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SERUM SUPEROXIDE DISMUTASE AND PARAOXONASE-1 ACTIVITY IN PREECLAMPSIA PATIENTS

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ABSTRACT

Preeclampsia (PE) is a multisystem disorder characterized by hypertension, proteinuria and edema. Endothelial cell (EC) injury plays an important role in the pathogenesis of PE. The antioxidant enzyme SOD is a scavenger of superoxide anion and prevents oxidative damage of EC. Dysfunction of EC is associated with dyslipidemia due to oxidation of LDL, which is lowered by the enzyme PON-1. The aim of present study is to determine superoxide dismutase and paraoxonase-1 activity in preeclamptic women. In this study we found that serum SOD and PON-1 activity was decreased in preeclamptic women (3.614±0.539, 45.815±4.725) as compared to normal pregnant women (5.796±1.242, 65.012±6.318). But, SOD and PON-1 activity in between mild and severe PE women's were not-significant. Our observed results show decrease in the antioxidant SOD and PON-1 activity point towards their role in the pathogenesis of PE.

KEYWORDS

Preeclampsia, Endothelial cell dysfunction, Superoxide Dismutase, Paraoxonase-1

INTRODUCTION

Preeclampsia (PE) is one of the most serious complications during pregnancy and one of the top five causes of maternal death in the world. It increases perinatal mortality at about 5 fold and 50,000 deaths of women yearly worldwide. The worldwide prevalence of PE is 9% and in India it is 8-10%. Preeclampsia is mainly a disease of primigravidas. The incidence is 14.1% in primigravidas versus 5.7% in multigravidas.[1]

The preeclampsia is one of the oldest diseases known to mankind. In 1999 Robert and Patrick observed proteinuria and oedema; and further they propounded, that maternal endothelial dysfunction is the key event resulting in the diverse clinical manifestations of PE.[2] Friedman et al (1981) observed that preeclampsia is multisystem disorder and increase in blood pressure is responsible for multi-organ dysfunction.[3] Liver function abnormalities and renal function impairment were suggested by Lindheimer and Kutz.[4] From ancient years to till date, there is no any unifying etiology identified which can explain the pathophysiology of preeclampsia. American college of Obstetrics and Gynecology has put forth criteria for the diagnosis of preeclampsia as; development of hypertension with proteinuria, edema or both induced by pregnancy after 20th weeks of gestation.[5]

Preeclampsia is systemic disorder caused by vasoconstriction of unknown etiology. Endothelial cell (EC) injury plays significant role in the pathogenesis of PE. The EC injury is mediated by reactive oxygen species (ROS) because, vascular EC are in close contact with blood and they are exposed to variety of pro-oxidants including ROS, activated neutrophils and platelets, results in EC damage and immune response.[6] During this process neutrophils undergo respiratory burst associated with 2-20 folds rise in oxygen consumption leading to secretion of superoxide anion and hydrogen peroxide which causes oxidative stress. Superoxide Dismutase (SOD) being antioxidant enzyme protects EC against oxidative damage.[7]

Paraoxonase-1 (PON-1) [Aryl di-alkyl phosphatase] is a serum aryl esterase that was initially identified by hydrolysis of aromatic carboxylic esters, nerve gases etc. Its name itself reflects the ability to hydrolyse paraoxone, a metabolite of the insecticide Parathion. There are three members of the PON family; PON-1, PON-2 and PON-3 located on chromosome number-7. All of them possess antioxidant property. Human PON-1 is widely distributed among tissues such as; Liver, kidney and intestine. Mostly, they are synthesized in liver and secreted into blood stream and it is exclusively associated with HDL. Serum PON-1 is Ca- dependent esterase that is known to catalyze the hydrolysis of organophosphates.[8] A PON-1 enzyme metabolizes pro-inflammatory lipids formed during the oxidation of low density lipoproteins (LDL) and destroys LDL lipid peroxide and therefore, it is considered as anti-atherogenic. PON-1 functions in preventing not only lipid peroxidation but also HDL itself.[9] Circulating lipids have diverse effect upon EC function and dyslipidemia is associated with EC dysfunction.Paraoxonase-1 (PON-1) has a significant role in the reduction of LDL-oxidation. Therefore, the aim of present study is to determine the activity of SOD and PON-1 in PE

MATERIAL AND METHODS

Study includes 30 preeclamptic women and 30 normal pregnant women as controls. These patients were attending the indoor patient Department in antenatal care unit and outpatient Department of our hospital. All subjects were in the age group 19-30 years. This study was approved by the institutional ethical committee.

The distributions of subjects were done in two categories;

Group-1: Control Group (n=30) - normal pregnant women of third trimester, singleton, primigravidas having no apparent medical complication and without history of hypertension, diabetes etc were included in the study.

Group-2: Preeclampsia Group (n=30) – preeclamptic subjects of third trimester were selected for the study. The subjects were selected after the diagnosis of preeclampsia by hospital gynaecologists. The diagnosis was confirmed by criteria of hypertension, edema and proteinuria. This group was again sub-categorized into: Mild and severe Preeclampsia. The patients with blood pressure >140/90 mmHg but <160/110 mmHg without proteinuria were included in mild cases, and subjects with blood pressure of ≥160/110 mmHg with proteinuria were included in severe preeclampsia.

The blood samples were collected in a plain bulb with aseptic conditions. After two hours of collection, sample was centrifuged at 3000 rpm for 5 minutes; serum was separated and collected in polyethene tubes with cork. The sera with no sign of hemolysis were used for analysis of superoxide dismutase and paraoxonase-1.

