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EFFECT OF TRADITIONAL BIOCHEMICAL MARKERS ON ENDOTHELIAL DYSFUNCTION IN PREECLAMPSIA

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ABSTRACT

The present study was undertaken to investigate endothelial dysfunction as root cause in pathogenesis of preeclampsia, which has not yet been clearly understood. Elevated oxygen free radicals partially explain endothelial cell damage. Our aim is to measure NO, LPO and uric acid levels as endothelial dysfunction markers in preeclamptic women. Thirty preeclamptic women and thirty gestational age matched normal pregnant women were included in the study. Mild and severe preeclampsia cases were evaluated for serum MDA, NO and uric acid levels. Serum MDA and uric acid levels were significantly raised in women with mild and severe preeclampsia when compared with normal pregnancy. Progressive increase in MDA levels were statistically significant with increased severity of disease from mild to severe. Significant reduction in mean NO levels were observed in preeclampsia as compared to normal pregnant women. We conclude decreased concentration of NO observed that point towards endothelial dysfunction which may be due to oxidative stress reflection as of MDA & uric acid.

KEYWORDS : Preeclampsia, endothelial damage, Lipid peroxidation, nitric oxide, uric acid

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INTRODUCTION

Preeclampsia (PE) is a hypertensive disorder during pregnancy. It is one of the top five causes of maternal death in the world. Hypertensive disorder during pregnancy complicates 7- 10% of total pregnancies out of which 70% are preeclamptic. It increases perinatal mortality by five folds and kills 50,000 women yearly worldwide. PE is conventionally diagnosed by gestational hypertension produced after 20th week, proteinuria and edema. (1)

Preeclampsia is multisystemic disorder in which intense vasospasm may be due to increased sensitivity of the vasculature to pressor agents like angiotensin II and prostacyclin which results in endothelial cell injury. This compromises perfusion to most of the organs, which further aggravates the activation of coagulation pathway and microthrobi formation. In PE plasma volume is decreased, thereby reducing uteroplacental blood flow. This acute stage of preeclampsia might be the biological expression of endothelial injury and perhaps part of more extensive and exaggerated inflammatory response by placental oxidative stress. (2)

Lipid peroxidation is event of oxidative stress. Low density lipoproteins are more susceptible for free radical oxidation leading to generation of malondialdehyde (MDA). This can be the major factor that induces endothelial dysfunction. (3)

Nitric oxide is an inorganic free radical having important biological functions like vasoactive functions of inhibiting platelet aggregation, relax perivascular smooth muscle and tissue injury.(4)

Uric acid is marker of oxidative stress, tissue injury and renal dysfunction. Increased uric acid is also an independent risk factor for cardiovascular diseases which mediate altered vascular function and inflammation. (5) Hence increased uric acid may be more than simply a marker of severity in Preeclampsia.

Therefore, we made an attempt to evaluate serum malondialdyde, Nitric oxide and uric acid levels to understand their role in the mechanism of developing preeclampsia.

MATERIALS AND METHODS

The present study includes total 60 subjects, of which 30 normotensive pregnant women and 30 preeclamptic women attending antenatal OPD and labour room of the Dept of Obstetrics and Gynecology of our hospital.

Control group comprised 30 normotensive pregnant women with gestational age of 24 – 34 weeks (mean gestational age is 30 weeks) with no apparent complications and no history of hypertension.

Study group included 30 preeclamptic women with gestational age of 27 - 38 weeks (mean gestational age 32 weeks) with following diagnostic features

MILD PE (n=19): Blood pressure > 140/ 90 – 150/ 109 mmHg,
Urinary protein > 0.3 gm/day

SEVERE PE (n=11): Blood pressure ≥ 160/ 100 mmHg
Urinary Protein ≥ 3 gm/day

Pregnant women with Eclampsia, Intra Uterine Growth Retardation (IUGR), Hemolysis Elevated Liver enzymes and low platelet (HELLP) syndrome, Gestational Diabetes Mellitus were excluded from the study.

