

Human protein C concentrates in adult septic patients

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ABSTRACT

Some case reports and case series suggest that protein C concentrates may improve the outcome in patients with congenital or acquired protein C deficiency (not only in those with sepsis induced purpura fulminans). We reviewed the published literature on the use of protein C concentrates in adult septic patients and found that it is limited to less than 70 patients reported in observational studies with a 70% survival, and added our personal experience (two adult patients with sepsis and contraindications to recombinant activated protein C).

Key words: sepsis, protein C, cardiac surgery

Protein C (PC) is a vitamin K-dependent product of the liver, present in the blood similar to inactivated zymogene pro-enzyme and has antithrombotic, anti-inflammatory, and pro-fibrinolytic properties. During severe sepsis there is a reduction in PC concentration. PC deficiency leads to increased activation of the coagulation system, resulting in thrombin generation and, eventually, intravascular clot formation with thrombosis. (1) Numerous studies have demonstrated that decreased circulating levels of PC in septic patients are associated with increased morbidity and mortality. (2-7) The inflammatory and pro-coagulant host responses to infection are closely related. Inflammatory cytokines can activate coagulation, inhibit fibrinolysis and stimulate multiple inflammatory pathways, resulting in multi-organ dysfunction and death. PC is converted to activated PC (APC) by thrombin coupled to thrombomodulin in a selective way during the coagulation cascade by inhibiting platelet

activation and fibrin production, and is an important modulator of the coagulation and inflammation associated with severe sepsis. (8)

PC is presently utilized as therapy for patients with congenital deficiency of PC, and for purpura fulminans treatment. (9-11) In children and in patients with contraindications to the activated form of PC, such as those at high risk of bleeding, PC administration seems to be a useful alternative to APC: we'll review the published evidence on this topic.

Even if Recombinant Human Activated Protein C (rhAPC, Xigris, Lilly) reduces all cause mortality in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II \geq 25 or multiple organ failure), (12) its use is associated with an increased risk of serious bleeding: 2% vs 3.5% (PROWESS study), (13) 2.2% vs 3.9% (ADDRESS study), (14) 6.5% (ENHANCE), (15) with registry studies of rhAPC (16,17) reporting higher bleeding rates than randomized controlled trials, suggesting that the risk of bleeding in actual practice may

be greater than reported in PROWESS and ADDRESS.

Contraindications for the use of rhAPC as per recent international guidelines for the management of severe sepsis and septic shock (12) are illustrated in table 1. Furthermore, the same guidelines indicate weak recommendations and low quality of evidence for the use of rhAPC in adult patients within 30 days of surgery. (12)

Some case reports suggest that PC concentrates (PCc, Ceprotin, Baxter) may improve the outcome in patients with congenital or acquired PC deficiency such as purpura fulminans induced by sepsis. Most of these reports consider children with meningococcal infections. (9-11) Overall, PCc in adult septic patients has been reported in 8 papers (9 with the case reports presented in this paper) with overall less than 70 patients included in case reports or case series (18-25) as described in table 2. Only this paper and three others reported the use of PCc in adult patients without meningitis. Other papers include double publications, (26,27) patients younger than

Table 1. Contraindications to the use of rhAPC as per recent international guidelines for the management of severe sepsis and septic shock. (12)

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation
- Known hypersensitivity to rhAPC or any component of the product

18 years of age, (10,28) or use of PCc in healthy volunteers. (29) Rintala E et al. (26) were the first (year 1998) to report on the use of PCc in 3 adult patients with meningitis. In 2000, Rintala and al. (25) increased their published experience describing the use of PC as repeatable boluses of 100 u/kg four-a-day, associated with anti thrombin III (AT III) supply to reach normal values in 12 patients affected by purpura fulminans, one manifestation of disseminated or overt disseminated intravascular coagulation (DIC), characterized by thrombocytopenia, petechiae, ecchymoses associated

with thrombosis of small vessels, resulting in tissue hypoperfusion that leads to peripheral gangrenes and acute renal failure. Nine of 12 patients were in septic shock and others in severe sepsis; median APACHE II score was 16. Median PC activity was 26%, median platelet count 27000. Etiology of infection was N. meningitidis in 4 patients, S. pneumoniae in 2, C. canimorsus in 2 and 1 S. aureus, in 2 the etiology was unknown. Authors reported withdrawal of acrocyanosis, restriction of ischemic regions and improvement of peripheral temperature within the first few days of treatment, with concurrent improve-

