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BRIEF REPORT

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Protein C concentrate to restore physiological values in adult septic patients

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Abstract *Objective:* To describe the efficacy and safety of protein C (PC) concentrate to restore physiological values in adult septic patients having clinical contraindications to activated PC. *Design:* Case series (pilot study). *Setting:* Three adult ICUs of a University Hospital. *Patients and participants:* Twenty adult patients affected by severe sepsis or septic shock with plasma values of PC < 50%. *Interventions:* Patients were treated with PC concentrate (*Ceprotin*®—Baxter) with a starting bolus followed by a continuous infusion for 72 h [3 IU/(kg h)]. *Measurements and results:* PC activity, WBC, platelets, D-Dimer, fibrinogen, PT, aPTT, AT III, lactate, Sepsis-related Organ Failure Assessment (SOFA), Disseminated Intravascular Coagulation (DIC) score, adverse events, and mortality were measured. Baseline plasma PC activity was 34.5 ± 9.1%. PC concentrate normalized the PC activity in all patients within 48 h, and then remained stable for the following days. At baseline, several patients showed abnormal PT, aPTT, platelets values, and lactate levels. During the study period, there was a significant increase of platelets, fibrinogen, PT, AT III, and a significant decrease of D-Dimer, aPTT, DIC score, and lactate. No adverse reactions (hemorrhage or thrombosis) were observed. Mortality at 28 days was 35%. *Conclusions:* Our pilot study shows that the administration of PC concentrate to patients having contraindications to the treatment with activated PC was safe and possibly useful to control the coagulopathy triggered and sustained by sepsis. A randomized, double blind study in patients with severe sepsis and contraindications to activated PC administration would be advisable to state the safety and the possible role of this product in the treatment of severe sepsis.

Keywords Sepsis · Therapy · Shock · Septic · Protein C

Introduction

The protein C pathway is a modulator of the coagulation system. Protein C (PC) plays an integral role in the host response to infection, modulating the inflammatory and immunomodulatory processes [1, 2]. PC is synthesized by the liver as a vitamin K-dependent zymogen (proenzyme) of a serine protease, and is activated in the blood (activated PC) by the endothelial and platelet thrombin–thrombomodulin complexes and by an endothelial receptor (EPCR) [3].

During severe sepsis, there is a reduction in PC concentration due to decreased hepatic synthesis (decreased liver PC mRNA concentration), increased consumption, inactivation by increased endothelial PC receptor uptake, and degradation by proteolytic enzymes released from white blood cells. The onset of PC deficiency probably

occurs before clinical diagnosis of sepsis-dependent organ dysfunction.

PC deficiency leads to increased activation of the coagulation system, resulting in thrombin generation and, eventually, intravascular clot formation with thrombosis. In septic patients, the extent of PC deficiency assessed at the time of diagnosis correlates with increased morbidity and mortality, and also with the major outcome measures of severe sepsis (shock, ICU stay, ventilator dependence) [4–6].

Some case reports and open-label studies reported in literature indicate that an early substitution of protein C may improve the outcome in patients with purpura fulminans induced by sepsis. Most of these reports consider children with meningococcal infections [7–9].

Data regarding adult patients are rare, are obtained from a low number of patients, and are sometimes published as abstracts [10–12]. Based on the hypothesis that purpura is the final expression of an extremely deranged coagulation system, and that organ failures secondary to severe sepsis are caused by alteration of microcirculation due to an excess of pro-coagulative activation, we carried out a case series pilot study with the aim of evaluating the dose of PC concentrate to restore physiological values in adult septic patients having clinical contraindications to the treatment with activated protein C and low plasmatic values of PC activity. The results of our study have been presented in part previously at the 19th ESICM Annual Congress, Barcelona, 24–27 September 2006 [13].

Materials and methods

The study was approved by the local ethics committee. PC concentrate (*Ceprotin*®, Baxter) was administered in addition to the standard intensive care sepsis therapy (from April 2004 based on the guidelines of the Surviving Sepsis Campaign) and according to the ethical principles of the Declaration of Helsinki for medical research involving human subjects [14].

From February 2003 to June 2006, we enrolled 20 consecutive patients (ten females and ten males) over 18 years with severe sepsis (five), severe sepsis and purpura (one), or septic shock (14) admitted to our ICUs, having plasma values of PC activity lower than 50%, and not eligible for the treatment with activated protein C for the presence of contraindications as platelets < 30,000 (nine patients), neurological pathologies (four), high bleeding risk (three), pending major surgical interventions (two), and anticoagulant drugs therapy (two). Patients' characteristics are reported in Table 1. Fifty percent of them were surgical patients submitted to an urgent intervention (mostly with diagnosis of peritonitis), while 50% had a medical diagnosis and came from a medical ward or ER department (mostly with diagnosis of respiratory infection). The associated pathogens are listed in Table 2.