About 5 ml of random blood samples from PE patients and controls were collected and estimated for following parameters.

Serum Malondialdehyde level by Kei Satoh Method. (6)

Serum Nitric Oxide by kinetic method of Cortas and Wakid (7)

Serum uric acid by Uricase- Pap method Henry R J method [8]

Student's t Test was employed for statistical analysis of data to compare each group. The data was expressed as mean ± SD. Pearson's correlation coefficients were used to observe correlation between two parameters.

TABLE NO.1

Comparison of parameters between normotensive pregnant women and preeclamptic patients

Demographic Criteria	Control group	Preeclamptic Patients (n=30)	Mild preeclampsia (n=19)	Severe Preeclampsia (n=11)
Mean age in yrs	26.78 ± 6.02	24.66 ± 3.86	23.98 ± 2.79	26.42 ± 4.33
Gestational age in weeks	30.69 ± 4.62	33.53 ± 6.01	34.12 ± 3.39	32.66 ± 4.20
Systolic BP mmHg	116 ± 3.29	155.5 ± 12.5	150 ± 6.02	160 ± 5.98
Diastolic BP mmHg	78 ± 6.34	98.5 ± 9.8	89.9 ± 3.62	108 ± 4.49
Serum MDA nmol/ml	1.62 ± 0.42	2.976 ± 0.44*	2.69 ± 0.45	3.278 ± 0.23**
Serum NO µmol/L	75.44 ± 16.37	37.91 ± 9.89*	40.08 ± 3.62	35.84 ± 6.26^{ns}
Serum Uric acid mg/dl	5.09 ± 0.30	6.35 ± 0.56*	5.98 ± 0.68	6.73 ± 0.44**

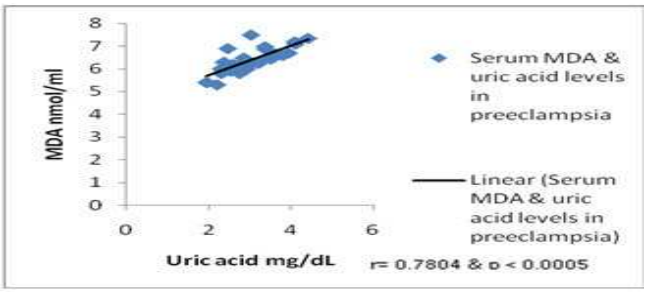
P<0.001 (Preeclampsia/control group), ** p<0.001 (Severe PE/Mild PE), ns = non significant

RESULTS

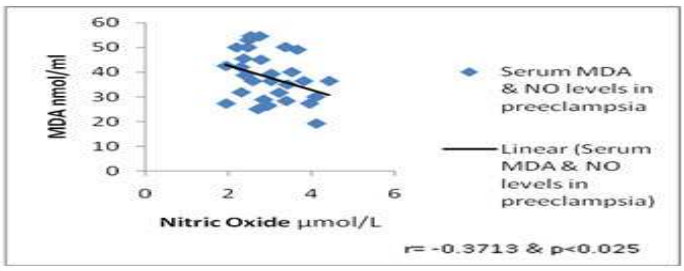
The demographic data of all subjects are given in table no.1. Elevated serum MDA level observed in mild (2.69±0.45) and severe preeclampsia (3.27±0.23) when compared with normotensive pregnant women (1.62±0.42) shows statistical significance (p <0.001). A progressive and significant rise in lipid peroxidation is observed as disease progresses from mild to severe condition. In Preeclamptic patients significantly reduced values of nitric oxide are observed when compared with control (p <0.001) but stage wise fall of NO from mild to severe remains insignificant. The significant elevation of uric acid levels are observed in preeclampsia compared to normotensive pregnant women. The uric acid levels are found to be significantly increased from mild to severe preeclampsia (5.97±0.68 to 6.73±0.44)

Graph no.1 shows strong positive correlation (r = 0.7804 and p < 0.0005) between MDA and uric acid levels among preeclamptic subjects which is statistically significant. When values of MDA and NO are compared, negative correlation (r = 0.3713 and p<0.025) was observed among PE subjects which also remains statistically significant (Graph no.2). But there was no significant correlation found between serum uric acid and nitric oxide.

