Med Clin (Barc). 2017;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Original article

Plasmatic levels of N-terminal pro-atrial natriuretic peptide in preeclamptic patients and healthy normotensive pregnant women☆

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ARTICLE INFO

Article history:
Received 4 April 2017
Accepted 29 June 2017
Available online xxx

Keywords:
N-terminal pro-atrial natriuretic peptide
Atrial natriuretic peptide
Preeclampsia
Pregnancy

ABSTRACT

Background and objective: To compare plasma N-terminal pro-atrial natriuretic peptide concentrations in preeclamptic patients and healthy normotensive pregnant women.
Methods: A cases–controls study was done with 180 patients at Hospital Central Dr. Urquinaona, Maracaibo, Venezuela, that included 90 preeclamptic patients (group A; cases) and 90 healthy normotensive pregnant women selected with the same age and body mass index similar to group A (group B; controls). Blood samples were collected 1 h after admission and prior to administration of any medication in group A to determine plasma N-terminal pro-atrial natriuretic peptide and other laboratory parameters.
Results: Plasma N-terminal pro-atrial natriuretic peptide concentrations in group A (mean 1.01 [0.26] pg/ml) showed a significant difference when compared with patients in group B (mean 0.55 [0.07] pg/ml; $p < 0.001$). There was no significant correlation with systolic and diastolic blood pressure values in preeclamptic patients (p = ns). A cut-off value of 0.66 ng/ml had an area under the curve of 0.93, sensitivity of 87.8%, specificity of 83.3%, a positive predictive value of 84.0% and a negative predictive value of 87.2%, with a diagnostic accuracy of 85.6%.
Conclusion: Preeclamptic patients have significantly higher concentrations of plasma N-terminal pro-atrial natriuretic peptide compared with healthy normotensive pregnant women, with high predictive values for diagnosis.

Concentraciones plasmáticas de fragmento N-terminal del propéptido natriurético auricular plasmático en pacientes con preeclampsia y embarazadas normotensas sanas

Palabras clave:
Fragmento N-terminal del propéptido natriurético auricular
Péptido natriurético auricular
Preeclampsia
Embarazo

RESUMEN

Fundamento y objetivo: Comparar las concentraciones plasmáticas del fragmento N-terminal del propéptido natriurético auricular en pacientes con preeclampsia y embarazadas normotensas sanas.
Métodos: Se realizó un estudio de casos y controles con 180 embarazadas en el Hospital Central Dr. Urquinaona, de Maracaibo (Venezuela), que incluyó 90 pacientes con preeclampsia (grupo A; casos) y un grupo de control seleccionado por tener una edad y un índice de masa corporal similares al grupo A,

☆ Please cite this article as: Reyna-Villasmil E, Mejia-Montilla J, Reyna-Villasmil N, Mayner-Tresol G, Herrera-Moya P, Fernández-Ramírez A, et al. Concentraciones plasmáticas de fragmento N-terminal del propéptido natriurético auricular plasmático en pacientes con preeclampsia y embarazadas normotensas sanas. Med Clin (Barc). 2018. https://doi.org/10.1016/j.medcli.2017.06.064

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el cual consistió en 90 embarazadas normotensas sanas (grupo B; controles). Las muestras de sangre se tomaron una hora después del ingreso y antes de la administración de cualquier medicamento en el grupo A para determinar las concentraciones plasmáticas del fragmento N-terminal del propéptido natriurético auricular y otros parámetros de laboratorio.
Resultados: Las concentraciones plasmáticas del fragmento N-terminal del propéptido natriurético auricular entre las pacientes del grupo A (media 1,01 [DE 0,26] pg/ml) mostraron diferencias significativas comparadas con las pacientes del grupo B (media 0,55 [DE 0,07] pg/ml; p < 0,001). No se observaron correlaciones significativas con los valores de presión arterial sistólica y diastólica en las pacientes con preeclampsia (p = ns). Un valor de corte de 0,66 ng/ml presentó un valor por debajo de la curva de 0,93, una sensibilidad del 87,8%, una especificidad del 83,3%, un valor predictivo positivo del 84,0% y un valor predictivo negativo del 87,2%, con una exactitud diagnóstica del 85,6%.
Conclusión: Las pacientes con preeclampsia presentaron concentraciones plasmáticas significativamente más altas del fragmento N-terminal del propéptido natriurético auricular al compararlo con embarazadas normotensas sanas, con altos valores predictivos para el diagnóstico.

