Research Paper

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Evaluation of Calcitonin Gene Related Peptide and Parathyroid Hormone Related Peptide Levels in Normotensive, Mild and Severe Preeclampsia.

Medical Science

KEYWORDS : Pregnancy, Preeclampsia, Calcitonin gene related peptide and Parathyroid hormone related peptide.

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ABSTRACT

The objective of the study was to determine whether serum circulating peptides, calcitonin gene related peptide and parathyroid hormone related peptide differ between normotensive women and women developing mild and severe preeclampsia. A case-control study of 132 women with preeclampsia (mild = 117; severe = 15) and 132 matched women with normotensive pregnancy. Samples were collected at the time of diagnosis. CGRP and PTHrP levels were highest in normotensive followed by mild preeclampsia and severe preeclampsia. Mean calcitonin gene related peptide (CGRP) and parathyroid hormone related peptide (PTHrP) levels show inverse relation with severity of Preeclampsia.

Introduction:

Pregnancy is associated with profound change in maternal hemodynamic, including increase in plasma volume and decrease in mean arterial pressure and peripheral vascular tone in women. The mechanism underlying this adaptation of normal pregnancy and the low resistant of fetal circulation are not fully understood (Dong et al, 2006).

Preeclampsia is a medical disorder during pregnancy that could lead to high risk of fetal growth retardation, premature delivery and even maternal death (Williams et al, 2011, Young et al, 2010). Despite unexplained pathogenesis, preeclampsia is thought to be result of generalized endothelial dysfunction. The mechanisms by which CGRP dilates blood vessels through endothelium dependent and/or independent manners are varied in different vascular beds (Bell et al, 1996). CGRP is a 37 amino acid neuropeptide synthesized by tissue specific alternative splicing of primary transcript of the calcitonin gene. It is widely distributed in the central and peripheral nerves system and has been shown to have a potent vasodilatory effect of vascular tone. It was reported before that systemic administration of CGRP decrease arterial blood pressure in a dose dependent manner in normotensive and hypertensive individual and also in experimental animals. It was found that this effect was due to peripheral arterial dilatation (Yallampalli et al, 1996).

PTHrP is another potent vasodilator and the fetoplacental unit is considered as a non tumor site of PTHrP production. It may possible that alteration of the expression, localization and or action of PTHrP might contribute to the genesis of condition such as preeclampsia and intrauterine growth retardation (IUGR) in which placental vascular resistance is increased (Gude et al, 1996).

Several in vitro studies have suggest that CGRP and PTHrP play an important role in regulating vascular resistance and regional organ blood flow both under normal physiological condition and pathophysiology of hypertension (Bell et al, 1996, Maggi et al, 1988). Both peptides may have a role in blood pressure regulation because of their vasorelaxant properties, Hence we conducted a case control study to evaluate maternal serum CGRP and PTHrP concentration in normotensive, mild & severe preeclamptic pregnancies.

Materials and Methods: Study design & setting: This was a tertiary care teaching hospital based case control study of 132 patients with preeclampsia and 132 matched normal pregnant controls. With the approval of the institutional ethics committee and a written informed consent from each woman, samples were collected at the time of diagnosis. Serum was separated and stored in multiple aliquots at -80^{0}c for estimation of CGRP & PTHrP. The women with history of essential hypertension, renal disease, epilepsy, diabetes or any other chronic or preexisting disease were excluded from the study.

Out of 132 preeclamptic women 117 women were developed mild preeclampsia and 15 women were developed severe preeclampsia. The criteria for diagnosis of mild preeclampsia was defined as a systolic blood pressure of 140 mm Hg and/or a diastolic blood pressure of 90mm Hg recorded on at least 2 occasions 6 hours apart plus proteinuria (300 mg in a 24-hour collection or 1+ on a urine dipstick). Severe preeclampsia was defined as systolic blood pressure≥160 mmHg and/or diastolic≥110 mmHg in two consecutive measurements and/or proteinuria > 5 g in 24 hour urine collection.

Statistical analysis:

Data were summarized as Mean ± SE. Groups were compared by one way analysis of variance (ANOVA) and the significance of mean difference between the groups was done by Tukey HSD (honestly significant difference) test. Discrete data were compared by Chi-square (χ^2) test. A two-sided (α=2) $p<0.05$ was considered statistically significant.

