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Clinical significance of serum N-terminal of the prohormone brain natriuretic peptide level in pregnant hypertensive patients with retinopathy.

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Abstract

Serum level of the N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) is an important factor in pregnancy-induced hypertension. The purpose of the present study was to evaluate the clinical significance of serum NT-proBNP level in pregnant hypertensive patients with retinopathy. Patients divided into gestational hypertension, mild preeclampsia, and serious preeclampsia groups underwent routine fundus examination; each group included 60 patients. Serum NT-proBNP level was concurrently measured by using an immunochromatographic assay. Fundus examination results were generally normal in the gestational hypertension and mild preeclampsia groups. The serum NT-proBNP level was normal or slightly high in these two groups, but without a significant difference (P>0.05). However, in the serious preeclampsia group, fundus lesions were obvious and the serum NT-proBNP level was increased, with a significant difference compared with those in the other groups (P<0.01). When serum NT-proBNP level is increased significantly in patients with pregnancy-induced hypertension, fundus examination should be involved.

Keywords: NT-proBNP, Gestational hypertension, Retinopathy.

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Introduction

Gestational hypertension, also called pregnancy-induced hypertension (PIH) [1], is a common complication. It occurs from 20 weeks of gestation up to 48 h postpartum. Conditions related to onset include hypertension, edema, and proteinuria, as well as other maternal organ dysfunctions [2]. Intrauterine growth retardation, stillbirth, and premature birth may occur, and are among the major causes of death in pregnant and lying-in women and fetuses. Therefore, identifying a new method to reduce the incidence of gestational hypertension and predict outcomes in pregnant women and the perinatal fetus is of great significance.

The N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) is a neuroendocrine hormone and a member of the atrial natriuretic peptide hormone family [3,4]. Wall stress and ventricular load affect myocardial cells due to various causes. The gene expression level of BNP increases rapidly, and the final products include BNP, which is a biologically active 32-amino acid polypeptide, and NT-proBNP, which is a biologically inactive 76-amino acid N-terminal natriuretic peptide [5,6]. NT-proBNP has a higher serum concentration and longer half-life, which is useful in clinical practice. Recent studies indicated that the NT-proBNP level has excellent stability at different temperatures and flexibility in different sample types [7]. Moreover, some studies confirmed that NT-proBNP level is a sensitive indicator of response to Left Ventricular (LV) dysfunction in patients with hypertension, and that elevated NT-proBNP level is correlated with LV dysfunction and LV remodeling [8], as well as cardiovascular disease and spontaneous myocardial infarction [9]. Patients who have undergone percutaneous coronary intervention [10], have diabetes [11] have chronic kidney disease [12], and have acute heart failure have high sensitivity [13]. Meanwhile, the NT-proBNP level is also recommended as the rule-out threshold in the 2012 European Society of Cardiology guidelines for heart failure [14]. In pregnancies complicated by preeclampsia, the NT-pro-BNP level has been found to be increased in comparison to that in normal pregnancy [15]. Furthermore, higher serum NT-proBNP levels may be an indicator of high LV filling pressure and LV diastolic dysfunction [16].

Gestational hypertension is the development of new hypertension in pregnant women, usually causing retinopathy, and renal, liver, neurological, and cardiovascular complications [17]. In the past, PIH patients with eye diseases were not adequately monitored. A previous study concluded that the examination of the fundus is a valuable and necessary

diagnostic procedure in pregnant women with preeclampsia [18]. NT-proBNP level closely correlates with heart injury and could reflect the degree of heart impairment, whereas the eye is a target organ of hypertension, and experiences effects similar to those of heart injury.

Therefore, this study aimed to compare the difference in NT-proBNP levels in patients with different stages of hypertension. In addition, fundus examination was performed in pregnant women to analyze the relationship between the NT-proBNP level and retinopathy in pregnant hypertensive patients. This will provide useful evidence for treatment of gestational hypertension.

Material and Methods

Subjects

In this study, 180 patients with PIH were enrolled from January 2012 to January 2014, including patients with gestational hypertension, mild preeclampsia, and serious preeclampsia. Each group included 60 cases. The demographic and clinic information for the three groups of patients are presented in Table 1. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Tangshan Maternity and Child Care Hospital. Written informed consent was obtained from all participants.

