ROLE OF BRAIN NATRIURETIC PEPTIDE IN PREDICTING THE SHORT TERM CARDIOVASCULAR OUTCOMES IN PREECLAMPSIA AND ECLAMPSIA PATIENTS

Thesis

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Nader Haroun

Abstract

Background: Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and can present as late as 4-6 weeks postpartum. It is clinically defined by hypertension and proteinuria, with or without pathologic edema. The association between preeclampsia/eclampsia and adverse cardiovascular events might reflect a common cause for preeclampsia and cardiovascular disease, or an effect of preeclampsia on disease development, or both.

Objectives: B-type natriuretic peptide (BNP) is synthesized in cardiac ventricles in response to volume expansion. This study evaluated BNP levels to determine trends during pregnancy, and to assess BNP as a diagnostic tool in preeclampsia.

Patients and methods: The study involved 50 patients admitted at Al Galaa Teaching Hospital and doing echocardiography at Kasr Al Ainy Hospital during the period from 5/2012 to 5/2013 prelabour and postlabour for 6 months. Venous samples were withdrawn from all patients, pre-labor to measure BNP level, and discover any cardiovascular outcome with it. Re measure BNP level to the heighest ten BNP. The data of hospital admission were analyzed retrospectively.

Results: BNP plasma level showed significant positive correlation with LVEDD (p value= 0.001), LVESD (p value< 0.001) and LA dimensions (p value= 0.02), while it showed no correlation with the EF (p value= 0.1), the PASP (p value= 0.1) or the presence of diastolic dysfunction (p value= 0.07). Elevated BNP level could predict higher incidence of maternal complication and thus preeclampsia patients with high BNP level are to be managed cautiously and thus blood pressure should be controlled more

vigorously. In our study, there was a positive correlation between BNP plasma level and both proteinuria and hypertension before delivery. After delivery, despite that blood pressure was still high in a sample of our patients (n=10), yet their BNP plasma level returned back to normal.

Conclusion: In severe preeclampsia/eclampsia, BNP levels are elevated. BNP levels of the heighest ten patients declines to normal. This may reflect ventricular stress and hypertension associated with preeclampsia.

BNP plasma level may predict adverse cardiovascular events in patients with preeclampsia/eclampsia syndrome. We could not prove this in our study may be because a larger number of patients are to be studied and the follow up period should have been larger than 6 months.

Elevated BNP level could predict higher incidence of maternal complication and thus preeclampsia patients with high BNP level are to be managed cautiously and thus blood pressure should be controlled more vigorously.

Conversely, an elevated baseline level indicates the need for further cardiac assessment and indicates that the patient is at increased risk for future heart failure and mortality.

Keywards:

- **Preeclampsia and eclampsias patients.**
- **Brain natruretic peptide.**
- **Echocardiography studies.**
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Table of Contents

List Of Tables

List Of Figures

INTRODUCTION

Worldwide, hypertension represents one of the most common complications of pregnancy. Its incidence varies from 2 to 8% of pregnancies in developed countries, reaching 10% or more in developing countries. It is associated with high rates of perinatal morbidity and mortality (5–20%) and is the third most common cause of maternal death worldwide **(1)**.

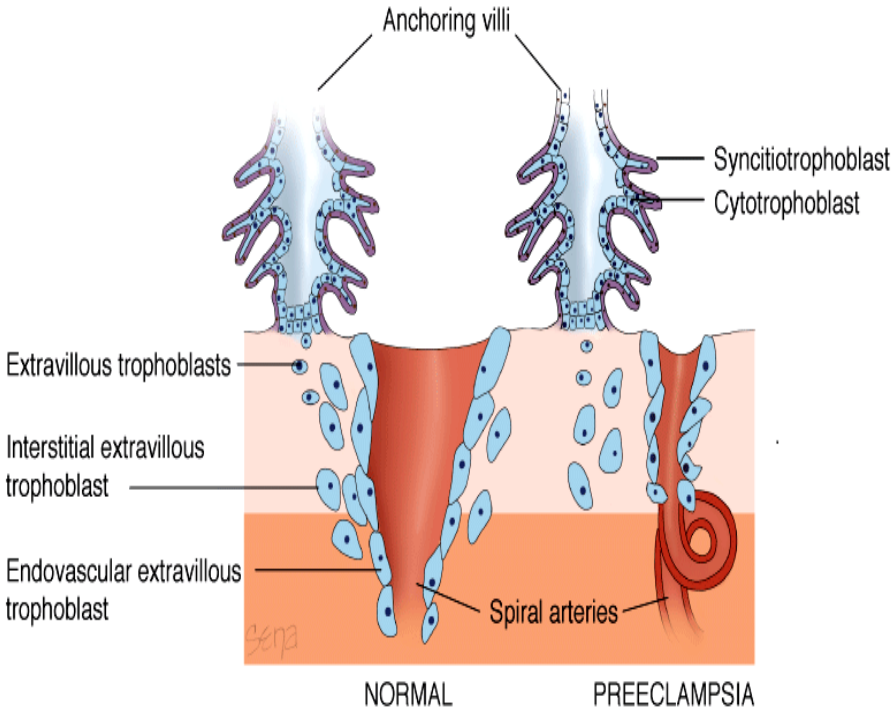
Five to 7% of all pregnancies are complicated by preeclampsia. Proteinuria and hypertension dominate the clinical picture, because the chief target organ is the kidney (glomerular endotheliosis). The pathogenesis of preeclampsia is complex; numerous genetic, immunologic, and environmental factors interact. It has been suggested that preeclampsia is a two-stage disease. The first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of placental materials into the maternal circulation. This in turn leads to the second, symptomatic stage, where in the pregnant woman develops characteristic hypertension, renal impairment, and proteinuria and is at risk for the HELLP syndrome (hemolysis, elevated liver function enzymes and low platelets), eclampsia, and other endorgan damage **(2)**.

