analesdepediatría

www.analesdepediatria.org

ORIGINAL ARTICLE

Citrulline and arginine kinetics and its value as a prognostic factor in pediatric critically ill patients☆,☆☆

J. Blasco-Alonso[a,*], P. Sánchez Yáñez[b], V. Rosa Camacho[b], J.M. Camacho Alonso[b], R. Yahyaoui Macías[c], R. Gil-Gómez[b], G. Milano Manso[b,d]

[a] *Pediatric Gastroenterology, Hepatology and Nutrition Unit, Department of Pediatrics, Materno-Infantil Hospital, Málaga, Spain*
[b] *Pediatric Critical Care and Emergency Unit, Materno-Infantil Hospital, Málaga, Spain*
[c] *Laboratory Department, Carlos Haya Children's Hospital, Málaga, Spain*
[d] *IBIMA Group Pediatría Integral, Spain*

Received 3 July 2014; accepted 28 October 2014
Available online 30 March 2015

KEYWORDS
Citrulline;
Arginine;
Systemic inflammatory response syndrome;
Critical illness;
Pediatrics

Abstract
Introduction: Low concentrations of plasma citrulline and arginine have been reported in children under various pathological conditions. Hypothesis: Plasma citrulline and arginine levels undergo different kinetics during the early days of critical illness in children according to the severity of symptoms and can be correlated with other clinical and laboratory parameters associated with the SIR.
Patients and methods: A single-center prospective observational study was done in patients aged 7 days to 14 years admitted to PICU. Citrulline and arginine blood levels (blood in dry paper, analysis by mass spectrometry in tandem), acute phase reactants and clinical data were collected on admission, at 12 h, 24 h, 3 and 7 days.
Results: Forty-four critically ill patients were included and the control group was formed by 42 healthy children. The citrulline and arginine kinetic analysis showed: (1) citrulline falls significantly ($p < 0.05$) at 12 h of admission; levels remain low until day 7 and begin progressive increase again; (2) arginine is already lowered at 6 h, although an earlier rise occurs (3rd day); and (3) the decrease of citrulline in the first three days of admission positively correlates with arginine kinetics. Bivariate analysis showed: (1) correlation of elevated citrulline on the 7th day with shorter duration of mechanical ventilation, lower PICU stay and lower occurrence of complications. The levels of citrulline still descended at day 7 are associated with increased CRP/procalcitonin elevation at first 24 h; (2) the greatest decrease of arginine in the first 12 h is associated with a longer PICU stay and greater number of complications and increase of acute phase reactants at 3 days.

☆ Please cite this article as: Blasco-Alonso J, SánchezYáñez P, Rosa Camacho V, Camacho Alonso JM, Yahyaoui Macías R, Gil-Gómez R, et al. La cinética de la citrulina y la arginina y su valor como factor pronóstico en pacientes pediátricos críticamente enfermos. An Pediatr (Barc). 2015;83:257–263.

☆☆ Presentation: Presentations of preliminary data at Spanish Society of Critical Care, (SECIP) in the National Congress held in Pamplona on May 2013.

* Corresponding author.
E-mail address: javierblascoalonso@yahoo.es (J. Blasco-Alonso).

Conclusions: There are decreased levels of arginine and citrulline in the first days at PICU, with recovery at the 3rd and 7th day respectively, and a relationship between a greater decrease and a worse outcome and between a longer income and a higher serum CRP/procalcitonin.

PALABRAS CLAVE
Citrulina;
Arginina;
Síndrome de respuesta inflamatoria sistémica;
Enfermedad crítica;
Pediatría

La cinética de la citrulina y la arginina y su valor como factor pronóstico en pacientes pediátricos críticamente enfermos

Resumen
Introducción: Se ha documentado bajas concentraciones de citrulina y arginina plasmáticas en niños en diversas condiciones patológicas. Hipótesis: La cinética de citrulina y arginina plasmáticas durante la enfermedad crítica pediátrica se correlaciona con parámetros evolutivos clínicos y bioquímicos.
Pacientes y métodos: Estudio observacional unicéntrico prospectivo en pacientes de 7 días a 14 años ingresados en unidad de cuidados intensivos pediátricos (PICU). Los datos bioquímicos y clínicos fueron recogidos al ingreso, a las 12 h, a las 24 h, al 3° y al 7° día.
Resultados: 44 pacientes críticamente enfermos fueron incluidos y un grupo control de 51 niños sanos. La citrulina desciende de forma significativa ($p < 0,05$) a las 12 h de ingreso con niveles bajos mantenidos hasta el día 7, comenzando un aumento progresivo después. La arginina ya está descendida a las 6h, aunque tiene una subida más precoz (día 3). La disminución de citrulina al tercer día se correlaciona directamente con la arginina. Hay correlación entre la elevación de la citrulina al séptimo día con menor duración de ventilación mecánica, menor estancia en (PICU) y menos complicaciones. Los niveles de citrulina aún descendidos el día 7 se asocian con un mayor aumento de PCR y procalcitonina en primeras 24h. La disminución de arginina en las primeras 12h se correlaciona inversamente con estancia más larga, mayor número de complicaciones y aumento de reactantes de fase aguda en día 3.
Conclusiones: Hay disminución de arginina y citrulina en los primeros días de la enfermedad crítica, con recuperación al tercero y séptimo día, respectivamente, y existe una relación entre mayor disminución y peor evolución.

Introduction

Citrulline is a non-protein amino acid produced by the intestinal mucosa from glutamine and amino acid derivatives.[1] Arginine is a conditionally essential amino acid and the most abundant nitrogen carrier in our body; it is obtained from dietary sources and endogenously synthesized in the kidney from citrulline in the urea cycle.[2] Arginine has secretagogue (insulin, IGF-I, glucagon, prolactin), and timotrophic (increased production of lymphocytes and macrophages) effects. It is a precursor of various molecules of great importance in the compensatory mechanisms involved in the systemic inflammatory response syndrome (SIRS) as well, through specific enzymes with different functions, such as: arginase, arginine–glycine aminotransferase and nitric oxide synthase (NOS).

In systemic inflammatory response syndrome (SIRS) situations, an increased activity in inducible NOS (iNOS) calcium independent has been demonstrated. This leads, through vasodilation, to hypotension and septic shock; peroxynitrils released within this context generate tissue damage and myocardial depression. Activation of the inducible isoform causes arginine depletion which limits their availability and the activity of T cells leading to reduced response to infection. Recent reviews on intestinal barrier dysfunction have explored how the intestine, both as culprit and victim, influences the pathophysiology of SIRS.[3]

The gut is hypothesized to play a central role in the pathophysiology of critical illness and is frequently called the ''motor'' of the systemic inflammatory response. Perturbations to the intestinal barrier can lead to distant organ damage and multiple organ dysfunction syndrome (MODS). Small intestinal function in critically ill patients should ideally be assessed in order to determine the preferred feeding route, timing, and composition of enteral nutrition. Additionally, evaluation of small bowel function may lead to new insights aimed to maintain enterocyte integrity. Critically ill patients are likely to have impaired enterocyte function mainly as a consequence of diminished splanchnic blood flow associated with mucosal hyperpermeability and bacterial translocation, a pathological state believed to be pivotal in the development of sepsis and MODS.[4]

Low plasma citrulline and arginine concentrations have been described in children with various pathological