The treatment was performed in three intensive care units of a university hospital. Enrolled patients were treated with PC concentrate (*Ceprotin*®, Baxter) administered as a starting bolus followed by continuous infusion for 72 h. Four patients received fresh frozen plasma and concentrates of red blood cells during the surgical intervention before the ICU admission; no patient was submitted to surgery during the period of PC infusion. AT III was never administered. The bolus dose of PC concentrate was calculated with the aim of obtaining 100% of the plasma PC activity using this formula:

$$\text{IU of PC concentrate} = (100 - \text{PC plasma level}) \times \text{body weight (kg)}.$$

The continuous infusion started with 3 IU/(kg h), adjusted to maintain plasma PC activity between 70 and 120% for 72 h.

Table 1 Baseline characteristics and outcome

	All patients	Survivors	Non-survivors
Number of patients, female/male	20, 10/10	13 (65%), 6/7	7 (35%), 4/3
Median age (years)	68 (43–82)	68 (43–82)	68 (52–78)
Weight (kg) (mean ± SD)	72 ± 21.4	77.3 ± 25.84	62.9 ± 5.72
Type of infection (number of patients)			
Peritonitis	7	1	6
Lung infection	6	3	3
Trauma	2	1	1
Immunosuppression[a]	3	2	1
Urinary tract infection	1	0	1
Skin infection	1	0	1
Clinical presentation (number of patients)			
Septic shock	14	6	8
Severe sepsis	5	0	5
Severe sepsis + purpura	1	1	0
Base line SAPS II (mean, SD)	55.1 ± 13.2	60.3 ± 12.7	53.1 ± 13.9
Baseline SOFA (mean, SD)	13.1 ± 3.3	12.6 ± 3.5	13.25 ± 3.24
PC dose (bolus) U.I.	4,510 ± 922.4	4,577 ± 1,091	4,385 ± 651
PC dose (daily total amount) U.I.	4,810 ± 1,540	5,152 ± 1,510	4,485 ± 477
Interval between diagnosis and PC administration (h)	20.15 ± 9.8	23.3 ± 10.7	14.28 ± 4.42

SAPS Simplified Acute Physiology Score

[a] Bloodstream infection of unknown source in patients with immunosuppressive therapy

Table 2 Associated pathogens

	Blood	BAL	Surgical drainage
1. Lung infection			
2. Immunosuppression[a]	*Staphylococcus* A	*Pneumocystis* C	
3. Lung infection	*Pseudomonas* A	*Pseudomonas* A	
4. Peritonitis		*Pseudomonas* A	*Serratia*, *Enterobacter*
5. Lung infection		*Streptococcus* Pn	
6. Soft tissue infection		*Staphylococcus* A	
7. Immunosuppression[a]	*Aspergillus*		
8. Urinary tract	*Escherichia coli*		
9. Peritonitis		*Candida albicans*	*Enterobacter*, *Candida*
10. Lung infection		*Staphylococcus* A	
11. Peritonitis	*Serratia*, *Candida*		*Serratia*, *Enterobacter*
12. Skin			
13. Peritonitis			
14. Lung infection	*Legionella*	*Legionella*	
15. Peritonitis			*Enterobacter*
16. Peritonitis			*Serratia*, *Enterobacter*
17. Lung infection			
18. Peritonitis	*Serratia*		*Enterobacter*
19. Soft tissues	Strepto βemol.		
20. Immunosuppression[a]	Enterococci		

In four patients (20%), all the cultures were negative
BAL Broncho Alveolar Lavage
[a] Bloodstream infection of unknown source in patients with immunosuppressive therapy

Laboratory measurements of PC activity were performed every 12 h with a Chromogenic method (amidolytic assay Chromatic Protein C assay, Chromogenix IL, Milan, Italy; range 70–140%). White blood cells, platelets, D-Dimer, fibrinogen, PT, aPTT, AT III, Disseminated Intravascular Coagulation (DIC) score, lactate, and Sepsis-related Organ Failure Assessment (SOFA) were evaluated before PC infusion (baseline), after 24, 48, 72, and 96 h, and on the 10th day. Mortality was evaluated at 28 days.

Parameters evaluated during the study period were analyzed by repeated measures ANOVA and post-hoc comparison (LSD test). $P < 0.01$ was the criterion of significance.