Results:

The basic (demographic and clinical) characteristics of two groups at enrollment are summarized in Table 1. At presentation, the demographic characteristics viz. age, weight, height, BMI and parity were similar ($p>0.05$) between the two groups i.e. not differed statistically. However, clinical characteristics gestational age (GA) at delivery lowered significantly ($p<0.001$) in cases as compared to controls. Further, the frequency (% age) of preterm (<37 wks) was significantly ($p<0.001$) higher in cases as compared to controls. However the infants' birth weight lowered significantly in cases as compared to controls.

Table 2 represents the mean CGRP and PTHrP levels in all three groups (normotensive, mild preeclampsia and severe preeclampsia). CGRP and PTHrP levels were highest in normotensive followed by mild preeclampsia and severe preeclampsia. In other words, mean CGRP and PTHrP levels show inverse relation with severity of preeclampsia. Comparing the mean CGRP and

PTHrP levels between the groups, the CGRP and PTHrP in both mild and severe preeclampsia differed and lowered significantly ($p<0.001$) as compared to normotensive, but no significant difference were observed between mild and severe preeclampsia in both markers.

Table 1: Demographic and clinical characteristics of two groups

Characteristics	Controls (n=132)	Cases (n=132)	p value
Age (yrs)	25.39 ± 0.36	25.58 ± 0.36	0.708
Weight (kg)	55.66 ± 0.68	55.83 ± 0.72	0.867
Height (cm)	157.32 ± 0.45	156.48 ± 0.49	0.208
BMI (kg/m^2)	22.53 ± 0.29	22.90 ± 0.33	0.404
Parity: Primigravida Multigravida	 42 (31.8%) 90 (68.2%)	 54 (40.9%) 78 (59.1%)	0.125
Delivery periods: Preterm (<37 wk) Term (≥37 wk)	 8 (6.1%) 124 (93.9%)	 28 (21.2%) 104 (78.8%)	p<0.001
Infant's birth weight (kg)	2.94 ± 0.03	2.59 ± 0.03	p<0.001

Table: 2 Serum circulating peptides concentrations (mean±SE) in the study groups

Circulating peptides (pg/ml)	Normotensive (n=132)	Preeclampsia		P value[a]	P value[b]	P value[c]
		Mild (n=117)	Severe (n=15)			
CGRP	8.29 ± 0.03	7.69 ± 0.03	7.22 ± 0.05	p<0.001	p<0.001	0.063
PTHrP	658.83 ± 3.10	443.89 ± 2.33	413.36 ± 2.75	p<0.001	p<0.001	0.872

[a] Normotensive vs. Mild hyperstension, [b] Normotensive vs. Severe hypertension, [c] Mild hypertension vs. Severe hypertension

Discussion:

CGRP is a potent vasodilatory peptide which increases in maternal circulation during pregnancy. A low level of circulating CGRP was found to be increase peripheral resistance and BP, thus it may be important in pathogenesis of preeclampsia (Ariza et al, 2009, Halhali et al, 2001).

In present study, we observed that levels of CGRP and PTHrP were lowered significantly in mild and severe preeclampsia as compared with normotensive (Table 2). Further, the decrease of CGRP and PTHrP was evident highest in severe preeclampsia followed by mid preeclampsia and normotensive, the least. In other words, our study further demonstrates that women with mild and severe preeclampsia (compared with women with a normal pregnancy) have a significant difference in the degree of circulating peptides imbalance (i.e, the mean concentration of CGRP and PTHrP).

CGRP is involved in uterine relaxation during pregnancy(Thota et al, 2003).Increased receptor number in pregnancy signifies its importance in the maintenance of normal systemic hemodynamics in that condition(Gangula et al, 2003). It is suggested that the peptide is involved in maintaining the human myometrium in quiescence during pregnancy by antagonizing the actions of uterine stimulants like oxytocin, and a decrease in the CGRP receptors towards the end of pregnancy aids in the initiation of labor. Down regulation of the receptors at the end of term and in postpartum is evident in rats also (Dong et al, 2002).

The strength of our study was that we had adequate number of preeclamptic and normotensive subjects to demonstrate statistically significant difference between mild, severe preeclampsia and normotensive groups of these two marker (CGRP, PTHrP).

In summary we have demonstrated a marked decrease in the circulating peptides, CGRP and PTHrP concentration in mild and severe preeclamptic pregnancies. A longitudinal study to support the relationship between preeclampsia and both PTHrP and CGRP to establish potential indicators for the development, prediction of its severity, prevention, and treatment of the disease would be valuable.

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