It is believed that HELLP syndrome affects about 0.2 to 0.6 percent of all pregnancies. About 4-12% of women with diagnosed preeclampsia will develop HELLP syndrome. Unfortunately since the symptoms of HELLP syndrome may be the first sign of preeclampsia, this is what can often lead to a misdiagnoses. The symptoms of HELLP may cause misdiagnoses of other conditions such as hepatitis, gallbladder disease, or

idiopathic/thrombotic thrombocytopenic purpura (ITP, which is a bleeding disorder.) **(3)**

Although gross pathologic changes are not always seen in the placentas of women with preeclampsia but also mechanical constriction of the uterine arteries produces hypertension, proteinuria, and, in some species, glomerular endotheliosis, supporting a causative role for placental ischemia in the pathogenesis of preeclampsia **(4).**

Placental profiles including abnormal uterine artery **(5)** as showed in figure (1):



Source: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY: *Williams Obstetrics, 23rd Edition:* http://www.accessmedicine.com

A. Normal third-trimester placental implantation shows proliferation of extravillous trophoblasts from an anchoring villus. These trophoblasts invade the decidua and extend into the walls of the spiral arteriole to replace the endothelium and muscular wall. This remodeling creates a dilated low-resistance vessel. **B.** Placenta in preeclamptic or fetal-growth restricted pregnancy shows defective implantation. This is characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts and results in a small-caliber vessel with high resistance.

Fig (1):

Severe pre-eclampsia was defined by the presence of any of the following signs or symptoms: systolic pressure > 160mmHg or diastolic >110 mmHg, proteinuria > 2g/L in 24 hours of tape or proteinuria 3 + or more, oliguria, creatinine >1.2mg/dl, acute pulmonary edema or cyanosis, characteristic laboratory findings of HELLP syndrome, fundus findings of papilledema or retinal exudates. The imminence of eclampsia was defined as the presence of the following signs and symptoms in patients with hypertensive syndrome in pregnancy: continuous headache, scotomata (blind spots), blurred vision, epigastric pain and pain in right hypochondrium **(6)**.

Eclampsia and pre-eclampsia are important causes of morbidity and mortality during pregnancy childbirth and puerperium. **(7).**

Natriuretic peptides : comprise a family of 4 structurally related molecules atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide, (CNP), encoded by a gene symbolized NPPC **(8),** and Recently, a new member of the natriuretic peptide family, Dendroaspis natriuretic peptide (DNP), has been reported (**9).** ANP and BNP protect the heart from volume overload by inducing potent natriuresis, diuresis, and vasodilatation. These peptides possess potent natriuretic, diuretic, and vasodilating activities and are implicated in body fluid homeostasis and blood pressure control**(8).** Unlike ANP and BNP, CNP does not have direct natriuretic activity. This is because CNP is a selective agonist for the B-type natriuretic receptor (NPRB) whereas ANP and BNP are selective for NPRA**(10).**

Natriuretic peptides are quantitative markers related to the extent of left ventricular (LV) dysfunction and the severity of HF, Despite the increase in circulating ANP and BNP, the natriuretic, diuretic, and vasodilatory efficacy of these peptides are dramatically reduced in HF **(11,12).** Pregnancy represents a state of physiologic volume expansion as maternal blood volume increases ~40%–45% above non pregnancy volumes **(13).** It has been shown that BNP concentrations are higher in preeclampsia and other hypertensive disorders of pregnancy than in normal pregnancy**(13-16).**

AIM OF THE WORK

1- Role of elevated BNP in predicting the cardiovascular outcome in preeclampsia and eclampsia patients.