Results

Baseline plasma PC activity was 34.5 ± 9.1% (range 22–49%). The regimen chosen to administer PC concentrate (i.v. bolus plus continuous infusion for 3 days) increased plasma PC activity in all patients. Plasma PC activity normalized after 48 h and remained stable in the following days. Only in one patient, the PC activity decreased to 52% on the 10th day. The average bolus dose was 4,510 ± 922.4 IU (range 2,500–6,200 IU) and the daily total amount was 4,810 ± 1,540 IU (range 3,200–8,000 IU). The average total dose received by the patients (starting bolus plus 3-day infusion) was 19,065 IU (range 15,100–30,000 IU). In one patient, it was necessary to increase the infusion rate to 5 IU/kg/h for less than 24 h.

At baseline, several patients showed abnormal values of PT, aPTT, and platelets, and increased lactate levels. During the study period, there was a progressive and significant increase of platelets, fibrinogen, PT, AT III, and a progressive and significant decrease of D-Dimer, aPTT, DIC score, and lactate (Table 3). No adverse reactions or events were observed during protein C replacement therapy, even if most of the patients had

Table 3 Changes in SOFA score and laboratory findings obtained from all patients during the study period (mean ± SD)

	Baseline	24 h	48 h	72 h	96 h	10th day
SOFA	13.1 ± 3.3	12.8 ± 2.9	11.9 ± 3.1	10.9 ± 3.7	*10.5 ± 3.3**	*9.4 ± 3.4**
PC (%)	34.5 ± 9.1	*75 ± 26.6**	*97.9 ± 15.5**	*96.7 ± 12.6**	*98.2 ± 15.6**	*96.2 ± 17.6**
WBC ($\times 10^9$/L)	14.2 ± 12.1	16.8 ± 14.2	15.5 ± 10.9	16.7 ± 10.5	17.3 ± 9.5	15.5 ± 7.6
Platelet ($\times 10^9$/L)	69.3 ± 60.7	63 ± 59.3	75.2 ± 73.5	95.7 ± 78.1	112.1 ± 84.1	194.9 ± 113*
D-Dimer (μg/L)	4,143.6 ± 3,643	2,246 ± 2,481	*1,300 ± 1,354**	*1,002 ± 1,186**	*480 ± 245**	*901 ± 942**
Fibrinogen (g/L)	4.8 ± 1.7	5.6 ± 1.5	6.2 ± 2.2	*6.7 ± 2.4**	*6.5 ± 2.2**	6.2 ± 2.3
PT (%)	48.4 ± 12.5	56.2 ± 15.1	57.8 ± 16.8	*63.4 ± 19**	*65.4 ± 16.8**	*69.5 ± 19.3**
aPTT (s)	40.3 ± 15.4	37.1 ± 8.6	37.4 ± 8.1	36.4 ± 8.1	34.6 ± 5.5	33.2 ± 6*
ATIII (%)	56.2 ± 19.2	65.6 ± 26.3	70.1 ± 25.4	*80.7 ± 25.1**	*80.2 ± 19**	*87.9 ± 23.1**
Lactate (mmol/L)	6 ± 3.7	*3.6 ± 2**	*2.9 ± 1.5**	*2.5 ± 1.2**	*2.1 ± 1.3**	*2.1 ± 1.5**
DIC score	5.06 ± 1.34	4.38 ± 1.77	4.36 ± 0.93	3.36 ± 1.39	*3.08 ± 1.75**	*2.71 ± 2.52**

* $P < 0.01$ versus baseline

altered coagulation or were at risk of hemorrhage because of neurological problems or submission to surgery.

Baseline PC levels were lower in non-survivors (NS) than in survivors (S) (29.86 vs. 35.58%), although the difference was not statistically significant ($P = 0.09$), and there was no difference between PC levels in patients who died early and the others (Table 4). As an average, the total amount of PC concentrate infused was similar in the S and NS group, but non-survivors, having lower PC levels at baseline, initially received a higher dose of PC concentrate according to the formula used, with the aim of obtaining 100% PC activity as reported in the "Materials and methods". Then, the rate of infusion was adjusted on the basis of PC measurements. Baseline AT III levels were similar in the S and NS group (52.91 vs. 58.71%; $P = 0.56$). Mean D-Dimer concentration at baseline was 4,143.6 ± 3,643 μg/L, decreasing in the following days, a reduction which became significant at day 2, 3, 4 and 10. There was no significant difference between the S and NS group. An evolving DIC score [15] was given to each patient with one point for each of the following: 20% decrease in platelet count, increase in PT > 0.3 s, and fibrinogen level <1.0 g/L. For a moderate increase of fibrin-related markers, (e.g., FDP) 2 points were given and for a strong increase, 3 points were given [16]. A DIC score ≥ 5 was compatible with overt-DIC; a score < 5 was suggestive (not affirmative) for non-overt DIC. At baseline, the DIC score was 5.06 ± 1.34. Eight patients had overt DIC, (DIC score ≥ 5). There was a significant difference ($P = 0.01$) between the S (6.2 ± 1.16) and NS (4.5 ± 1.07) groups. The DIC score decreased significantly at day 4 and 10 ($P < 0.05$) and from day 3 (72 h), only three patients had an overt DIC status.

