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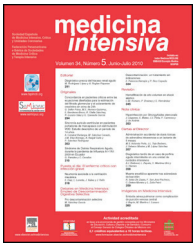

ORIGINAL

Protein C zymogen in adults with severe sepsis or septic shock

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KEYWORDS
Protein C zymogen;
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Abstract
Introduction: Activated protein C is associated with a risk of bleeding and its effects on survival in septic shock patients are questionable. Protein C zymogen has no risk of bleeding and improves the outcome of patients with septic shock. We hereby describe the largest published case series of adult patients receiving protein C zymogen.
Design, setting and participants: A prospective study on 23 adult patients with severe sepsis or septic shock, two or more organ failures and at high risk for bleeding, treated with protein C zymogen (50 IU/kg bolus followed by continuous infusion of 3 IU/kg/h for 72 h).
Results: The *Z*-test evidenced a significant reduction between the expected mortality (53%) and the observed mortality 30% (*Z* value = 1.99, $p = 0.046$) in our sample population. Protein C levels increased from 34 ± 18% to 66 ± 22% at 6 h after PC bolus ($p < 0.001$), and kept on increasing during 72 h of administration ($p < 0.001$ to baseline). Sequential Organ Failure Assessment (SOFA), score of organ dysfunction, decreased from baseline to 7 days after administration of protein C from 14 ± 2 to 7 ± 4 ($p < 0.001$). No adverse event drug related was noted.
Conclusion: Protein C zymogen administration is safe and its use in septic patients should be investigated through a randomized controlled trial.

PALABRAS CLAVE
Zimógeno de proteína C;
Hemorragia;
Sepsis;
Cuidados intensivos;
Cuidados críticos

Zimógeno de proteína C en adultos con sepsis grave o choque séptico

Resumen
Introducción: La proteína C activada se asocia a un elevado riesgo de hemorragia, y sus efectos sobre la supervivencia en los pacientes con choque séptico son cuestionables. El zimógeno de proteína C no presenta ningún riesgo de hemorragia, y mejora los resultados en los pacientes con choque séptico. Describimos la serie de casos más amplia publicada de pacientes adultos tratados con zimógeno de proteína C.
Diseño, ámbito y participantes: Se ha llevado a cabo un estudio prospectivo en el que han participado 23 adultos con sepsis grave o choque séptico, 2 o más fallos orgánicos, y un elevado riesgo de hemorragia, tratados con zimógeno de proteína C (dosis en bolo de 50 UI/kg seguida de una infusión continua de 3 UI/kg/h durante 72 h).

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Resultados: La prueba Z puso de manifiesto una disminución significativa entre la mortalidad prevista (53%), y la mortalidad observada 30% (valor Z = 1,99; p = 0,046) en nuestra serie. Las concentraciones de proteína C incrementaron de 34 ± 18% a 66 ± 22% a las 6 h de la dosis en bolo (p < 0,001), y siguieron incrementando durante las 72 h siguientes a la administración (p < 0,001 respecto a la situación basal). La puntuación en la evaluación secuencial del fallo orgánico (SOFA) disminuyó entre la situación basal, y 7 días después de la administración de proteína C de 14 ± 2 a 7 ± 4 (p < 0,001). No se registraron reacciones farmacológicas adversas.
Conclusión: El zimógeno de proteína Z debería investigarse su utilización en los pacientes con sepsis mediante un estudio aleatorizado y controlado.

Introduction

Severe sepsis and septic shock are life-threatening medical emergencies and are among the most significant challenges in critical care. Mortality rates approach 30–50%, and can be as high as 90% when multiple organ dysfunctions ensue.[1,2] Improvement in survival rates was achieved through early broad-spectrum antibiotic administration, organ supportive therapy, and, until recently, through Recombinant Human Activated Protein C (rhAPC) in selected patients at low risk of bleeding. A recent randomized study showed that rhAPC did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock.[3]

Protein C (PC) is the vitamin K-dependent zymogen of a serine protease with antithrombotic, anti-inflammatory, and profibrinolytic properties.[4] Due to its action on the coagulation pathway, rhAPC, the active form of drug, exposes treated patients to a serious hemorrhagic risk[5–8] and its administration was subject to careful evaluation of the risk-to-benefit ratio. Attempts were made to use protein C zymogen, its ''inactive'' precursor, endowed with anti-inflammatory activity but devoid of anticoagulant properties. Among its advantages, PC is activated ''on demand'' in sites of major thrombin formation, and this is expected to limit or eliminate unwanted bleeding.

Few case series have been published on adult septic patients receiving protein C zymogen. We hereby describe the largest case series of adult patients with severe sepsis or septic shock receiving PC in a single center.

Patients and methods, setting and study population

After ethical committee approval and with patients' written consent, we collected data from 23 adult patients with severe sepsis or septic shock admitted to two intensive care units (ICU) of San Raffaele Scientific Institute over a 2-year period. Eleven of these 23 patients were already reported in other publications.[9,10] Inclusion criteria were represented by age >18 years, diagnosis of severe sepsis (acute organ dysfunction secondary to documented or suspected infection) or septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) and two or more organ failures due to sepsis of recent onset (less than 48 h); contraindication to receive rhAPC (recent major surgery in most patients); being admitted in the ICU. Exclusion criteria were represented by known allergy to the study product and inclusion in other studies.

In addition to current standard-of-care therapies for severe sepsis and septic shock, patients received PC concentrates (Ceprotin®, Baxter, Wien) administered as a starting bolus (50 IU/kg) plus a 3 IU/kg/h continuous infusion over 72 h.

We measured plasma PC activity, prothrombin time (PT), activated partial thromboplastin time (aPTT), Platelets (PLTs), C-reactive protein (CRP), white cell count (WBC), D-dimer and fibrinogen (FG) values at baseline, at 6 and 12 h after PC concentrate administration, then every 12 h for 60 h. The sequential organ assessment failure (SOFA) score, the Acute Physiology and Chronic Health Evaluation (APACHE II) score, and the simplified acute physiology score (SAPS II) were recorded at baseline (when patient received PC zymogen), daily for 7 days.

Laboratory methods

Serial venous samples (4.5 ml) were collected in siliconized Vacutainer tubes (Becton-Dickinson, Plymouth, UK) containing (0.5 ml) tri-sodium citrate (0.129 M) and in tubes containing 0.5 ml of a mixture of tri-sodium citrate and benzamidine–HCl (200 mM) at the following times: before the bolus dose, 6 h after bolus and every 12 h thereafter up to 72 h. Within 1 h from collection, platelet poor plasma was obtained by centrifugation for 10 min at 2000 × *g* at room temperature. PT (Hemoliance Recombiplastin, Instrumentation Laboratory, Lexington, MA), aPTT (STA aPTT Kaolin, Diagnostica Stago, Asnier sur Seine, France), FG (clotting assay, STA Fibrinogen, Stago), and D-dimer (STA Liatest D-D, Stago) determinations were performed on fresh citrated plasma samples with an automated coagulometer (STA, Stago). Plasma aliquots were snap-frozen with methanol and dry ice and stored at −70 °C for additional measurements in citrated plasma of PC anticoagulant activity (STA Protein C, Stago), and antithrombin (amidolytic activity, STA Antithrombin, Stago). Blood samples collected in tri-sodium citrate and benzamidine–HCl were also centrifuged as described above with plasma aliquots snap-frozen and stored at −70 °C. Within one month, prothrombin fragment 1 + 2 (F1 + 2, Enzygnost F1 + 2, Dade-Behring, Marburg) and thrombin-antithrombin III complex (TAT Enzygnost TAT