Journal of Critical Care (2011) **26**, 539–545

ELSEVIER

Journal of Critical Care

Sepsis/Septic Shock

Severe protein C deficiency is associated with organ dysfunction in patients with severe sepsis☆,☆☆

Andrew D. Shaw MB[a,*], George M. Vail MD[b], Douglas J. Haney PhD[b], Jin Xie MS[b], Mark D. Williams MD[b]

[a]*Department of Anesthesiology, Duke University, DUMC 3094, Durham, NC 27710, USA*
[b]*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, USA*

Keywords:
Sepsis;
Protein C;
Organ dysfunction;
SOFA;
Outcome

Abstract

Purpose: The aim of this study was to assess the relationship between protein C levels and temporal changes in organ dysfunction.

Materials and Methods: Using data from the placebo arm of Recombinant Human Activated *PRO*tein C *W*orldwide *E*valuation in *S*evere *S*epsis trial (N = 775), we compared the development of organ dysfunction over time, in adult severe sepsis patients with and without severe protein C deficiency.

Results: At study enrollment (baseline), patients with and without severe protein C deficiency were similar in age and likelihood of comorbidities. Patients with severe protein C deficiency had lower arterial blood pressure ($P = .0006$), greater serum creatinine concentration ($P < .0001$), elevated markers of thrombosis and inflammation, and impairment of fibrinolysis ($P < .0001$). The baseline PaO_2/FiO_2 ratio was not significantly different between the 2 groups. Seven days after study enrollment, cardiovascular and renal function remained significantly worse in patients with severe protein C deficiency ($P < .0001$), and respiratory dysfunction was greater ($P < .0001$). Baseline protein C deficiency was seen to be associated with subsequent pulmonary, renal, and hematologic organ failure.

Conclusions: Severe protein C deficiency in patients with severe sepsis is associated with both the incidence and severity of organ dysfunction and subsequent worsening of organ function and may be a useful predictor of organ failure in severe sepsis.

1. Introduction

Severe sepsis, defined as sepsis complicated by acute organ dysfunction, is a common and frequently fatal condition [1-3]. The estimated annual incidence of severe sepsis in the United States is 176 cases per 100 000 people, with a mortality rate between 30% and 50%. Systemic infection and the resulting inflammatory response may result in widespread endothelial injury and an accompanying hypercoagulation state with increased thrombus

☆ Financial support: This work was sponsored by Eli Lilly and Company.

☆☆ Competing interests: Author Ms. Xie is employed by and is a stockholder in Eli Lilly and Company. Drs. Vail, Haney, and Williams are previous employees of Eli Lilly and Company. Dr. Shaw has received speaker bureau and advisory board fees from Eli Lilly and Company.

* Corresponding author. Tel.: +1 919 286 6938; fax: +1 919 286 6853.
E-mail address: andrew.shaw@duke.edu (A.D. Shaw).

0883-9441/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jcrc.2011.05.006

formation in the systemic microcirculation. This, in turn, may lead to multiple-organ dysfunction and ultimately death [4-6].

The protein C (PC) pathway is known to play an integral role in the host response to infection [7]. Inflammation in sepsis reduces circulating levels of endogenous activated PC (APC), a key regulator of the procoagulant factors Va and VIIIa [8]. Multiple other factors are also thought to contribute to reduced APC levels in severe sepsis. These factors include decreased hepatic production of PC, increased consumption of PC, and loss of surface thrombomodulin and endothelial PC receptor, both of which are required for conversion of PC to APC on the vascular endothelial cell surface [9]. This reduction of APC results in disruption of the intricate balance between inflammatory and procoagulant regulators, creating a hypercoagulation state [10-14]. Previous studies have reported decreased plasma PC as an independent predictor of increased disease severity and mortality risk in critically ill patients [6,7,15-17], with Brunkhorst et al [15] establishing that PC deficiency was not only independently associated with mortality in a cohort of patients admitted to a surgical intensive care unit (ICU) but also correlated with the maximum sequential organ failure assessment (SOFA) score.

