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Working

Cortisol and adrenal androgens as independent predictors of mortality in septic patients_protocol

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ABSTRACT

Objective: To determine the prognostic value of cortisol, Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone-sulfate (DHEAS), together with their ratios (cortisol/DHEA and cortisol/DHEAS), as independent predictors of mortality in septic patients.

Methods: Prospective cohort study of 139 consecutive patients with a diagnosis of severe sepsis or septic shock. Adrenal hormones were determined within the first 24 hours of the septic process. To determine and compare the predictive ability of each marker for the risk of unfavorable evolution (in-hospital, 28-day and 90-day mortality), ROC (Receiver Operating Characteristic) curves were constructed and the area under the curve (AUC) was determined. As measures of association, adjusted odds ratios (OR) with their 95% confidence intervals (95%CI) were estimated by unconditional logistic regression. Cortisol, DHEA and DHEAS results were compared to lactate, CRP, SOFA and APACHE II Scores.

Results: Cortisol showed the best predictive ability, with AUCs of 0.758, 0.759 and 0.705 for in-hospital mortality, and 28-day and 90-day mortality, respectively; whereas AUCs for 28 days mortality for SOFA and APACHE II scores, and other biomarkers studied, such as Lactate or CRP, were 0.644, 0.618, 0.643 and 0.647, respectively. Associations between high cortisol levels (>17.5 µg/dL) and mortality were strong and statistically significant for in-hospital and 28-day mortality: adjusted ORs 10.13 and 9.45 respectively, and lower for long term mortality (90 days): adjusted OR 4.26 (95% CI 1.34-13.56), p trend 0.014.

Regarding adrenal androgens, only positive associations were obtained for DHEAS and most of these positive associations did not yield statistical significance.

Regarding Cortisol/DHEA and cortisol/DHEAS ratios, they did not improve the predictive ability of cortisol. The only exception was the cortisol/DHEAS ratio, which was the best predictor of mortality at 90 days (AUC 0.737), adjusted OR for highest cortisol/DHEAS ratio values 6.33 (95%CI 1.77-22.60), p trend 0.002.

Conclusion: Basal cortisol measured within the first 24 hours of the septic process was the best prognostic factor for in-hospital and 28-day mortality, even superior to the Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. The cortisol/DHEAS ratio was an independent predictor of long-term mortality

EXTERNAL LINK

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THIS PROTOCOL ACCOMPANIES THE FOLLOWING PUBLICATION

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PROTOCOL STATUS

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GUIDELINES

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[2] Dellinguer RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: International Guidelines for Manegement of Severe Sepsis and Septic Schock: 2012. Crit Care Med. 2013;41 (2): 580-637.

MATERIALS TEXT

In a prospective cohort study conducted in the ICU of the Sierrallana Hospital in Torrelavega (Spain), we analyzed serum samples from 139 consecutive patients included in the first 24 hours of severe sepsis or septic shock diagnosis, between November 2011 and December 2017.
The inclusion criteria consisted of patients aged 18 years or older and admitted to the ICU within 24 hours after diagnosis of severe sepsis or septic shock, according to the 2001 International Sepsis Definitions Conference [1].
The exclusion Criteria were: patients who received corticosteroid treatment or who were treated with drugs that affect adrenal function within a six month period prior to admission; patients with known HPA axis disease or adrenal insufficiency (AI); patients with acute liver failure or chronic stage Child-Pugh B or C liver disease.
All patients included in the study were treated according to the recommendations of the Surviving Sepsis Campaign 2012 guidelines [2].
Either the patient or a responsible family member signed the informed consent form. The study was approved by the Clinical Research Ethics Committee of Cantabria (CEIC).

Determination of specific parameters:

CRP: Serum quantification by automated turbidimetric immunoassay on an Architect cSystems Analyzer (ABBOTT Diagnostics, Wiesbaden, Germany). Analytical sensitivity: 0.5 mg/L. Method inaccuracy is <5%. Normal values <5.0mg/L.
Arterial Lactate: Sample collected without compressor with heparinized syringe for gasometry and transported cold. Quantification by specific electrode potentiometry test on a GEM series analyser (Werfen Diagnostic Solutions for Life, Barcelona, Spain). Imprecision 6.3%. Analytical sensitivity from 0.5 to 10 mmol/L. Normal values <1.6 mmoL/L.
Cortisol: For the determination of total cortisol, the chemiluminescent immunoassay of microparticles ARCHITECT (Abbot, Wiesbaden, Germany), was used, which has a sensitivity ≤ 1 (µg/dL), and a specificity of 0-0.9%, determined by studying the cross-reactivity of compounds whose chemical structure or simultaneous use could interfere with Abbott's ARCHITECT Cortisol assay, except for fludrocortisone (36.6%) and prednisolone (12.3%).
DHEAS: Serum quantification using competitive chemiluminescent enzyme immunoassay in solid phase in a Siemens IMMULITE2000 (SiemensHealthCareDiagnostics, Gwynedd, UK). Sensitivity: 10 g/dL. Specificity: Cross-reactivity <0.1% with related steroids: DHEAS, Aldosterone, Androstenedione, Cortisol, Estradiol, Estriol, Progesterone and Testosterone. The intra-assay reproducibility of the method is 7.1% and the interassay is 9.8%. Reference values by age and sex.
DHEA: Serum quantification by DRG specific Radioimmunoassay (DRG Instruments, Marburg, Germany). Sensitivity: 0.06 ng/ml. Specificity: Very low cross-reactivity <0.001% with DHEAS, Isoandrosterone, Androstenedione and other related steroids. Intra-assay reproducibility of the method is <3.8% and interassay is <8.6%. Reference values by age and sex.

SAFETY WARNINGS

1 The collection of blood samples was performed in all cases between 8:00 a.m. and 9:00 a.m.

2 Patients did not ingest any food in the previous 10 hours.

3 Blood samples were then collected in silicone-vacuum tubes with a silica gel filter without anticoagulant to obtain serum, as well as a venous extraction syringe obtained without a compressor and placed in cold quickly for the specific determination of lactate.

4 All samples were stored before, during and after extraction at a temperature of 0-12ºC. All samples were processed within one hour of extraction. The serum tubes were left to coagulate for 20-30 minutes and then centrifuged at 2000g at room temperature.

5 General biochemical measurements were performed on the same day as the extraction. The serum to be used for the determination of specific hormonal parameters (DHEA and DHEAS) was distributed in properly identified cryotubes and frozen from -40ºC to -60ºC until further processing.

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