

Pulmonary septic shock with or without concomitant acute kidney injury. Does activated protein C make a difference?

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Abstract

Objective: Treatment with recombinant human activated protein C (APC) decreases mortality in patients with severe sepsis, mainly by faster resolving cardiorespiratory failure. Whether the concomitant presence of sepsis-induced acute kidney injury (AKI) could alter this beneficial effect, remains speculative. We investigated whether APC influenced outcome and evolution of sepsis-induced cardiorespiratory failure complicated by AKI.

Design: Open-label, randomized, controlled study.

Setting: 24-bed medical-surgical intensive care unit.

Patients: Patients with bilateral pneumonia-induced septic shock were enrolled and divided in two groups according to the presence (group A) or absence (group B) of AKI. Only patients with AKI, classified as “failure” according to the RIFLE criteria were included.

Interventions: All patients were adequately fluid-resuscitated, mechanically ventilated, and received norepinephrine treatment. APC was given as a

continuous infusion of 24 µg/kg/h for 4 days. Continuous venovenous hemofiltration at a rate of 35 ml/kg/h was started upfront in all patients of group A.

Measurements and results: 32 patients were available for analysis (group A; n=17 and group B; n=15). Oxygenation, vasopressor requirement, and renal outcome were evaluated daily during APC infusion. Catecholamine need could be lowered significantly in both groups but the decrease was more rapid and pronounced in group A. Oxygenation improved markedly in both groups. ICU mortality remained high and comparable between groups. All patients who remained oligo-anuric during APC treatment died.

Conclusions: We confirmed the previously reported beneficial effects of APC on respiratory and cardiovascular dysfunction in septic shock. ICU mortality was high but unaffected by concomitant AKI. Persistent oligo-anuria during APC infusion was associated with a poor prognosis.

Key words: Septic shock, acute kidney injury, activated protein C, organ failure.

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Introduction

Severe sepsis and septic shock are the most important causes of acute kidney injury (AKI) in critically ill patients. (1) The mortality rate of AKI complicating severe sepsis is about 30% higher as compared to that of non-septic AKI. (2) The PROWESS trial established that treatment with recombinant human activated protein C (APC, Xigris®, Eli Lilly Co, Indianapolis, IN, USA) increased survival in patients with severe sepsis, mainly by improving cardiovascular and respiratory organ function and by preventing or delaying the development of hematological dysfunction. (3) However, any clinical benefit of APC on sepsis-associated AKI remains speculative.

We conducted an observational study to investigate the effect of adding APC to a standardized sepsis resuscitation protocol on outcome of patients with pulmonary septic shock complicated by AKI.

Patients and methods

Patients with bilateral pneumonia and no pre-existing renal failure (i.e. normal baseline creatinine serum levels), who developed septic shock and received APC were studied prospectively. The study was approved by the hospital's ethical committee. Due to its observational nature in patients receiving standard treatment according to currently accepted guidelines, the need for informed consent was waived. All patients were mechanically ventilated under continuous analgesic sedation. Empiric broad spectrum antibiotic therapy was immediately started and adapted within 24 h according to culture results. Diuretics were not administered. Standard resuscitation treatment comprised fluids, vasopressor and (when needed) inotropic support, stress doses of hydrocortisone, red blood cell transfusion aiming at a hemoglobin level between 8 and 10 g/dL, insulin to maintain blood glucose <150 mg/dL, stress ulcer and deep venous thrombosis prophylaxis, and adequate nutrition. APC was given as a continuous infusion of 24 µg/kg/h for 96 h.

Patients were divided into two groups according to the presence (group A) or absence (group B) of AKI. AKI was defined according to the RIFLE criteria (4) as a twofold increase in serum creatinine and/or urine output <0.5 mL/kg/h following adequate fluid resuscitation (i.e. associated with maximal

cardiac output evaluated by repeated echocardiography). In all patients of group A, renal replacement therapy (RRT) was provided upfront after initial hemodynamic stabilization as continuous pump-driven veno-venous hemofiltration (CVVH, Baxter, BM25). A high-flux hemofilter was used, maintaining extracorporeal blood flow at 110 mL/min. Ultrafiltrate was replaced at a rate of 35 mL/kg/h by a bicarbonate buffered substitution solution.

