Replacement Therapy with Human Protein C Concentrate in Paediatric Septic Patients

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Summary

Sepsis and its sequelae are a major cause of mortality and morbidity in intensive care units. Coagulation protein C (PC) is reduced in > 85% of septic patients and there is a correlation between PC levels and morbidity and mortality. The aim of our study is to assess the efficacy and safety of replacement therapy with human protein C concentrate (Ceprotin, Baxter) in children and neonate with sepsis. Eight children, all presented with septic shock, were treated with the PC concentrate in addition to conventional therapy: 5 preterms, 1 term newborn, 2 children. In six of them PC levels rose to normality with a concomitant clinical improvement, two patients died without completing the treatment because of fulminant sepsis. No adverse effects were observed with the PC concentrate administration.

Introduction

Alterations in the levels of coagulation and fibrinolysis’ mediators have been reported to be associated to a negative outcome in septic patients. Recent studies report that >85% of patients with severe sepsis have acquired PC deficiency and that PC levels inversely correlate with morbidity and mortality outcome of septic patients both in adult and paediatric patients. Replacement therapy with human PC concentrate have been used in several trials in adults and paediatric patients with sepsis and meningococcal sepsis resulting safe and effective, but no data are available about its use in preterms.
Materials and methods

Eight patients were treated: 5 preterms (median G.E. 30 weeks) with respiratory distress syndrome (RDS), one term newborn who underwent abdominal surgery, 2 children, 10 and 14 years old, the first one who presented with septic shock after bone marrow transplantation, and the other presented with acute haemorrhagic syndrome after abdominal surgery. A complete blood cell count and platelet count, chemistry data and microbiologic cultures were obtained at admission. Coagulation tests, including PC levels and D-Dimer were performed before starting the drugs infusion and soon after the first cycle of treatment. PC levels were measured by chromogenic assays “Berichrom Protein C” (Dade Behring).

All the patients at the time of treatment presented with severe sepsis and clinical signs of septic shock and coagulopathy, and underwent aggressive treatment with fluid resuscitation, antibiotics, vasoactive amines. Six patients needed mechanical ventilation, 3 also received ATIII and 5 blood transfusions. Human protein C concentrate was administered, when signs and symptoms of coagulopathy appeared (purpuric skin lesions or bleeding) with initial i.v. bolus of 100 UI/Kg followed by 80-100 UI/Kg every 6 hours for 72 hours. (Tab1)

Results

Median dosage of PC before treatment was 24% (n.v. 70-130%). The lowest levels were associated to most severe infections (as demonstrated by PCR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (weeks or years)</th>
<th>Sex</th>
<th>Initial diagnosis</th>
<th>Clinical signs</th>
<th>Laboratory</th>
<th>PCR infusion from PLS/bleeding (hrs)</th>
<th>PCR infusion from PCR increasing (days)</th>
<th>Concentrate administered (IU)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td></td>
<td>27 w</td>
<td>M</td>
<td>Respiratory distress</td>
<td>Respiratory distress</td>
<td>24100 100000 46 (mg/L)</td>
<td>4300 59000 78.4 (mg/L)</td>
<td>53800 107000 139 (mg/L)</td>
<td>7500 55000 &lt;3.5 (mg/L)</td>
<td>15 6 4 0</td>
</tr>
<tr>
<td>1</td>
<td>40 w</td>
<td>M</td>
<td>G.I. surgery</td>
<td>G.I. surgery</td>
<td>7 7</td>
<td>15</td>
<td>22 None</td>
<td>23700 38000 7.7</td>
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<tr>
<td>2</td>
<td>10y</td>
<td>M</td>
<td>Splenectomy</td>
<td>Splenectomy</td>
<td>3700 79000 1.0</td>
<td>20</td>
<td>None</td>
<td>13000 70000 5.9</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>35w</td>
<td>M</td>
<td>Renal failure</td>
<td>Renal failure</td>
<td>3700 79000 1.0</td>
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<td>13000 70000 5.9</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>28w</td>
<td>F</td>
<td>RDS</td>
<td>RDS</td>
<td>3700 79000 1.0</td>
<td>20</td>
<td>None</td>
<td>13000 70000 5.9</td>
<td>3</td>
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<tr>
<td>5</td>
<td>26w</td>
<td>M</td>
<td>RDS</td>
<td>RDS</td>
<td>3700 79000 1.0</td>
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<td>13000 70000 5.9</td>
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<tr>
<td>6</td>
<td>14y</td>
<td>M</td>
<td>CP</td>
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<td>None</td>
<td>13000 70000 5.9</td>
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</tr>
<tr>
<td>7</td>
<td>34w</td>
<td>M</td>
<td>G.I. surgery</td>
<td>G.I. surgery</td>
<td>3700 79000 1.0</td>
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<td>13000 70000 5.9</td>
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<tr>
<td>8</td>
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<td>20</td>
<td>None</td>
<td>13000 70000 5.9</td>
<td>3</td>
</tr>
</tbody>
</table>

BM= Bone Marrow; CP= cerebral palsy; PSL=purpuric skin lesions; G.I.=gastro intestinal; NEC=necrotizing enterocolitis; N.D.= not detectable; DIC=disseminated intravascular coagulation; MOF = multi organ failure; CNSH central nervus system haemorrhage
levels), and negative outcome (patient 2 and 3).

In all the cases reported PC concentrate was administered in the presence of extensive, enlarging purpuric skin lesions, or active bleeding, when conventional therapies failed and after receiving the results of coagulation tests. In two patients (patient 1 and 6) despite PC levels resulted undetectable before starting treatment, PC concentrate was administered because of severe conditions and bleeding (bleeding after skin puncture and haematuria in patient 1, bruises and bleeding after puncture in patient 6). In six patients PC levels progressively improved after starting treatment, with concomitant clinical signs improvement (arresting of bleeding, reduction in purpuric skin lesions and improvement of the vital parameters). No adverse effects were noted with the PC concentrate administration. Four patients recovered without sequelae. Two patients (n.2 and 3) who presented with the lowest PC levels at admission, died during the first day of hospitalization from fulminant sepsis, and received just the first i.v. bolus of PC concentrate. Patient 1 developed a central nervous system haemorrhage and 10 days later a new systemic infection from a different germ (Klebsiella Pneumonia) and died because of DIC and heart failure. Patient 6 developed arterial thrombosis of the left leg and died 20 days later because of heart failure.

Discussion

Physiologically, the protein C (PC) pathway, represents one of the most important regulatory systems of haemostasis. Activated C protein (aPC) proteolytically inactivates both factor VIIIa and Va, limiting thrombin formation and down-regulating the activation of coagulation and facilitates fibrinolysis inhibiting plasminogen activator inhibitor-1 (PAI-1) and preventing the activation of thrombocyte activatable-fibrinolisis inhibitor (TAFI). Furthermore it has been recently found that aPC also has antiinflammatory properties down regulating the NFkB pathway and reducing the release of pro-inflammatory cytokines in vivo and in vitro11. That suggested its use in patients with severe sepsis.

In our study replacement therapy with human protein C concentrate in septic patients resulted safe and effective, as support to conventional therapy, in reducing coagulopathy secondary to sepsis, both in paediatric patients and neonates (preterm and term neonates). The best results have been obtained with precocious administration of PC concentrate soon after the first signs of coagulopathy. The only two patients who developed sequelae received the concentrate 15 and 96 hours after the first signs of bleeding. That could suggest to use the Protein C concentrate precociously soon after the first manifestations of microcirculation damage, in all the subjects with severe sepsis at high risk to develop sepsis-induced coagulopathy. Evidence of this can be obtained through further studies.
References