Superoxide dismutase was measured by Marklund and Marklund.[10]

Paraoxonase-1 was determined by Spectrophotometric method. [11]

The results were analysed by students 't'- test.

RESULTS

Table no. 1 shows the demographic criteria and clinical parameters of preeclampsia and control groups. In our study, mean serum SOD activity in preeclampsia was 3.614 ± 0.539 U/ml and that of control group was 5.796 ± 1.242 U/ml, whereas in mild and severe preeclampsia cases, serum SOD activity was 3.70 ± 0.612 U/ml and 3.50 ± 0.424 U/ml respectively. Serum superoxide dismutase (SOD) activity in preeclampsia patients showed significant decrease ($p<0.001$) when compared with normal pregnant women. But, SOD activity in between mild and severe PE cases was non-significant.

The PON-1 activity in PE, mild PE, severe PE and normal pregnant women's were 45.815 ± 4.725 U/ml, 46.428 ± 4.516 U/ml, 45.010 ± 5.051 U/ml and 65.012 ± 6.318 U/ml respectively. Thus, PON-1 activity in preeclampsia patients was significantly decreased ($p<0.001$) than normal pregnant women. But, among the preeclampsia group; serum PON-1 activity doesn't show any correlation with severity of disease.

Table No. 1

Demographic criteria and Clinical Parameters	Control Group	Preeclampsia Patients	Preeclampsia Group	
	Normal Pregnant Women (n=30)	Preeclampsia (n=30)	Mild (n=17)	Severe (n=13)
Gestational age (weeks)	30.99 ± 6.72	32.92 ± 3.58	32.89 ± 2.72	32.96 ± 4.58
Systolic Blood Pressure (mmHg)	116.26 ± 4.35	149.6 ± 10.12	142.70 ± 3.46	162.23 ± 8.73
Diastolic Blood Pressure (mmHg)	75.33 ± 4.37	97.33 ± 7.52	91.76 ± 2.44	104.61 ± 5.25
SOD (U/ml)	5.796 ± 1.242	3.614 ± 0.539*	3.70 ± 0.6128^{NS}	3.50 ± 0.424^{NS}
PON-1 (U/ml)	65.012 ± 6.318	45.815 ± 4.725*	46.428 ± 4.516^{NS}	45.010 ± 5.051^{NS}

Values are given in mean ± SD, *p<0.001-compared with normal pregnant women (highly significant). NS- Not significant

DISCUSSION

There is a lot of research going on to incur the etiology of PE. Several studies point towards abnormal trophoblast invasion of uterine blood vessels, immunological intolerance between fetoplacental and maternal tissues, maladaptations to the cardiovascular changes or dietary deficiencies and genetic abnormalities as probable causes. EC dysfunction and inflammation are considered to have a crucial role in the pathophysiology of PE.[12]

In our study, we found significant decrease in serum SOD activity as compared to normal pregnant women. SOD is an important antioxidant enzyme which is capable of preventing excessive superoxide accumulation and any potential oxidative effects by free radicals and it may contribute to the continuation of pregnancy by preventing the accumulation of superoxide radicals.[13] The mechanism leading to reduction in activity of SOD is not well known. But, observed decline in SOD activity may be due to utilization of this enzyme towards detoxification of H_2O_2 and other toxic metabolites produced during gestation in preeclampsia. Our observations of decreased SOD in PE concur with Nirmala et al (2001), Kharb S et al (2000), Madhur Gupta et al (2004).[14,15,16]

Abnormal trophoblast invasion and inadequate uterine artery remodeling occurs in preeclampsia which causes uteroplacental perfusion and injury to placenta which may lead to generation of oxidative stress. Lipid peroxidation (LPO) can occur by free radical chain process or alternatively by enzymes such as; cyclooxygenases and lipooxygenases. The formation of reactive oxygen species initiates and propagates LPO chain. The excess placental LPO has been linked to placental production of tumor necrosis factor (α-TNF), Interleukin-6 (IL-6).[17] The activation of maternal neutrophils occur during their transit through the placenta could provide a pathway for transfer of oxidative disturbances into the maternal circulation in PE. The substances such as; elastase and proteases are released from activated neutrophils, which destroy the integrity of endothelial cells mainly basement membrane and sub endothelial matrix. Post ischemic reoxygenated cells release factors that induce neutrophils to discharge oxidants, superoxide anion, H_2O_2 etc. NADPH oxidases are important sources of O_2^- in phagocytic cells and non-phagocytic vascular cells.[18] These generated free radicals enhance the LPO and lead to formation of Lipid hydro peroxide which could damage the endothelial cell membrane and causes endothelial cell dysfunction. This damage of endothelial cell may be a cause of reduced SOD activity located in vascular endothelial cells.

The present study shows, PON-1 activity was significantly decreased ($p<0.001$) in PE patients as compared to normal pregnant women. But, among the preeclampsia group serum PON-1 activity does not change according to severity of disease. Our observations of decreased PON-1 in PE match with Kumru S (2004), H Uzun, A Benian (2005), Sarandol E (2004). [19, 20, 21]

To conclude; our results of decrease in the antioxidants SOD and PON-1 point towards their role in the pathogenesis of PE. Further research is needed to study the serum levels of these enzymes before and after treatment of PE in order to evaluate whether reduced enzyme activity constitutes a risk for PE or is an increased utilization of antioxidant capacity.

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