Statistical analysis

Baseline balance for gender distribution, age, and APACHE II score between treatment groups was assessed with a Student's t test. A one-way analysis of variance for repeated measurements followed by Bonferroni test was used to assess the evolution in time of vasopressor use and oxygenation. A p value <0.05 was considered to be significant. All values were expressed as mean±SD.

Results

34 patients, recruited from the emergency and hospital wards, were included. Two patients -one in each group- developed significant bleeding during APC administration and were withdrawn from the study. The remaining thirty-two patients (group A; n=17 and group B; n=15) were available for final analysis. Patient characteristics and mortality are presented in **Table 1**. Within group A, 11 patients (65%) had both an urinary output <0.3 mL/kg/h and a serum creatinine level >4 mg/dL, 4 patients (23%) had a creatinine level above 4 mg/dL and a preserved diuresis and 2 subjects (12%) had a urinary output <0.3 mL/kg/h in the presence of creatinine levels below 4 mg/dL. Time from admission to start of RRT for the whole group was 6±2 h.

Mean daily norepinephrine dose decreased significantly in group A (from 0.28±0.28 µg/kg/min at d0 to 0.05±0.10 µg/kg/min at d4; p<0.001) and in group B (from 0.38±0.42 µg/kg/min at d0 to 0.09±0.17 µg/kg/min at d4; p<0.01). This decrease was more outspoken in patients with AKI during the first two days of APC treatment (**Figure 1**, upper panel). Oxygenation also improved markedly in both groups (from 119.2±36.6 mmHg at d0 to 225±65.5 mmHg at d4 in group A and from 128.5±45.4 mmHg at d0 to 231.8±75.9 mmHg at d4 in group B; both p<0.001) (**Figure 1**, lower panel).

Four patients (23.5%) in group A and two patients (13.3%) in group B died during APC infusion. In all of them, evolving organ failure was at the origin of demise. ICU mortality was high and comparable between groups (**Table 1**). Causes of death following treatment with APC were multi-organ failure (n=1), heart failure/cardiogenic shock (n=3), and new sepsis (n=3) in group A and multi-organ failure (n=3), heart failure/cardiogenic shock (n=1), and new sepsis (n=5) in group B. Eleven patients (85%) with baseline urine output <0.3 mL/kg/h remained oligo-anuric during APC infusion. ICU mortality in this cohort was 100%. Patients who either had normal diuresis upfront or who regained normal urine output during treatment had a better survival, respectively 50% (2/4) and 100% (2/2).

Discussion

Recovery from severe sepsis and septic shock is largely determined by fast resolution of concomitant organ failure. In a large number of patients enrolled in the control arm of two sepsis trials, early improvement of cardiovascular (p=0.001) and respiratory (p=0.05) failure was clearly related to survival. However, early recovery from AKI had the most significant (p<0.0001) beneficial impact on mortality. (5)

The pathophysiological processes underlying septic AKI are complex and incompletely understood. Given recent trends in sepsis resuscitation, including early and aggressive goal-directed treatment, renal hypoperfusion likely is of negligible importance. Rather, systemic inflammation, coagulation abnormalities, renal cell apoptosis, oxidative stress, endothelial dysfunction and microcirculatory damage are considered to be key players in causing AKI in the setting of sepsis. (6) These disturbances can all be potentially corrected by APC. (7) APC indeed reduced intrarenal inflammatory oxidative reactions, lowered endothelial permeability and increased renal blood flow in experimental ischemia/reperfusion (8) and significantly improved renal and peritubular capillary blood flow in endotoxin-shocked rats. (9)

