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Effect of Omega-3 and Vitamin E Administration On C-Reactive Protein (CRP) and Nitric Oxide (NO) Levels in White Rats (*Rattus Norvegicus*) Pregnant Preeclampsia Model

Arni Amir

Department of Biology, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

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ABSTRACT

Background: Omega-3 fatty acids play an essential role in maintaining cell membranes and anti-inflammatory processes that are in line with vitamin E as a fat-soluble antioxidant that can prevent oxidative stress, inhibit pro-inflammatory cytokines and protect fatty acids from oxidation. This study aimed to determine the effect of omega-3 and vitamin E administration on blood pressure, CRP, and NO levels in PE model pregnant mice.
Methods: This study was experimental with the design of the Post Test Only Control Group Design sample of 35 pregnant mice. Measuring instruments use a spectrophotometer. The data were analyzed using the Shapiro Wilks normality test. After the parametric test is met, the hypothesis test uses One Way ANOVA and LSD. Type Post Hoc Test tests are continued.
Result: The results showed that omega-3 and vitamin E administration significantly differed between control groups and treatment of CRP levels ($p = 0.001$) and NO levels ($p = 0.001$).
Conclusion: Combined administration of omega-3 and vitamin E can lower systole blood pressure, CRP levels, and NO levels; however, there is no decrease in individual administration of diastole blood pressure and NO levels.

Keywords: Omega-3, Vitamin E, Oxidative Stress, CRP, NO, Preeclampsia

INTRODUCTION

One of the complications that causes almost 75% of all maternal deaths is high blood pressure during pregnancy (preeclampsia and eclampsia) (1). Preeclampsia is one of the most significant contributors to maternal and perinatal mortality rates in developing countries such as Indonesia. In 2019, the cause of maternal death due to hypertension in pregnancy was 1066 cases (2).
Preeclampsia has a varied clinical picture, and its complications are hazardous during pregnancy, childbirth, and the puerperium (3). Preeclampsia is diagnosed at 20 weeks gestational age. It is clinically characterized by systole blood pressure > 140 mmHg , diastolic blood pressure >90 mmHg measured twice with an interval of 4 hours, proteinuria in 24 hours > 300mg, or protein/creatinine with a ratio of > 0:3 (4).
The exact cause of preeclampsia is not yet known with certainty. One of the most frequently used theories to explain the pathophysiology of preeclampsia is the inflammatory theory. CRP is an acute-phase reactant produced by the liver in response to placental pro-inflammatory cytokines, especially 1L-6 in TNF alpha. CRP is an acute-phase protein produced by the liver or placenta cells in response to inflammatory stimuli. It is converted into neurokinin B (NKB) by phosphocholine transferase. It activates neurokinin receptor 3 (NK3R), resulting in damage to the placenta or kidneys and promoting the secretion of sFlt, which is involved in the pathogenesis of PEPE. It was found that serum CRP levels in PEPE patients were significantly higher than in normotensive pregnant women and

were positively correlated with the severity of the disease (5).

Changes in inflammatory proteins indicate the presence and intensity of inflammation. CRP decreases NO production by endothelial cells, thereby indirectly inhibiting vasodilation. On the other hand, CRP increases leukocyte adhesion, platelet activation, oxidation and thrombosis. CRP increases the regression of angiotensin type–1, thereby mediating an increase in blood pressure mediated by angiotensin–II (6). In endothelial cells, CRP facilitates the release of PAI–1 and endothelin–1 (ETET–1), improves the expression of cell adhesion molecules, reduces the bioavailability of NO, and decreases vascular dilatation. In vascular smooth muscle cells (VSMCs), CRP stimulates the expression of Angiotensin II type 1 receptors (AT1) and AT1 receptors that stimulate the formation of reactive oxygen species (ROS), reducing the availability of NO bioavailability (7).

Studies show that antioxidants play an essential role in preventing hypertension by reducing oxidative stress caused by endothelial dysfunction (8). Antioxidant supplementation in patients who experience a decrease in antioxidant status plays a critical role in reducing the incidence of hypertension in pregnancy (9). Vitamin E also plays a vital role in inhibiting the production of pro-inflammatory cytokines or inflammation (8,10). Vitamin E can pass through the placenta easily and has a strong antioxidant effect on some tissues making it essential for early embryonic development during implantation and protection against oxidative stress damage (11). As a fat-soluble antioxidant, vitamin E is responsible for protecting cells against the inflammatory response and lipid peroxidation, which shows a regulatory effect on blood pressure and may be beneficial in preventing PEPE (12).