2- The relation between BNP level and proteinurea and hypertension.

NATRIURETIC PEPTIDES

Since its approval by the United States Food and Drug Administration (FDA) in November 2000, the interest in clinical and research applications in BNP testing in the United States and around the world has been staggering. In the United States alone, it is estimated that up to 70% of all hospitals utilize BNP testing **(17).**

Indeed, understanding the role and nature of the natriuretic peptide system in health and disease is occupying the minds of clinicians and investigators alike.

Initially focused on the emergent, bedside diagnosis of HF, subsequent research has supported the value of testing BNP in settings outside of the emergency department (ED) **(18).**

Natriuretic peptides comprise a family of 4 structurally related molecules: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), C-type natriuretic peptide, (CNP), encoded by a gene symbolized NPPC and Recently, a new member of the natriuretic peptide family, Dendroaspis natriuretic peptide (DNP). These peptides possess potent natriuretic, diuretic, and vasodilating activities and are implicated in body fluid homeostasis and blood pressure control **(19).**

Atrial natriuretic peptide (**ANP**), atrial natriuretic factor (ANF), atrial natriuretic hormone (ANH), Cardionatrine, Cardiodilatine (CDD) or atriopeptin, is a powerful vasodilator, and a

protein (polypeptide) hormone secreted by heart muscle cells **(20-22).**

It is involved in the homeostatic control of body water, sodium, potassium and fat (adipose tissue). It is released by muscle cells in atrial myocytes in response to atrial pressure. ANP acts to reduce the water, sodium and adipose loads on the circulatory system, thereby reducing blood pressure **(20).** ANP has exactly the opposite function of the aldosterone secreted by the zona glomerulosa, in regards to its effect on sodium in the kidney - that is, aldosterone stimulates sodium retention and ANP generates sodium loss **(23,24).**

C-type natriuretic peptide (CNP) is the major natriuretic peptide in human cerebrospinal fluid".

Unlike ANP and BNP, CNP does not have direct natriuretic activity. This is because CNP is a selective agonist for the B-type natriuretic receptor (NPRB) whereas ANP and BNP are selective for NPRA **(10).**

Dendroaspis natriuretic peptide (DNP) is a new member of the natriuretic peptide family that has 38 amino acids and a 17-amino acid disulfide ring structure resembling ANP, BNP, and CNP **(9).** This novel peptide was originally isolated from the venom of the green mamba (Dendroaspisangusticeps), but was found to have in vitro vasorelaxing properties in experimental animal preparations **(9,25).** Like ANP and BNP, DNP activates the NPRA.

However, little is known regarding the effects of this peptide on the human vasculature.

B-type, or brain, natriuretic peptide (BNP) was first isolated from brain tissue, but is synthesized primarily in the ventricles of the heart. Cleavage of the 108-amino acid precursor of BNP (proBNP) produces two molecules: 1) BNP, the active C-terminal, 77 to 108-amino acid molecule; and 2) N-terminal proBNP (NT-proBNP), the inactive 1 to 76-amino acid molecule **(26)**, as showen in figure (2). Studies indicate that NT-proBNP testing has the same clinical utility as BNP **(27,28).** The assay results, however, are not interchangeable even though levels are similar in healthy subject.

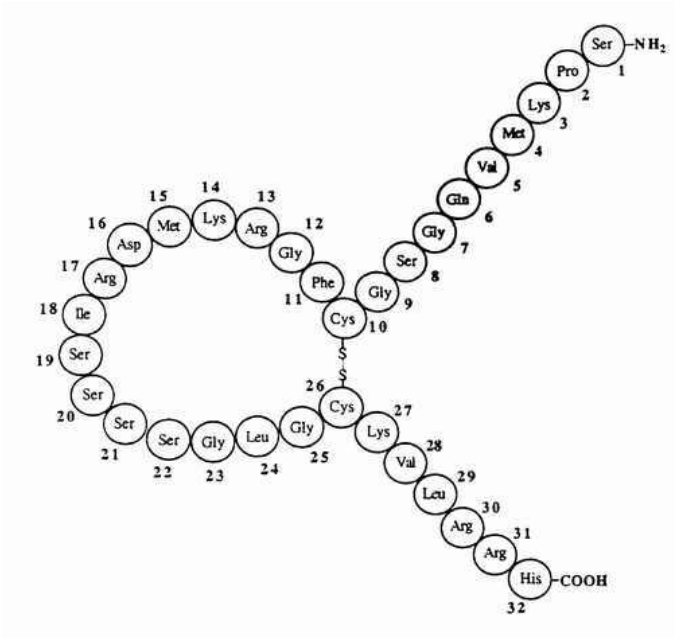


Fig. (2): The molecular structure of BNP hormone