Graph no. 1
Pearson's rank correlation between parameter MDA and Uric acid



Graph no.2
Pearson's rank correlation between parameter MDA and NO



DISCUSSION

The clinical course of pregnancy induced hypertension is progressive and characterized by continuous deterioration which ultimately stops only by delivery. Detection of the disease in early stages and appropriate management of such pregnancy may improve the outcome for both mother and baby. Discovering solutions to improvement of healthy survival of mother and newborns is essential for achieving global health equity.

The development of preeclampsia begins with loss of vascular refractoriness to vasoactive agents, followed by vasoconstriction. A functional imbalance between vasodilator and vasoconstriction appears to cause a disease. The most contributory factor for hypertension is altered prostaglandin and thromboxane production. [9]

Nitric oxide synthesized by vascular endothelial cell causes vasodilation and decreases the affinity of endothelium for platelets, like prostacyclin, thereby contributing to normal homeostasis of endothelial function. Platelets once activated releases serotonin and bradykinin, which in turn stimulates endothelial nitric oxide synthase activity, in healthy endothelium thereby preventing excessive platelet aggregation and adhesion to endothelium. There are substantial evidences for endothelial cell dysfunction in preeclampsia created with the effect of more oxygen free radicals generated by organ reperfusion. [10, 11] In our study, we observed decreased NO level in preeclampsia. Endothelial cell damage may have contributed to decreased activity of nitric oxide synthase activity in endothelial cell of vascular system expressing low levels of NO.[12]As generation of free radicals due to placental oxidative stress and tissue hypoxia have inhibited NO release from vascular ring leading to decrease in NO level. Our

observations are found similar to Var et al and pinhera et al. [13, 14]

Free radicals play an important role in pathophysiology of preeclampsia. Evidences point that oxidative stress is a mediator of endothelial cell dysfunction. [15] Deficient trophoblast invasion, uteroplacental perfusion, placental hypoxia and subsequent induction of placental tissue damage are resulting in oxidative stress. This oxidative stress will cause ischemia to reperfusion injury of placenta which elevates lipid peroxidation. [16] Our findings of significantly increased MDA levels in preeclampsia correlates with the finding of Pasoglue et al [17] and mohanty et al. [18] Excessive production of free radicals generated from a primary sites acts upon endothelial cell membrane lipids causing peroxidative damage. Lipid peroxide has powerful oxidizing potency which inhibit production of Endothelium derived relaxing factor like NO. Inhibition of endothelium derived vasodilator would disrupt the defensive activities of the endothelium against vasospasm and thrombosis. [19] These evidences supports strong negative correlation found between MDA and NO in present study.

As our results suggest positive correlation between MDA and uric acid and progression of disease condition from mild to severe PE is associated with progressive increase in serum uric acid level. Plausible culprit of this accumulation of uric acid may lie with increase ROS generation. ROS affects on three distinct site to produce increased serum uric acid. Its action on placental tissue leads to excessive lipid peroxidation and endothelial damage with the result of decreased NO release.[20] On renal tissue endothelial cell injury provides characteristic lesions i.e. glomerular endotheliosis resulting in decreased renal urate clearance.[21] Whereas developing fetal tissue under hypoxic condition triggers xanthene oxidase activity which in turn increase purine catabolism leading to increased uric acid release in maternal circulation.[22] Thus overall effect of increased uric acid observed may be the cumulative effect of ROS induced oxidative damage on various tissues.

To conclude, oxygen free radicals and nitric oxide impact towards endothelial dysfunction. According to our findings there is an important imbalance occurring between nitric oxide and dysfunctional endothelium in preeclampsia. Thus increase blood pressure and increase uric acid levels are the result of imbalance between oxygen free radicals and NO levels.

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