Table 1. *The demographic and clinic information for pregnancy hypertension patients in the study.*

Variables	Range	Mean
age	23–41 years	28 years
gestational period	27+5 weeks to 39+2 weeks	33 ± 2 weeks
Number of single pregnancy	170	-
Number of double pregnancy	6	-

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) previously healthy without history of hypertension, retinopathy, ocular disease, immune disorder, cardiovascular disease, and liver or renal disease; (2) pregnancy of more than 20 weeks; (3) and blood pressure higher than 140/90 mmHg during pregnancy. The exclusion criteria were as follows: (1) secondary hypertension and (2) onset of hypertension within 12 weeks of pregnancy.

The clinical characteristics of gestational hypertension include blood pressure (BP) ≥ 140/90 mmHg, first appearing in pregnancy, with postpartum recovery within 12 weeks, and with urine protein (-) and thrombocytopenia. The clinical characteristics of mild preeclampsia include BP ≥ 140/90 mmHg, appearing at 20 weeks of pregnancy, with urine protein ≥ 300 mg/24 h or (+), and associated with abdominal discomfort, headache, and other symptoms. The clinical characteristics of serious preeclampsia include BP ≥ 160/110 mmHg, urine protein ≥ 2.0 g/24 h or (++), serum creatinine>106 umol/L, blood platelets<100 × 10^9/L, partial microangiopathic hemolysis, elevated aspartate transaminase (AST) or alanine transaminase (ALT), persistent headache or other cranial nerve or visual impairment, and persistent epigastric discomfort.

Data collection and interventions

From January 2012 to January 2014, 180 patients with PIH from Tangshan Maternity and Child Care Hospital were randomly selected, including those with gestational hypertension, mild preeclampsia, and serious preeclampsia. Each group included 60 cases. While hospitalized, they received drug therapy, including oral magnesium sulfate and labetalol. Blood samples were collected from all patients.

Immunochromatographic test for NT-proBNP level

NT-proBNP level was measured by performing an immunochromatographic assay (with test reagents from Guangzhou Wondfo Bio-tech Co., Ltd., and Finecare Multi-channel FIA meter from Guangzhou Wondfo Bio-tech Co., Ltd., China). The immunochromatographic assay combines the sandwich method with chromatography. The NT-proBNP detection requires 75 µl of whole blood. The reaction time is 15 min, the sensitivity is range of 18-35,000 ng/L, and the cutoff is 300 ng/L.

Ophthalmoscopic examination

The abnormal eye signs and symptoms of hypertensive retinopathy include headaches, vision problems, narrowing of blood vessels, fluid oozing from the blood vessels, retinal cotton wool spots and hard exudates, swelling of the macula and optic nerve, and bleeding in the back of the eye. The fundus was examined with an ophthalmoscope. CsE9 tropicamide was used to dilate the pupil for examination in severe preeclampsia patients. Changes in the retinal artery and vein and optic nerve were examined and recorded.

Statistical analysis

Statistical analysis was performed by using SPSS 20.0 software [19], and all results were presented as mean ± standard deviation (SD). The t test was used for comparisons between two groups. Analysis of variance (ANOVA) was used for continuous variables (serum-proBNP levels) and the chi-square test for binary variables (eye symptoms). A P-value of >0.05 denoted no significant statistical difference.

Results

Serum NT-proBNP level was increased in the serious preeclampsia group

The serum NT-proBNP level was normal or slightly high in the PIH and mild preeclampsia groups. The value was 83.42 ± 28.38 in the PIH group, with no significant difference

(P>0.05). The serum NT-proBNP level in the serious preeclampsia group was increased (496.12 ± 154.58), with a significant difference compared with those in the PIH and mild preeclampsia groups (P<0.01).

Fundus lesions significantly differed in the serious preeclampsia groups

Significant differences were observed, with an abnormal retinal artery (31%), papilledema (26%), retinal hemorrhage (12%), and retinal detachment (10%) in the serious preeclampsia group, compared with the PIH and mild preeclampsia groups (P<0.01). Changes in serum NT-proBNP level, numbers and ratios of abnormal fundus examinations, and abnormal eye symptoms according to the different hypertension types are presented in Table 2.