Introduction

Preeclampsia, defined as the *de novo* appearance of hypertension and proteinuria after 20 weeks of pregnancy, affects 7–10% of pregnancies. Its pathophysiology remains unknown. However, immunological factors have been suggested as the origin of placentation disorders that lead to inadequate transformation of the maternal spiral arteries.[1] All these disorders produce an increase in oxidative stress with the release of circulating factors that cause an excessive and widespread maternal inflammatory response.[2,3]

The levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide increase in response to cardiac overload. The physiological function of these peptides is to increase natriuresis and diuresis, improving capillary permeability and dilating peripheral vasculature. The ANP is synthesized and secreted mainly by the atria of the adult heart. During circulation it is divided by a protease in N-terminal fragment of the pro-atrial natriuretic peptide (NT-ProANP) and the biologically active molecule.[4,5]

Previous studies of maternal circulation ANP during pregnancy-induced hypertension show contradictory results, with reports of increased levels[6] while others did not find variations[7] when compared with those of normotensive pregnant women. However, ANP is unstable and the different tests used may underestimate plasma levels due to the early degradation of the precursor molecule.[8–13] For clinical purposes, NT-ProANP is a marker of abnormal diastolic or systolic function and structural changes of the left ventricle, especially in chronic heart failure in non-pregnant women.[9]

There is no consensus in the medical literature about whether there is an increase or not in the levels of ANP and its fragments in preeclampsia. To clarify the possible role of NT-ProANP in the pathophysiology of preeclampsia, a study was designed to compare the plasma levels of NT-ProANP in preeclamptic patients and healthy normotensive pregnant women.

Materials and methods

The present research was a case–control study conducted between January 2014 and February 2016 that included women with singleton pregnancies who were treated at the Dr. Urquinaona Central Hospital in Maracaibo (Venezuela). The research was approved by the hospital's Clinical Research and Ethics Committee and written consent was obtained from all patients.

A total of 180 pregnant women were selected for the research, of which 90 were preeclamptic patients who were chosen as cases (group A) and another 90 were healthy normotensive pregnant women, with a maternal age and a body mass index similar to those of the study group, and that were included in the control group (group B). Based on the assumed difference of 50% in NT-ProANP levels between groups, it was calculated that this number of subjects was sufficient to satisfy the statistical power calculations (alpha = 0.05 and beta = 0.20). This allowed to rule out the null hypothesis that the levels of the NT-ProANP are no different between cases and controls.

Pregnant women with polyhydramnios, third trimester haemorrhage (abruptio placentae, placenta previa), suspected foetal intrauterine growth retardation (head circumference, abdominal circumference, and femur length lower than the 10th percentile of reference with postnatal weight confirmation lower than the 10th percentile of reference), HELLP syndrome – haemolysis, increased liver enzymes and thrombocytopenia, foetal heart rate anomalies, multiple gestations, presence of active intrauterine or maternal infection, chronic hypertensive disease (hypertension before 20 weeks of pregnancy), cardiac, haematological, hepatic, renal or chronic systemic disease, pre or gestational diabetes mellitus, smoking, pregnant women in whom blood samples were not drawn and those who had used drugs that could have altered the NT-ProANP concentration (for example, antihypertensives) were excluded. Also excluded were patients who expressed their wish not to participate in the research.

Preeclampsia was defined as a systolic blood pressure of 140 mmHg or more, or a diastolic blood pressure of 90 mmHg or more, confirmed by a minimum time interval of 6 h. Proteinuria was defined as 300 mg or more of protein in a 24 h urine sample, or 1–2 plus proteinuria in a qualitative examination after 20 weeks of gestation. Blood pressure was measured in a sitting position after a 15 min rest using a standard mercury sphygmomanometer with a 14 cm cuff. Systolic and diastolic blood pressures (taken in relation to the fifth Korotkoff sound) were measured in relation to the nearest 2 mmHg point. The systolic and diastolic blood pressures were calculated from the average blood pressure of each arm.

Blood samples were collected 1 h after admission and before the administration of any medication in the group of preeclamptic patients. All blood samples were taken from the antecubital vein with the patient in a sitting position, in dry tubes using EDTA, and subsequently centrifuged at room temperature with a relative force of 3000 × *g* for 10 min. Serum and plasma aliquots were stored at −80 °C until the analysis. The standard laboratory parameters were determined with an autoanalyzer using the manufacturer's *kits* in the clinical laboratory of the hospital. Haematological parameters were measured with the Advia 120 Haematology system (Advia Centaur, Siemens Healthcare Diagnostics, Norwood, MA, USA) and blood chemistry and 24 h proteinuria, with the Beckman Coulter AU5800 system (Beckman Coulter Inc., Brea, CA, USA). Creatinine levels were measured with an automatic autoanalyzer using Jaffé's non-enzymatic method.

For NT-ProANP measurements, blood samples were stored in an EDTA tube and placed immediately on ice. The sample was centrifuged at 1800 × *g* for 10 min at 4 °C and the isolated plasma