The SOFA score decreased significantly after PC infusion. A difference, albeit statistically not significant, was observed in the SOFA score between survivors and non-survivors at day 10 (8.08 ± 3.14 and 12 ± 3.39, respectively; $P = 0.064$). The baseline SAPS II and SOFA scores did not differ between survivors and non-survivors. Seven patients died (28-day mortality = 35%), one after 72 h, three between day 3 and 8, and three between day 11 and 28; the causes were massive myocardial infarction (one patient) and multiorgan failure (six patients). The predicted mortality based on SAPS II (55.1 ± 13.2) was 58.9%.

Table 4 SOFA score and laboratory findings during the study period (mean ± SD)

	Baseline		24 h		48 h		72 h		96 h		10th day	
	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors	Survivors	Non-survivors
SOFA	12.6 ± 3.5	13.8 ± 3.2	12.2 ± 2.9	13.7 ± 3	11.2 ± 3.2	13 ± 2.7	10.8 ± 2.9	11.3 ± 3.6	9.5 ± 1.9	12.6 ± 3.4	8.08 ± 3.14	12 ± 3.39
PC (%)	35.58 ± 10	29.86 ± 6.2	94.6 ± 14	96 ± 33.6	97.6 ± 14.1	98.5 ± 20.6	94.1 ± 9.9	102.5 ± 17.5	99.5 ± 18.6	95.6 ± 9.7	94.7 ± 18.8	99.5 ± 17.5
WBC ($\times 10^9$/L)	14.6 ± 14.4	13.6 ± 8.4	17.9 ± 17.3	14.6 ± .9	15.5 ± 12.5	15.4 ± 9.9	16.1 ± 9.94	18 ± 13.4	15.7 ± 7.8	20.8 ± 13.9	12.1 ± 4.64	23.6 ± 8.3
Platelet ($\times 10^9$/L)	85.6 ± 64.2	38.4 ± 48.3	74 ± 68.1	42.5 ± 41.8	90.9 ± 87.8	45.8 ± 32.5	115.4 ± 89.5	53 ± 27.4	135.8 ± 94.25	60.1 ± 30.5	*241.6 ± 101.7**	*82.8 ± 59.4**
D-Dimer (μg/L)	2,891 ± 3,377	3,379 ± 4,851	1,822 ± 1,392	3,201 ± 4,443	*1,518 ± 1,605**	*755 ± 525**	1,122 ± 1,436	704 ± 456	504 ± 284	427 ± 200	*594 ± 762**	*1,453.8 ± 1,163**
Fibrinogen (g/L)	5.09 ± 1.8	4.09 ± 1.6	5.9 ± 1.5	4.9 ± 1.5	6.6 ± 2.07	5.2 ± 2.4	6.9 ± 1.9	5.7 ± 3.9	6.5 ± 2.4	6.3 ± 2.1	5.7 ± 2.8	6.36 ± 2.13
PT (%)	53.6 ± 10.7	38.6 ± 10.7	61 ± 16.5	47.2 ± 8.5	65.4 ± 16.8	43.7 ± 8.5	68.5 ± 20.5	52.5 ± 12.5	69.8 ± 15.6	55.8 ± 18.1	*78.8 ± 11.5**	*47 ± 18.1**
aPTT (s)	39.3 ± 16.26	42 ± 16.1	38.3 ± 9.9	34.8 ± 6.2	36.9 ± 9.1	38.14 ± 7	37.3 ± 9.2	34.4 ± 5.8	34.7 ± 5.6	34.17 ± 6.1	31 ± 3.5	38.6 ± 8.2
ATIII (%)	52.9 ± 21.3	58.7 ± 18.1	58.5 ± 16.3	78.7 ± 38.24	69.5 ± 26.3	71.4 ± 27.4	79.7 ± 28.9	82.8 ± 19.5	73.6 ± 13.7	93.3 ± 23.9	89 ± 20.8	84.5 ± 35.12
Lactate (mmol/L)	5.9 ± 3.6	6.1 ± 4.4	3.64 ± 1.8	3.4 ± 2.4	2.5 ± 1.2	3.5 ± 1.9	2.2 ± 0.6	3.2 ± 1.9	1.7 ± 0.5	3.3 ± 2.1	1.6 ± 0.6	3.7 ± 1.8
DIC score	*4.5 ± 1.07**	*6.2 ± 1.16**	4 ± 1.65	5.25 ± 1.7	3.9 ± 0.6	5.5 ± 0.6	3.1 ± 0.9	4 ± 2.2	2.4 ± 1.4	4.5 ± 1.7	*1.5 ± 1.2**	*4.8 ± 3.03**