ment of hemodynamic disturbance. Laboratory tests showed improvement of DIC status. Two patients required amputations. Twenty-eight day mortality was 33% (4 of 12) and hospital mortality 42% (5 of 12). They didn't observe any drug related adverse events. In a post hoc analysis, authors showed that the recovery of the platelet count was retarded in the non- survivor group. The largest experience so far has been reported by Baratto e al. (19) who described the efficacy and safety of PCc to restore physiological values in 20 adult septic patients having clinical contraindications to treatment with rhAPC such as platelets <30.000 (9 patients), neurological pathologies (4 patients), high bleeding risk (3 patients), pending major surgical interventions (2 patients), and anticoagulant drug therapy (2 patients). They found a significant increase of platelets PT, AT III, and a significant decrease of D-Dimer, aPTT, DIC score and lactate. They administered PCc with the aim to obtain 100% of the plasma PC activity using the formula: IU of PCc= (100 – PC plasma level) x body weight (Kg). Continuous infusion lasted 72 hours and started at 3 IU/kg/h, adjusted it to

Table 2. Summary of all published papers reporting on adult patients receiving protein C concentrates (PCc).

Author	Year	Journal	N	Setting	Survival	Bolus dose	Following doses
Landoni G	2008	Signa Vitae	2	Sepsis	100%	50 IU /kg	3 IU/kg/h
Crivellari M (18)	2008	SIAARTI Congress 2008	9	Sepsis after cardiac surgery	89%	50 IU /kg	3 IU/kg/h
Baratto F (19, 27)	2008; 2004	Intensive Care Med Minerva Anesthesiol	20	Sepsis (10 surgical and 10 medical patients)	65%	(100 – PC plasma level) x body weight (Kg)	According to plasma levels
Tuttolomondo A (20)	2008	Intern Emerg Med	2	Meningitis	100%	Various	Various
Schellongowski P (21)	2006	Vox Sang	≤8	Purpura fulminans	75%	Various	Various
Fourrier F (22)	2003	Intensive Care Med	≤5	Purpura fulminans	40%	100 IU/Kg	100 IU/Kg/day
Makris PE (23)	2003	J Thromb Haemost	7	DIC	71%	Various	Various
Vaccarella G (24)	2003	Minerva Anesthesiol	1	Purpura fulminans	100%	80 IU/kg	2000 IU every 4h * 4days
Rintala E (25,26)	2000; 1998	Critical Care Med	12	Purpura fulminans	58%	100 IU/Kg	100 IU/Kg every 6 hours
TOTAL			≤66		46/66=70%		

N = number of patients

DIC = Disseminated Intravascular Coagulopathy

maintain plasma PC activity between 70 and 120%. Baseline plasma PC activity was $34 \pm 9.1\%$. The average total dose received by the patients (starting bolus plus three-day infusion) was 19.065 IU. Baratto et al. observed a mortality of 35% while the predicted mortality based on SAPS II (55.1 ± 13.2) was 58.9%. Crivellari et al. (18) described their experience with the use of PCc after cardiac surgery. They observed a normalization of coagulative parameters in a cohort of nine patients with sepsis induced double organ failure, no drug related side effects, no hemorrhage and a 30 day mortality of 11%, when the predicted mortality at 30 days was 68% according to the SAPS II score. They administered a fixed dose of 50 IU/kg as a bolus followed by a continuous infusion at 3 IU/kg/h that lasted 72 hours. Baseline plasma PC activity was 33 ± 18.2 in our experience. The average total dose received by the patients (starting bolus plus three-day infusion) was 15650 IU. In 2003 Fourrier and al. (22) studied 15 patients (adults and children) admitted to intensive care unit (ICU) for a very severe form of meningococcal purpura fulminans. Patients were treated conjunctively with PC 100 IU/kg and 100 IU/kg AT III, followed by a maintenance dose of 100 and 100-150 IU/kg/day respectively of PC and AT III. That study mainly indicates that the dose regimen of AT and PC was not sufficient to compensate for the degree of consumption and/or inhibition of both coagulation inhibitors. Authors concluded that doses should be at least 150 IU/kg AT III and 250 IU/kg PC as a loading dose and 150 IU/kg and 200 IU/kg as daily maintenance, but taking into account the individual variability, repeated measurements of plasma levels of PC and AT III are mandatory to obtain a patient based adjustment of the supplementation. Nine of 15 patients studied (60%) died. In 2003 Makris and al. (23) treated 8 patients with an overt DIC status with PC concentrates as repeated boluses of 80-90 IU/kg every 6 h, as adjunctive therapy to treat the underlining DIC cause. Four patients had an infection

