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ORIGINAL ARTICLE

High levels of atrial natriuretic peptide and copeptin and mortality risk☆

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Abstract
Objective: To determine whether high levels of mid-regional pro-atrial natriuretic peptide (MR-proANP), copeptin, and procalcitonin (PCT) plasma concentrations are associated with increased mortality risk.
Methods: Prospective observational study including 254 critically ill children. MR-proANP, copeptin and PCT were compared between children with high (Group A; $n = 33$) and low (Group B; $n = 221$) mortality risk, and between patients with failure of more than 1 organ (Group 1; $n = 71$) and less than 2 (Group 2; $n = 183$).
Results: Median (range) of MR-proANP, copeptin, and PCT levels in group A vs B were, respectively: 209.4 (30.5–1415.8) vs. 75.0 (14.6–867.2) pmol/L ($P < .001$); 104.4 (7.4–460.9) vs. 26.6 (0.00–613.1) pmol/L ($P < .001$), and 7.8 (0.3–552.0) vs. 0.3 (0.02–107.0) ng/mL ($P < .001$). The area under the curve (AUC) for the differentiation of group A and B was 0.764 (95% CI: 0.674–0.854) for MR-proANP; 0.735 (0.642–0.827) for copeptin, and 0.842 (0.744–0.941) for PCT, with no statistical differences. The AUCs for the differentiation of group 1 and 2 were: 0.837 (0.784–0.891) for MR-proANP, 0.735 (0.666–0.804) for copeptin, and 0.804 (0.715–0.892) for PCT, with statistical differences between MR-proANP and copeptin, $P = .01$.

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Conclusions: High levels of MR-proANP, copeptin and PCT were associated with increased mortality risk scores. MR-proANP showed a higher association than copeptin with number of organs in failure.
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PALABRAS CLAVE
Riesgo de mortalidad;
Fallo de órganos;
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Asociación de valores elevados de péptido natriurético auricular y copeptina con riesgo de mortalidad

Resumen
Objetivo: Determinar si los niveles plasmáticos de región media del péptido natriurético proauricular (RM-proPNA), copeptina y procalcitonina (PCT) se asocian con aumento del riesgo de mortalidad.
Métodos: Estudio prospectivo observacional que incluyó a 254 niños críticamente enfermos. Se compararon los niveles de RM-proPNA, copeptina y PCT entre niños con alto (grupo A; n = 33) y bajo (grupo B; n = 221) riesgo de mortalidad y entre pacientes con un número de órganos en fallo mayor de 1 (grupo 1; n = 71) y menor de 2 (grupo 2; n = 183).
Resultados: Las medianas (rangos) de RM-proPNA, copeptina y PCT en grupo A vs. grupo B fueron, respectivamente: 209,4 (30,5-1.415,8) vs. 75,0 (14,6-867,2) pmol/l (p < 0,001); 104,4 (7,4-460,9) vs. 26,6 (0,00-613,1) pmol/l (p < 0,001) y 7,8 (0,3-552,0) vs. 0,3 (0,02-107,0) ng/ml (p < 0,001). El área bajo la curva (AUC) para diferenciar grupo A y B fue (intervalo de confianza del 95%): 0,764 (0,674-0,854) para RM-proPNA; 0,735 (0,642-0,827) para copeptina y 0,842 (0,744-0,941) para PCT, sin diferencias significativas. Las AUC para diferenciar los grupos 1 y 2 fueron: 0,837 (0,784-0,891) para RM-proPNA, 0,735 (0,666-0,804) para copeptina y 0,804 (0,715-0,892) para PCT, con diferencias significativas entre RM-proPNA y copeptina, p = 0,01.
Conclusiones: Los niveles elevados de RM-proPNA, copeptina y PCT se asocian con aumento de las puntuaciones de riesgo de mortalidad. RM-proPNA mostró mayor asociación que la copeptina con el número de órganos en fallo.
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Introduction

Determining the prognosis of a critically ill child within 12 h from admission in the paediatric intensive care unit (PICU) continues to be a clinical challenge. At present, the tools used most frequently to assess risk of mortality are scales based on clinical signs and routine laboratory tests. The abnormalities found in different sections of these scales give rise to a score that correlates to mortality in patients. The scales used most frequently are the Paediatric Risk of Mortality III (PRISM III) and the Paediatric Index of Mortality 2 (PIM 2).[1–5]

In recent years, it has been demonstrated that there are biomarkers whose plasma levels increase in relation to disease severity. Procalcitonin (PCT) emerged as a marker of sepsis[6] and later on was found to be helpful in determining disease severity and predicting patient outcomes.[7] Procalcitonin could help identify children at a higher risk of mortality.[8] There is also evidence that atrial natriuretic peptide (ANP) and copeptin are associated with severity in septic patients and mortality in critically ill adults.[9–16] The secretion of ANP is primarily determined by increases in atrial wall tension,[17] and it modulates the permeability of the endothelium, acting on the regulation of blood volume and arterial pressure.[18] Arginine vasopressin (AVP) is secreted in response to osmotic or haemodynamic stimuli. Copeptin is the C-terminal portion of provasopressin.[19–21] It has been regarded as an individual marker of the stress response[22] that is elevated during systemic infections.[23] Its levels have been associated with mortality risk in adult patients.[13,24,25]

Laboratory tests for measuring the levels of midregional pro-ANP (MR-proANP) and copeptin have recently become available. These peptides are synthesised from ANP and AVP, respectively, but they offer the advantage of having a longer half-life (ANP, 5–10 min vs MR-proANP, 100–120 min; AVP, 5–10 min vs copeptin, ex vivo, several days), which makes them more suitable for everyday clinical practice.[10,17,26]

We thought it would be interesting to learn whether the association described in adults is also found in children, as thus far no data have been published on the association of these markers with an increased risk of mortality in paediatric patients. Thus, the aim of our study was to determine the levels of MR-proANP, copeptin and PCT in the first 12 h following admission to the PICU to test the hypothesis that elevated levels of these markers could be associated with an increased risk of mortality. A secondary objective was to evaluate the hypothesis

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