In addition to vitamin E, omega-3 fatty acids play many important roles during pregnancy, especially in cardiovascular remodeling for women with hypertension (13). Omega-3s, including EPA/DHA, are precursors of metabolites and vital lipid mediators. They have an essential role in the body, especially in cell membranes, anti-inflammatory processes, and cell membrane viscosity (14). Omega-3 fatty acids, especially EPA and DHA, and the omega-6 family, i.e., AAAA, are essential for synthesizing eicosanoids, prostaglandins, leukotrienes, and thromboxanes and other oxidative factors, the primary mediators and regulators of inflammation. Studies have shown that omega-3 fatty acids control inflammation by reducing C-reactive proteins (CRP), eicosanoids, pro-inflammatory cytokines, chemokines, and other inflammatory mediators (15). Research conducted by Kemse et al. (16) supplementation of omega-3 fatty acids is beneficial in reducing inflammation and increasing angiogenesis in pregnant rats model of hypertension. Based on this, researcher is interested in conducting a study to see the "Effect of Omega-3 and Vitamin E Administration on CRP and NO Levels of White Rats (Rattus Norvegicus) Bunting Model preeclampsia".

MATERIALS & METHODS

This study is experimental with a Post Test Only Control Group Design design. The independent variables in this study were omega-3 doses (EPA/DHA: 180mg/120mg), vitamin E doses of 300 mg tocopherols that were converted to rat doses and administered orally, while the dependent variables were CRP levels and NO levels. The preeclampsia induction substance used is L-NAME dose 50 mg/kg/B.BB.B. The samples in this study were divided into five groups, namely the negative control group (K-) without treatment, the positive control group (K+) was given the induction substance L-NAME, the group (P1) was assigned L-NAME +omega-3, the group (P2) was given L-NAME + vitamin E, the P3 group was given L-NAME + omega-3 + vitamin E given at the gestational age of days 10-19. The sample criteria in this study were female mice with an aging period of 10 weeks, an average body weight of 200

gr, and mice in good health and did not experience abortus or die during the study. This research was carried out at the Animal House and Biomedical Laboratory of the Faculty of Medicine, Andalas University, Padang, from August 2020-May, to 2021. NO Inspection with Colorimetric Method Assay kit brand Elabscience no catalog : E-BC-K035-M while the CRP examination by Elisa method no catalog E0053Ra. Both measuring instruments use a spectrophotometer. This research was conducted after obtaining a research implementation permit and has been tested through an ethical test process by the ethics committee of the Medical Faculty, Universitas Andalas with Certificate No: 241 / UN.16.2 / KEP-FK / 2021. The data were analyzed using the Shapiro Wilks normality test. After the parametric test is met, the hypothesis test is continued using *One Way Anova*.

RESULT

In this study, the survey results included the average blood pressure levels of systole and diastole. Table 1 shows that group K's average systole blood pressure is 118.83 mmHg. The K+ group had a higher moderate blood pressure of the cycle than the other group, namely 149.83 mmHg. The P1 group has an average of 135.33 mmHg, the P2 group with an average of 142.17 mmHg, and the P3 group with an average of 119.50 mmHg. The average diastole blood pressure in group K- is 86.67 mmHg. The K+ group has an average of 115.67 mmHg. The P1 group has an average of 108.83 mmHg, the P2 group has a higher standard than the K + of 117.50, and the P3 group has an average of 92.83 mmHg.

Table 1. Average Blood Pressure of Systole and Diastole Rattus Norvegicus in the Control and Treatment Group

	Blood Pressure of Systole (mmHg)	***p***	**Blood Pressure of Diastole (mmHg)**	***p***
Group	**Mean±SD**		**Mean±SD**	
K-	118,83±5,742		86,67±14,473	
K+	149,83±2,858	0,001	115,67±7,339	0,001
P1	135,33±3,502		108,83±11,990	
P2	142,17±2,858		117,50±4,764	
P3	119,50±5,431		92,83±13,333	

Based on the results of the One Way ANOVA statistical test, there were significant differences between the control group and the treatment group against systole and diastole blood pressure with a value of p = 0.001 (p<0.05).