as the cause of DIC, 1 acute Wilson's disease, 3 hematological malignancies. All 8 patients had an amelioration of their DIC status that also affected mortality in 6 patients. In 2006 Schellongowsky et al. (21) reported the effect of PC administration in 8 adult patients affected by purpura fulminans. Five patients received 10 IU/kg as test dose, then a bolus of 100 IU/kg, then perfusion at 10 IU/kg/h; 3 patients received the same test dose, then 100 IU/kg every 6 h. Patients had a median APACHE II score of 18, the most frequent diagnosis was meningitis, the most frequent pathogen *N. meningitidis*. All patients had severe sepsis, 5 had septic shock. In all patients, during substitution PC values increased over supranormal values (range 100-200%) and coagulopathy could be controlled in seven cases. One patient died early, one at day 14 due to the onset of sepsis caused by invasive candidiasis. Two patients required amputation of one or more toes, one required skin necrosectomy. No adverse drug related events were observed. In 2007 Tuttolomondo et al. (20) described the use of PC in 2 patients. The first patient was a 78 year old man with pneumonia, not in septic shock but with a progressive worsening of clotting time and a severe risk of death (APACHE II score 33). Authors began early goal directed sepsis therapy and PC as a repeated bolus of 25-37.5 IU/kg with amelioration of clotting time. The patient survived and was discharged in good condition. The second patient was an 81 year old woman affected by a urogenital infection causing severe sepsis but not septic shock, at high risk of death (APACHE II score 31). Authors administered 15.3 IU/kg of PC, reported improvement of diuresis, consciousness and clotting time but the woman died of abrupt cardiac arrest. Vaccarella et al. (24) reported the use of PCc in an 18 y.o. patient who survived septic shock and purpura fulminans. The only randomized experience on PCc ever published is a dose finding study in a pediatric population that was not powered to show an effect on mor-

tality rate but did show a positive effect on sepsis induced coagulation disturbances. (11)

We hereby describe two case reports of adult patients who received PCc because they were at too high a risk of bleeding to receive rhAPC. Two male patients (69 year old patient A and 65 year old patient B) were admitted to the ICU of a teaching hospital because of septic shock (*E. coli* and *Enterococcus Faecium*) following urological surgery and chemotherapy with piasir-nopenia. In spite of aggressive medical therapy, based on the 2008 updated guidelines for the management of sepsis (1) and including norepinephrine after aggressive fluid resuscitation and renal replacement therapy, the patients developed progressive worsening of tissue perfusion with multiple organ failure and life threatening conditions. They received a PCc 6000 IU bolus followed by a continuous infusion of 200 IU/h for three days. PC values rose from less than 30 to more than 70% in both patients during the infusion. General conditions improved in both patients, they were discharged from the ICU with normal renal function and were alive at the 30 day follow up.

Conclusions

The published literature on the use of protein C concentrates in adult septic patients is encouraging (normalization of coagulative parameters, no bleeding complications and low 30 day mortality) even if limited to less than 70 patients, including those presented in this paper. While rhAPC evidenced an increased risk of bleeding complications in randomized controlled trials versus placebo, and registry studies report even higher bleeding rates than those present in the randomized controlled trials, (16-17) no bleeding complication has ever been reported following infusion of PCc in adults or children. Nonetheless, in order to recommend the use of PCc in the management of severe sepsis and septic shock it would be necessary to confirm these encouraging findings with a randomized multicenter controlled trial.

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