* $P < 0.01$ survivors versus non-survivors

Discussion

There is an open debate on the activation of protein C during severe sepsis, where the alteration of endothelium function plays a central role in the pathophysiology of derangement of inflammatory and hemostatic systems.

Faust et al. [17] reported that the level of endothelial thrombomodulin and the endothelial protein C receptor (EPCR) expression were lower in two patients with meningococcal sepsis than in control subjects. The conclusion of the authors was based on immunohistochemical studies of skin-biopsy specimen. One particular pitfall is that the decreased staining for thrombomodulin or EPCR could have been a secondary effect of tissue necrosis and, perhaps, a consequence, rather than a cause, of microvascular thrombosis.

De Kleijn et al. [9] conducted a randomized double blind, placebo controlled study on the activation of protein C following infusion of protein C concentrate in 38 children with severe meningococcal sepsis and purpura fulminans. The result was that the activation of PC occurred in a dose-dependent manner after the infusion of PC concentrate in 27 out of 28 treated patients.

Other studies have demonstrated that EPCR expression, which plays a critical role in activating the thrombin–thrombomodulin complex and in modulating the functions of the PC pathway, has also been detected in blood cells. The endothelial PC receptor is expressed by human neutrophils, lymphocytes, monocytes, and eosinophils whose active site legation with either PC or activated PC arrests the cell migration in response to potent stimuli [18, 19]. Inhibitory effects of these components of the PC pathway on neutrophil function may affect the inflammatory response with modulation of lymphocyte function and migration [20–22]

Recent studies performed by Feistritzer et al. [23] showed that the protective signaling in endothelial cells is linked to PC activation. They demonstrated that an efficient barrier enhancement is coupled with the endogenous PC activation pathway. This gives a rationale for the use of protein C zymogen in acquired protein C deficiency.

The use of PC can be safe because the anticoagulant effect occurs only when it is activated to activated PC. It requires the presence of the thrombin–thrombomodulin complexes; the consumption of these compounds leads to physiological self-limitation of the process, avoiding the risk of having "too much" activated PC, resulting in an increased risk of bleeding. The observed results of our series are limited to the effectiveness of the dosage and the lack of collateral effects. In our small group of patients, the regimen of PC concentrate infusion was safe and effective to restore physiological plasma PC activity. It has been previously reported that PC levels are correlated with poor outcome [4–6]. In our study, baseline PC levels were lower in non-survivors than in survivors, but the difference was statistically non-significant ($P = 0.09$). The apparent discrepancy between our data and those obtained from the literature can be due to the small number of patients enrolled in our study. At day 4, the PC levels were higher than those observed in the PROWESS study (98.2 vs. 79%). This difference can be due to the PC infusion and probably also due to the different characteristics of the two populations.

The total amount of PC concentrate infused in our patients was lower than that reported in pediatric patients [7–9] and in previous studies on adult septic patients [10–12], thus giving the possibility of reducing the cost of this expensive treatment that can be estimated approximately 35,000 € for a patient weight of 70 kg.

We do not think that the concentrate of protein C zymogen can be a substitute for activated PC for patients with severe sepsis or septic shock [24]. Activated PC remains the drug of choice, with demonstrated positive effects on outcome [25]. The question we raise is: could the PC zymogen (Ceprotin, Baxter) become an adjuvant therapy in those patients that cannot receive activated PC?

Our study is a small case series study, having the limits and biases associated with non-controlled study. In the absence of a control group, it is not possible to make comments on the efficacy of the treatment; we do not know how laboratory data, clinical parameters, and outcome would have been without PC replacement. Nevertheless, a randomized, double blind study in patients with severe sepsis and contraindications to activated PC administration would be advisable to define the safety of the product and its role in the therapy of sepsis.

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