Table 2 shows that the administration of omega-3 and vitamin E to the cystole blood pressure of white rats (Rattus Norvegicus) there was a significant difference between group K- with K+ (p value = 0.001), group K- with P1 (p value = 0.001), group K- with P2 (p value = 0.001), group K+ with P1 (p value = 0.001), group K+ with P2 (p value = 0.005), group K+ with P3 (p value = 0.001), group P1 with P2 (p value = 0,010), group P1 with P3 (p value = 0,001), group P2 with P3 (p value = 0,001).

Table 2. Multiple Comparisons Test Post Hoc LSD against Systole Blood Pressure

Group	**Negative Control (K-)**	**Positive Control (K+)**	**Administration of Omega-3 3 (P1)**	**Administration of Vitamin E(P2)**	**Administration of Omega-3 Vitamin E(P3)**
K-	-	0,000	0,000	0,000	0,789
K+	0, 000	-	0,000	0,005	0,000
P1	0,000	0,000	-	0,010	0,000
P2	0,000	0,005	0,010	-	0,000
P3	0,789	0,000	0,000	0,000	-

Table 3 shows that the administration of omega-3 and vitamin E to the diastole blood pressure of white rats (Rattus Norvegicus) there was a significant difference between group K- with K+ (p value = 0.001), group K- with P1 (p value = 0.002), group K- with P2 (p value = 0.001), group K+ with P3 (p value = 0.001), group P1 with P3 (p value = 0.019), group P2 with group P3 (p value = 0.001).

Table 3. Results of the LSD Hoc Post-test on Rattus Novergiccus Diastole Blood Pressure in the Control and Treatment Group

Group	Negative Control (K-)	Positive Control (K+)	Administration of Omega-3 3 (P1)	Administration of Vitamin E(P2)	Administration of Omega-3 Vitamin E(P3)
K-	-	0,000	0,002	0,000	0,342
K+	0, 000	-	0,293	0,776	0,001
P1	0,002	0,293	-	0,185	0,019
P2	0,000	0,776	0,185	-	0,001
P3	0,342	0,001	0,019	0,001	-

In this study, the survey results included the average CRP level and the average NO level. Table 4 shows that CRP levels in the K+ group were higher than in the negative group, and treatment was 21.1 ng / L. While among the three treatment groups in the P3 group, the CRP levels were lower than P1, and P2 was 16.3 ng / L. Decreased CRP levels have best occurred in the P3 group.

Table 4. Average CRP Levels of White Rats (Rattus Norvegicus) in the Control and Treatment Group

Group	Level of CRP (ng/L)	
	Mean±SD	*p*
K-	17,1±1,28	0,000
K+	21,1±1,27	
P1	17,5±1,07	
P2	18,6±2,26	
P3	16,3±1,04	

Based on result of statistical test One Way Anova, there was a significant difference between control group and treatment group on CRP level with p value=0,000 (p<0,05). Table 5 shows that the administration of omega-3 and vitamin E to the CRP levels of white rats (Rattus Norvegicus) there was a significant difference between the K- group with K+ (p-value = 0.000), K+ with P1 (p-value = 0.000), the K+ group with P2 (p-value = 0.006), the K+ group with P3 (p-value = 0.000).

Table 5. LSD Hoc Post Test Results on Rattus Novergiccus CRP Levels in Control Groups and Treatment Groups

Group	Negative Control (K-)	Positive Control (K+)	Administration of Omega-3 3 (P1)	Administration of Vitamin E(P2)	Administration of Omega-3 Vitamin E(P3)
K-	-	0,000	0,625	0,091	0,352
K+	0,000	-	0,000	0,006	0,000
P1	0,625	0,000	-	0,217	0,161
P2	0,091	0,006	0,217	-	0,012
P3	0,352	0,000	0,161	0,012	-

Table 6 shows that NO levels in the K+ group were lower than in the negative group and the treatment group was 26,053 ng/L. While among the three treatment groups in the P3 group, ros levels were higher than P1, and P2 was 32,278 ng/L. No classes were best in the P3 group.

