Effect of Vitamin E on sP-Selectin Levels in Pre-Eclampsia

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Abstract P-selectin, a cell adhesion molecule is elevated in many inflammatory conditions including preeclampsia which is characterized by generalized endothelial dysfunction and vasoconstriction presumably due to free radicals or mediators released by defective placentation. Vitamin E has been documented to protect cell membranes from oxidative damage and also decrease platelet aggregation. The role of vitamin E in pre-eclampsia is contradictory and hence the study was undertaken. Soluble P-selectin was measured by ELISA and Vitamin-E levels in plasma was estimated spectrofluorometrically. In our study the effect of supplementation of 400 IU/day of Vitamin E (a-tocopheryl acetate) to patients of pre-eclampsia showed significant decreased levels of soluble P-selectin by 2nd week as compared to patients given placebo ($P = 0.005$). In this short period of study no direct correlations were observed between Vitamin E or P-selectin levels with blood pressure as well as with proteinuria. Future studies may focus on the effect of a-tocopheryl acetate or the phosphate form of Vitamin-E, recently proposed to be the more active form on

other inflammatory markers like IL-6, an important stimuli of P-selectin release in pre-eclampsia.

Keywords Pre-eclampsia · P-selectin · Vitamin E · Inflammation

Introduction

Pre-eclampsia (PE) is characterized by increased blood pressure, proteinuria and/or edema developing after 20 weeks of gestation [1]. Though the exact etiology is unknown, early vascular dysfunction manifested as defective placentation and later systemic endothelial dysfunction have been documented to be a common feature of PE [2]. P-selectin, a cell adhesion molecule present in platelets and endothelial cells is expressed on the surface when cells are activated. It mediates interactions between leucocytes, platelets and endothelium. The soluble form of P-selectin (sP-selectin) is derived mainly from platelets after it has been cleaved from the cell surface [3]. It has been reported to be elevated in many inflammatory conditions including pre-eclampsia.

Vitamin E (Vit E), a lipid soluble antioxidant has been documented to prevent oxidative damage of cell membranes and decrease platelet aggregation by a non-oxidative mechanism. It has been shown to contain P-selectin levels in coronary angioplasty when given prior to the procedure [3]. The role of Vit E in pre-eclampsia is still not clear. Some have reported beneficial results, whereas, others found no beneficial effects. The present study was undertaken to see if Vit E could decrease inflammation whether any changes in the manifestations of the disorder could be observed.

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Materials and Methods

The study was conducted only on 24 patients on Vit E (α -tocopheryl acetate) and seven patients on placebo due to increase turnover of patients as well as noncompliance. Inclusion and exclusion criteria were followed and written consent was obtained from all patients. Patients were all PE cases and primigravida and were randomly allocated to receive either placebo or Vit E, 400 IU/day for 2 weeks. 25 normal pregnant women were included for baseline parameters in pregnancy. 10 normal non-pregnant women were also enrolled for baseline levels of the biochemical parameters. The study was approved by the Ethical Committee of the Institute.

After blood samples were collected in EDTA tubes, plasma was separated and analyzed for creatinine and stored frozen at -20°C till assay of P-selectin and Vit E. 24 h urine (or a shorter fixed period of time) were collected and estimated for protein and creatinine. Serum and urine creatinine were assayed for assessing kidney function and appropriateness of urine collection, respectively. Samples from PE patients were taken at baseline and at regular intervals of 1 week for the period of study of 2 weeks for the estimation of P-selectin and Vit E levels. Vit E was estimated spectrofluorometrically and plasma soluble P-selectin was measured by a commercially available ELISA kit (Diacalone, France).

Data were analyzed using SPSS version 10. Significance was assessed by paired or unpaired *t*-test and ANOVA with Bonferroni correction.

Results

Table 1 shows the levels of sP-selectin and Vit E at the time of enrollment of the four groups. By ANOVA, no significant differences have been noticed in the baseline levels of both the parameters between the groups. However, by the Students' *t*-test baseline sP-selectin levels were significantly higher in normal pregnant women as compared to non-pregnant women and PE patients had significantly higher levels than normal pregnant women (data not shown).