Table 2. *Eye symptoms, abnormal results of fundus examinations and plasma NT-proBNP levels.*

Group	No.	Abnormal symptoms Ratio (%)	Abnormal Fundus artery No. (%)	Papilledema No. (%)	Retinal Hemorrhage No. (%)	Retinal Detachment No. (%)	Plasma NT-proBNP
PIH	60	1 (%)	2 (%)	0	0	0	78.59 ± 27.92
Mild pre-eclampsia	60	3 (%)#	5 (%)#	4 (%)#	1 (%)#	0 (%)#	83.42 ± 28.38#
Serious pre-eclampsia	60	21 (%)*	31 (%)*	26 (%)*	12 (%)*	10 (%)*	496.12 ± 154.58*

Vs. two groups, #P>0.05,*P<0.01

Discussion

The aim of the present study was to evaluate the clinical significance of serum NT-proBNP levels in PIH patients with retinopathy. PIH only occurs in pregnant women and is a common complication [1,20-22]. It occurs from 20 weeks of gestation up to 48 h postpartum, and mainly presents with hypertension, edema, and proteinuria. It results in retinopathy, and renal, liver, neurological, and cardiovascular complications. Systemic arterial spasm is the most common finding. PIH leads to retinal arterial spasm and a narrowed vascular lumen, increases peripheral resistance, impairs endothelial cells, and increases permeability and leakage of fluid and protein. The eyes are impaired by ischemia and anoxia. Eye tissue ischemia, papilledema, and retinal detachment can cause petechial and localized purpuric hemorrhage, and lead to decreased visual acuity, chemosis, and even blindness [3]. Administering antihypertensive therapy and early transport to a tertiary hospital may reduce the maternal death rate [23]. A study showed that elevated NT-proBNP predicts excess morbidity and mortality in diabetic patients with an elevated urinary albumin excretion rate. NT-proBNP levels above the median (62 ng/L) were consistently associated with increased total and cardiovascular mortality in 315 type 2 diabetic patients with normoalbuminuria (n=188), microalbuminuria (n=80), and macroalbuminuria (n=47) [24]. Retinal tissue thickness is reduced in diabetic peripheral neuropathy.

Many factors have been associated with PIH, such as lower L-arginine concentration in early gestation, overweight before pregnancy, and primiparity. These factors could predict the development of PIH [25]. BNP was originally identified by Sudoh in 1988 in extracts of porcine brain [26], and was described as a type of neuroendocrine hormone, a member of the atrial natriuretic peptide hormone family. BNP gene expression is significantly increased due to wall stress and ventricular load, affecting myocardial cells for various reasons. The end products include BNP, which is a biologically active 32-amino acid polypeptide, and NT-proBNP, which is a biologically inactive 76-amino acid N-terminal natriuretic peptide. The NT-proBNP level is used as a marker in the early diagnosis of heart failure. One study [2] showed that NT-proBNP is cleared only through glomerular filtration. Renal dysfunction greatly affects the metallization of NT-proBNP. Recently, the high NT-proBNP concentration and longer half-life in serum have been applied in clinical tests. The physical effects of BNP include inhibition of the renin angiotensin aldosterone system (RAAS). BNP can selectively expand the renal arteries to increase renal blood flow volume and inhibit the transportation of sodium ions by the inner medullary collecting system. Moreover, it has a strong effect on diuresis and platoon sodium, which is 1,000 times more than the furosemide effect. BNP also inhibits the sympathetic nerves. It can relax vascular smooth muscle to expand peripheral vessels, and reduces peripheral vascular resistance to decrease blood pressure and reduce heart preload and afterload. BNP can also relax the coronary arteries. When this happens in myocardial ischemia, BNP expands the coronary artery under the epicardium to increase blood flow and inhibit myocardial fibrosis. Thus, it acts as a local regulatory factor in ventricular remodeling. BNP also inhibits plasminogen activation to prevent thrombosis [20]. Some researchers confirmed [4-6] that measurement of serum NT-proBNP level can guide therapy and assess prognosis in PIH. Some studies reported that the plasma BNP levels in PIH were evidently higher than in healthy women [7,9,11], and that BNP level was positively correlated with diastolic pressure.

This study mainly assessed retinopathy by observing changes in serum NT-proBNP levels in patients with PIH. Fundus examination should be involved once the serum NT-proBNP level is increased significantly in patients with PIH. This could ease the economic burden on families and provide useful clues for PIH therapy.

Study Limitation

The conclusions would be more significant with a larger number of patients.

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