Table 6. Average NO Levels of White Rats (Rattus Norvegicus) in Control Groups and Treatment Groups

Group	Level of NO (ng/L)	
	Mean±SD	*p*
K-	29,502±2,5047	0,001
K+	26,053±1,0098	
P1	27,250±3,0695	
P2	27,555±2,3030	
P3	32,278±2,0791	

Based on the results of the One Way ANOVA statistical test, there were significant differences between the control group and the treatment group for NO levels with a value of p = 0.001 (p<0.05). Table 7 shows that in the administration of omega-3 and vitamin E to the NO levels of white rats (Rattus Norvegicus), there was a significant difference between group K- and group K+ (p-value = 0.015), group K + and group P3 (p-value = 0.002).

Table 7. Results of the LSD Hoc Post Test on RATTUS Novergiccus Levels in control groups and treatment groups

Group	Negative Control (K-)	Positive Control (K+)	Administration of Omega-3 3 (P1)	Administration of Vitamin E(P2)	Administration of Omega-3 Vitamin E(P3)
K-	-	0,015	0,102	0,154	0,046
K+	0,015	-	0,375	0,268	0,000
P1	0,102	0,375	-	0,820	0,001
P2	0,154	0,268	0,820	-	0,002
P3	0,046	0,000	0,001	0,002	-

DISCUSSION

Systole Blood Pressure in preeclampsia with the administration of omega-3 and vitamin E

Previous studies assessed the dilation of flow from the brachial artery in patients given EPA and DHA-rich fish oil supplements by improving endothelial function and lowering blood pressure. Omega-3 fatty acids are particularly susceptible to peroxidation due to a high number of double bonds in their structure. Therefore, administering a combination of vitamin E and DHA will help reduce lipid peroxidation (17). Research by Kasture et al. (18) on the combined supplementation of omega-3 fatty acids and micronutrients (folic acid, vitamin B 12) on oxidative stress markers in pregnant mice model of hypertension found that supplementation given individually did not show a decrease in blood pressure, while combined supplementation was able to normalize systole blood pressure.

Diastole Blood Pressure in preeclampsia with the administration of omega-3 and vitamin E

Diastole dysfunction usually precedes systole function in hypertension and can tend to occur in heart failure or pulmonary edema. In one study, diastole dysfunction was found in one-fifth of patients with preeclampsia (19). Research of Utami et al. (20) concluded that omega-3 supplementation during pregnancy is good for the development of the placenta and fetus, while for effectiveness in preeclampsia, more research is needed. EPA and DHA are known to reduce blood pressure in hypertensive patients due to a decrease in PGE2 metabolites, the production of EDRF, and an increase in PGI2 production. In addition, EPA / DHA also has an anti-inflammatory effect by reducing the production of LTB4 pro-inflammatory (21). A meta-analysis of research by Emmami et al. (22) on the impact of vitamin E on blood pressure shows that vitamin E supplements only lower systole blood pressure and do not have a beneficial effect on diastole and MAP. Women who received vitamin C and vitamin E supplements compared to the placebo group had a high risk of gestational hypertension and the need for the use of antihypertensive drugs (23).

CRP levels in preeclampsia with the administration of omega-3 and vitamin E

From the results of this study, the positive control group showed that the average CRP level was higher than the negative control. This means the hypertension-induced rat group had higher CRP levels than the middle pregnant rat group. Angiogenic and inflammatory factors have been shown to play an essential role in the pathogenesis of preeclampsia. In normal pregnancy, uhs-CRP serum showed an increase depending on gestational age. In contrast, in women suffering from preeclampsia, uhs-CRP levels were higher than controls corresponding to gestational age (24). Mechanisms involving angiogenic factors and pro-inflammatory cytokines are known to play a critical role in the process of the placenta and the development of preeclampsia. Interleukin-6 (IL-6) is one of the most potent inducers of liver CRP production. The significant increase in pro-inflammatory and anti-angiogenic markers in preeclampsia supports the hypothesis that CRP and sFlt-1 play a central role in the pathogenesis of preeclampsia (24).