Severe PC deficiency at baseline was associated with greater 28-day all-cause mortality in the Recombinant Human Activated *PRO*tein C *W*orldwide *E*valuation in *S*evere *S*epsis (PROWESS) trial [6,7,17,18]. In addition, those patients in PROWESS [18] with severe PC deficiency derived a greater absolute mortality reduction with APC (drotrecogin alfa [activated]) than in patients without severe PC deficiency (13% vs 4%, Breslow-Day; P = .04). These data also suggest that PC may have utility as a biomarker of mortality and potential response to therapy but do not address the issue of whether or not low PC levels are associated with changes in organ function. This is an important issue because considerable resources are consumed in the management of organ failure for severe sepsis patients.

In the present study, data from patients randomized to the placebo arm of the PROWESS trial [18] were examined to test the hypothesis that severe PC deficiency was associated with both the incidence and severity of organ dysfunction in critically ill patients with severe sepsis over time. A cut point of one half the lower limit of normal (equivalent to ≤40% mean PC activity), prospectively defined in the PROWESS [18] trial, was used as an indicator of severe PC deficiency. It has previously been shown that PC levels less than half the lower limit of normal (equivalent to ≤40% mean activity) are associated with an increased risk of death [6]. Data relating to clinical and biochemical markers of organ function, thrombosis, inflammation, and antifibrinolysis were compared in patients with and without severe PC deficiency to explore whether measuring PC levels might be a useful biomarker of organ dysfunction in severe sepsis.

2. Materials and methods

2.1. Patients

The PROWESS trial, conducted at 164 study centers in 11 countries, evaluated the efficacy of a 4-day infusion of drotrecogin alfa (activated) (Xigris®; Eli Lilly and Company, Indianapolis, IN) vs placebo in patients with severe sepsis [18]. Data collected from this randomized, double-blind, placebo-controlled trial were used for the analyses reported in this study. Data from placebo-treated patients in whom PC values were assessed at baseline (N = 775) were analyzed to identify differences in indicators of disease severity, organ dysfunction, thrombosis, inflammation, and fibrinolysis according to whether or not patients exhibited evidence of severe PC deficiency at study enrollment. The PROWESS study was approved by the appropriate institutional review board at each participating study site, and informed consent was obtained for all patients. Patients were classified as having recent surgery if their surgery had occurred within the last 30 days. The following values were determined as previously described: SOFA scores, partial pressure of arterial blood O_2/fraction of inspired oxygen (PaO_2/FiO_2), and mean arterial pressure (MAP) [19].

2.2. Samples

Blood samples were obtained from patients at study enrollment (baseline) and on days 1 through 7 to assess PC activity (measured using Stago Staclot; Diagnostica Stago, Asnières, France), D-dimer (STA Liatest D-DI latex immunoassay), interleukin [IL]-6 and IL-8 (Quantikine Human IL-6 HS kit; R&D Systems, Minneapolis, MN), platelet count, prothrombin time (STA-Neoplastine CI plus; Diagnostica Stago), activated partial thromboplastin time (STA-APTT kit; Diagnostica Stago), thrombin-antithrombin complex (enzyme immunoassay; Behring Diagnostics, Westwood, MA), prothrombin fragment F1.2 (enzyme immunoassay; Behring Diagnostics), plasminogen activity (Stachrom Plasminogen; Diagnostica Stago), and plasminogen activator inhibitor 1 (PAI-1; Stachrom PAI; Diagnostica Stago) as previously described [4,5]. All measurements were performed by a central laboratory (Covance Central Lab Services, Indianapolis, IN). Serum creatinine, aspartate aminotransferase, and alanine aminotransferase were assessed using routine methodology as previously described [4,5].

2.3. Statistical methods

Data for categorical variables were summarized using percentages, and comparisons across groups were performed using Pearson χ^2 test. Data for continuous biomarkers were summarized using medians and associated interquartile ranges. P values for tests of differences in continuous