to the evidence that prevention of thrombin generation can prolong filter survival time during CVVH. UFH inhibits thrombin generation by inhibiting factor Xa and factor Ila, whereas rhAPC inhibits thrombin generation by inhibiting factor Va and factor Vlla. As suggested by Cardigan et al., thrombin generation in the extracorporeal circuit might be initiated by tissue factor. Both rhAPC and heparin are able to decrease tissue factor plasma levels [7,9] and in the present study the antithrombotic action of heparin and rhAPC were similar. Whether thrombosis in the CVVH circuit can be prevented by stronger inhibitors of the tissue factor/factor Vlla complex such as tissue factor pathway inhibitor (TFPI) or rNAPc2, remains to be determined.

In summary, the present study suggests that rhAPC is as effective as heparin in the prevention of thrombosis of the extracorporeal circuit during CVVH. The exact mechanism by which this effect is achieved, remains to be elucidated.
References