This study also found that the average value of CRP levels in the treatment group was lower than that of the positive control group. The decrease in CRP levels was best seen in the group that was given omega-3 plus vitamin E. Each group compared to the positive control group (K+), which had a significant influence on CRP levels, was in the omega-3 administration group only (P1) with a value (p=0.000), vitamin E (P2) with a value (p=0.000), and in the administration of omega-3 plus vitamin E (P3) value (p=0.006). Omega-3 fatty acids positively affect endothelial function, heart rate variability, stabilization of plaques, cell signaling, and apoptosis, as well as critical anti-inflammatory properties. Long chains of omega-3 fatty acids are known to competitively inhibit a cascade of pro-inflammatory arachidonic acid, thus potentially increasing vasodilation and inhibiting platelet aggregation. The anti-inflammatory effects of fatty acids can also be mediated by these agents' inhibition of NF-kB activation (25). In line with research of Muhammad et al. (26) stated that in randomized trials in healthy men and women with increased serum concentrations of CRP, treatment for eight weeks with omega-3 fatty acids resulted in a significant percentage decrease in CRP concentrations compared to the initial, further more extensive studies were needed to verify and expand these findings. Omega-3 supplementation is beneficial in reducing inflammation and improving angiogenesis in hypertensive model mice, so further studies need to be tested for humanity. Cardoso et al. (27) stated in their research on the supplementation of vitamin C and vitamin E for the prevention of preeclampsia, revealed a 46% reduction in the risk of preeclampsia events in the group treatment compared to the control. In hypertension in pregnancy, it has been proven that oxidant levels, especially fat peroxide, increase while antioxidants such as vitamin E decrease. Besides preventing or inhibiting oxidative stress and cell tissue damage, antioxidants (vitamin E) play an essential role in inhibiting the production of pro-inflammatory cytokines or inflammation (8, 9).

NO levels in preeclampsia with the administration of omega-3 and vitamin E

From the results of this study, NO levels in the positive control group had a low value compared to the negative control group. Placenta PE is associated with hypoxic/reoxygenation phenomena, fluctuations in oxygen gradients, altered antioxidant capacity, oxidative stress, and reduced bioavailability of nitric oxide (NO) (28). Several studies said there is a strong relationship between hs-CRP and NO in hypertensive patients. This shows a risk for complications due to increased levels of hsCRP, which affects the synthesis and production of NO as a potent vasodilator agent in blood vessels (6).

In this study, the average value of NO levels in the three treatment groups was higher than in the control group. NO levels were best found in the group given omega-3 plus vitamin E. Each group compared to the positive control group (K+), which had a significant influence on NO levels, was in the group given omega-3 plus vitamin E (P3) only with a value (p = 0.001). In line with the study Overall, the combination of omega-3 fatty acids and vitamin E is beneficial in plasma changes in TAC, MDA, and NO as well as the incidence of hyperbilirubinemia in infants (29). Research by Sepridarkish et al. (30) on the effect of omega-3 plus vitamin E combinations on oxidative stress factors obtained significant reductions in MDA levels, and vice versa, increased NO. TAC levels compared to the placebo group.

Based on research of Middleton et al. (31) on supplementation of omega-3 fatty acids during pregnancy obtained for secondary outcomes, there is some evidence of reduced risk of preeclampsia. Still, the certainty of the evidence is low, so more research is needed. In this study, the administration of vitamin E alone did not significantly affect the levels of rats

modeling preeclampsia. In line with the meta-analysis by Basu et al. (32) on antioxidant supplementation in preeclampsia and gestational diabetes, clinical trials on vitamin C and vitamin E have largely shown no effect in reducing the incidence of preeclampsia in pregnant women with and without type 1 diabetes.
Some studies have obtained conflicting results on no levels in PEPE incidence. Research by Sutton et al. (33) explained that in preeclampsia, nitrate/nitrites levels have been reported to be significantly lower, unchanged, or higher than in pregnant women. This difference is likely due to several factors such as food intake/diet, iron status, and kidney cleansing treatment.

CONCLUSION

In conclusion, there was an effect of giving omega-3, vitamin E, and omega-3 plus vitamin E on the blood pressure of white rat systole (Rattus Norvegicus) pregnant with preeclampsia model. Also, there was an effect of giving a combination of omega-3 plus vitamin E on the diastole blood pressure of white rats (Rattus Norvegicus) pregnant with preeclampsia, but it had no impact on the administration of omega-3 and vitamin E individually (without combination). Furthermore, there was an effect of omega-3, vitamin E, and omega-3 plus vitamin E administration on CRP levels of white rats (Rattus Norvegicus) pregnant with preeclampsia models and an effect of giving a combination of omega-3 plus vitamin E on the NO levels of white rats (Rattus Norvegicus) pregnant with preeclampsia models but no impact on individual administration (without combination).

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