Table 1 P-selectin and Vit E of all the groups at enrollment

	Pre-eclamptic patients		Normal pregnant subjects ($n = 25$)	Normal non-pregnant women ($n = 10$)
	Vit E group ($n = 24$)	Placebo group ($n = 7$)		
P-selectin, ng/ml	402.41 $\pm$ 169.09	451.14 $\pm$ 237.48	302.68 $\pm$ 86.76	266.70 $\pm$ 47.29
Vit E, mg/dl	1.03 $\pm$ 0.30	1.01 $\pm$ 0.18	0.80 $\pm$ 0.14	0.91 $\pm$ 0.21

Data between groups was analyzed by ANOVA with Bonferroni correction

Values are expressed as mean $\pm$ SD, *n* number

Table 2 P-selectin and Vit E levels of PE patients at baseline, 1st week and 2nd week

	Vit E group ($n = 24$)	Placebo group ($n = 7$)
P-selectin, ng/ml		
Baseline	402.41 $\pm$ 169.09	451.14 $\pm$ 237.48
1st week	337.13 $\pm$ 117.47	435.86 $\pm$ 172.89
2nd week	301.63 $\pm$ 153.15*	425.86 $\pm$ 201.13
Vit E, mg/dl		
Baseline	1.03 $\pm$ 0.30	1.01 $\pm$ 0.18
1st week	1.44 $\pm$ 0.41*	1.00 $\pm$ 0.12
2nd week	1.63 $\pm$ 0.34*	1.05 $\pm$ 0.17

Values are expressed as mean $\pm$ SD; *n* number, * $P \leq 0.05$ is considered statistically significant

As shown in Table 2, no significant differences were observed for P-selectin and Vit E at different time points in the placebo group of PE patients. However, in the Vit E group of PE patients significant decrease ($P = 0.005$) of P-selectin levels between baseline and after 2 weeks have been noticed (402.41 $\pm$ 169.09 vs. 301.63 $\pm$ 153.15 ng/ml). Supplementation of 400 IU of Vit E to PE patients caused a significant increase of Vit E in serum between baseline values and after 1 week ($P < 0.001$) and similarly, between baseline levels and after 2 weeks ($P < 0.001$). However, the Vit E levels are within the normal range of 0.5–1.8 mg/dl.

Discussion

Soluble P-selectin has been reported to be elevated in many inflammatory conditions and enhancing platelet and neutrophil aggregation when expressed on the cell surface. It has been reported to be increased in pregnancy which is a low grade physiological inflammatory condition. Much higher levels have been observed in PE where there is generalized endothelial dysfunction [4]. Though not shown in Table 1 directly, this is also an observation.

Though the underlying aetiology of PE is unclear, improper and deficient trophoblastic invasion of decidua and spiral arteries producing toxic substances has been

documented to be responsible for the pathology of the disease. It has been reported that dysfunctional endothelial cells produce variable quantities of vasoactive substances which causes vasoconstriction [5]. By preventing increase in P-selectin with Vit E, platelet aggregation may be contained to some extent and not exaggerate the compromised utero-placental circulation. If significant amount of free radicals or vasoactive mediators can be scavenged by Vit E it could curtail to some extent the excessive inflammatory response occurring in the disorder. The decrease in sP-selectin levels after 2 weeks of supplementation of 400 IU of Vit E (α -tocopheryl acetate) in patients of PE as shown in Table 2 is an indication towards this direction.

Vascular endothelial growth factor (VEGF) decreases vascular tone and blood pressure and also promotes survival of endothelial cells and formation of endothelial fenestrae. In PE an anti VEGF, sFlt-1 (soluble fms like tyrosine kinase 1) has been reported to be significantly increased [5]. Researchers have observed decreased plasma levels of hsCRP (high sensitive C-reactive protein) in patients with acute coronary syndromes when 600–800 units of RRR α -tocopheryl was given per day for 1–3 months. The same group also observed decreased levels of pro-inflammatory cytokines IL-6, TNF- α from monocytes in type 2 diabetic patients and control subjects with Vit E administration [6]. In our short period of study no correlations between Vit E or sP-selectin with blood pressure or proteinuria were found (data not shown). However, the decrease in sP-selectin levels after 2 weeks of Vit E supplementation assumes importance as when free radicals generated by defective placentation can be

scavenged to some extent by Vit E it could curtail to some extent the enhanced inflammatory response which produces the signs and symptoms of the disease. Studies need to be carried out to ascertain if any direct relationship exists between IL-6 and sP-selectin in PE. Also, new reports suggest Vit E in phosphate form (α -tocopheryl phosphate) is the more active form of the vitamin. This also needs to be studied in detail.

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