We have recently demonstrated that APC did not influence fractional excretion of sodium, a surrogate marker for tubular necrosis, during septic shock. Also, tubulointerstitial histology was not significantly altered

by APC. (10) To now, none of the emerging “kidney-specific” serum or urinary biomarkers has been used to better define AKI or to follow its evolution during clinical sepsis. As a consequence, urine output and serum creatinine still constitute cornerstone parameters to evaluate renal function in this condition. Both variables form the basis of the recently proposed RIFLE criteria (4) which were developed to better define the spectrum of “renal failure” and to offer a classification according to its severity. The RIFLE “Injury” (“I”) and “Failure” (“F”) population is of particular relevance in sepsis-induced AKI. RIFLE “F” was identified as an independent predictor of hospital mortality in critically ill patients. If admission serum creatinine exceeded 1.5 mg/dL, mortality of RIFLE “F” patients was 25% higher as compared to RIFLE “I” subjects. (11) Maccariello et al studied 214 critically ill patients with acute renal failure, of whom 75% had sepsis as a contributing factor. In patients who received mechanical ventilation and vasopressors in addition to RRT, those classified as RIFLE “F” had a 90% overall hospital mortality. (12) Our study reported a somewhat lower mortality rate in both groups of patients with severe cardiorespiratory failure, regardless whether AKI was present or not. However, it is not clear to what extent resuscitation *in se*, early start of RRT, administration of APC, or a combination of these treatment modalities may have played a role. Still, we observed an invariably poor outcome in patients who remained oligo-anuric during the (sub) acute treatment phase.

We acknowledge important shortcomings and flaws of our study. Data were observational, the number of patients studied was small, urinary or plasma biomarkers of kidney injury were not measured, and the proportional effect of different components of the resuscitation protocol, including RRT, could not be estimated. However, our study population was relatively “balanced” since all patients belonged to the RIFLE “F” severity class, had normal renal function before developing sepsis, and systematically received early RRT during resuscitation.

Conclusions

Our study confirms the improvement of respiratory and cardiovascular function in septic shock that has been

previously ascribed to APC but offers only indirect evidence that the drug beneficially affects the compromised kidney. Currently proposed criteria for AKI classification may

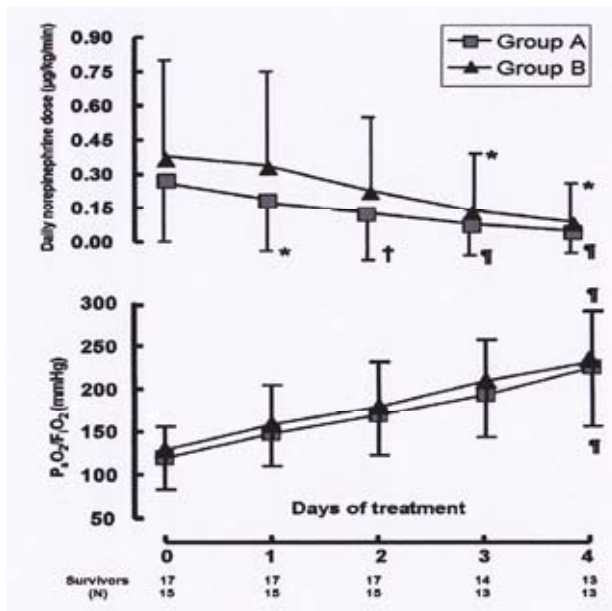
lack diagnostic, prospective, and clinical accuracy for substantiating a protective action of APC on the septic kidney.

Table 1. Patients' characteristics and mortality

	Group A (n=17)	Group B (n=15)
Gender (male/female)	13/4	11/4
Age (years±SD)	67±12	70±15
APACHE II (±SD)	30.9±9.9	29.7±7.8
Mortality during APC infusion (%)	23.5	13.3
ICU mortality (%)	70.6	73.3

Legend: No significant differences between groups. APC=activated protein C; ICU=intensive care unit; APACHE II=Acute Physiology and Chronic Health Evaluation score

Figure 1. Norepinephrine dose and oxygenation during APC treatment



Legend: Evolution of shock (upper panel) and respiratory failure (lower panel) during APC treatment. PaO₂/FiO₂=oxygenation index; * p<0.01; † p<0.05; ‡ p<0.001, as compared to d0; values are mean±SD

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