Relationship between Blood Lead Levels and Nitric Oxide (NO) Levels in Preeclampsia

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Abstract
Objective: This study aims to determine the relationship between blood lead levels and NO levels in preeclampsia.
Methods: This research applied analytical survey research with a cross-sectional design. Moreover, the samples were 99 pregnant women, 33 with normal pregnancies, 33 with preeclampsia living >10km from Semen Padang factory, and 33 with preeclampsia who lived ≤10km from Semen Padang factory. Spearman correlation test and logistic regression analysis is used for data analysis.
Result: The result of this study shows that the blood lead level median in preeclampsia ≤10km is 26.23 g/dL, and the lead level median in preeclampsia >10km is 23.52 g/dL. Meanwhile, the NO level median in preeclampsia ≤10km is 22.50μmol/L and NO level median in preeclampsia >10km is 28.00μmol/L. There is a relationship between blood lead levels and NO levels in preeclampsia ≤10km, with r-value = -0.601 and p-value <0.001, in preeclampsia >10km, there is no relationship with p-value >0.500 and the strength of the correlation is fragile. In addition, the results of multivariate analysis of reduced levels of NO in preeclampsia with high blood lead levels are two times compared to preeclampsia with normal blood lead levels with 95% CI (0.652-6.362) after being controlled by distance of residence, smoking status and living environment variables.
Conclusion: there is a relationship between blood lead levels and NO levels in preeclampsia.

Keywords: Blood lead levels, Nitric Oxide levels, Preeclampsia

Hubungan Kadar Timbal dengan Kadar Nitric Oxide (NO) pada Ibu Hamil Preeklamsia

Abstrak
Tujuan : Penelitian ini bertujuan untuk mengetahui hubungan kadar timbal dengan kadar *Nitric Oxide* (NO) pada ibu hamil preeklamsia.
Metode : Penelitian ini merupakan penelitian survei analitik, dengan rancangan *cross sectional.* Sampel diteliti sebanyak 99 orang ibu hamil, 33 orang ibu hamil normal dan 33 orang preeklamsia yang tinggal yang tinggal radius >10km, dan 33 orang preeklampsia yang tinggal radius ≤10km. Kadar timbal diperiksa menggunakan metode AAS dan Kadar *Nitric Oxide* (NO) diperiksa menggunakan metode ELISA. Analisis data menggunakan uji korelasi *Spearman* dan analisis regresi logistik.
Hasil : Hasil penelitian ini median kadar timbal pada preeklampsia ≤10km adalah 26,23 μg/dL, dan median kadar timbal preeklampsia >10km adalah 23,52 μg/dL. Median kadar *Nitric Oxide* (NO) preeklampsia ≤10km adalah 22,50μmol/L, median kadar *Nitric Oxide* (NO) preeklamsia >10km adalah 28,00μmol/L. Terdapat hubungan kadar timbal dengan kadar *Nitric Oxide* (NO) pada preeklampsia ≤10km, diperoleh nilai r = -0,601 dan nilai p < 0,001, pada preeklampsia >10km tidak terdapat hubungan dengan nilai p > 0.500 dan kekuatan korelasi sangat lemah. Hasil analisis multivariat penurunan kadar *Nitric Oxide* (NO) preeklamsia yang memiliki kadar timbal tinggi adalah 2 kali dibandingkan ibu hamil preeclampsia dengan kadar timbal normal dengan 95% CI (0.652-6.362) setelah dikontrol variabel jarak tempat tinggal, status merokok dan lingkungan tempat tinggal.
Kesimpulan : Terdapat hubungan kadar timbal dengan kadar *Nitric Oxide* (NO) pada ibu hamil preeklamsia.

Kata Kunci : Timbal, *Nitric Oxide*, Preeklamsia

Introduction

Preeclampsia is a specific condition to pregnancy. This condition is characterized by dysfunction of the placenta and an altered response to a systemic inflammation with endothelial activation and coagulation. Preeclampsia can be found from the 20th week of gestation. The basis of the diagnosis of preeclampsia is specific hypertension due to pregnancy and the presence of disorders in the mother's organ systems.[1]

Until now, the leading cause of preeclampsia remains unknown. However, inferential data show an imbalance between oxidants and antioxidants causes preeclampsia. Both may have a crucial role in the pathogenesis of this condition.[2] Oxidative stress can occur due to overexposure to toxic metals and bio-deficiency of elements needed in antioxidant defense mechanisms. It is believed that since centuries ago, many humans have experienced health problems due to lead exposure. [3]

Hypertension is very likely to occur due to lead exposure. In 2013, the American College of Obstetricians and Gynecologists (ACOG) suggested that proteinuria is the main diagnostic criterion for preeclampsia. In general, hypertension is associated with lead levels in the blood.[4] Furthermore, lead can also be associated with the enzyme glutathione as an endogenous antioxidant. Oxidative stress will increase and cause inflammation if there are insufficient antioxidants.[5] Lack of antioxidants also causes endothelial dysfunction, reducing levels of vasodilators such as plasma nitric oxide (NO) and endothelial-derived relaxation factors (EDRF). This reduction was due to the lead-mediated increase in reactive oxygen species (ROS). Membrane adenosine triphosphatase (ATPase) can cause blockage when intracellular calcium ions and vasoconstriction are significantly increased. It may increase the risk of preeclampsia by inducing vasoconstriction and placental ischemia. In addition, proteinuria (the main criterion of preeclampsia) may occur with direct toxicity to endothelial cells and renal function.[6]

One of the relaxation factors of the endothelium is nitric oxide (NO). Endothelium derived relaxing factor (EDRF) is a signal molecule widespread in the body and has an essential role in every cell and organ function.[7] The potential NO-centred mechanism for endothelial vascular dysfunction leading to preeclampsia is due to an increase in nitric oxide synthase (NOS) inhibitory molecules and anti-angiogenic factors.[8]

This study aims to determine the relationship between blood lead levels and nitric oxide (NO) levels in preeclampsia and providing additional information about lead level effect during pregnancy to prevent, reduce, and aid lead poisoning on pregnant women with preeclampsia and emphasizing mortality and morbidity of the mothers and infant born by giving socialization and counseling towards pregnant women.

Methods

This study was an analytical survey research with a cross-sectional design. The samples were as many as 99 pregnant women, 33 normal pregnancies, 33 preeclampsia who lived >10km from Semen Padang factory, and 33 preeclampsia who lived ≤10km from Semen Padang factory. Taking 3cc maternal blood samples and put into a centrifuge tube, the blood lead level later was checked at UNAND Environmental Engineering Laboratory and the nitric oxide (NO) levels at UNAND Biomedical Laboratory. The blood lead levels were checked using the Atomic Absorption Spectrophotometer (AAS) method, while blood levels of nitric oxide (NO) were studied using the Enzyme-Linked Immunosorbent Assay (ELISA) method. Moreover, Spearman correlation test and logistic regression analysis is used for data analysis. Spearman correlation test used in order to determine the strength of the correlation between blood lead levels and nitric oxide levels. Multivariate analysis shows the relationship between two or more variables, correlation analysis, and regression analysis for three variables. Meanwhile, logistic regression was used in order to determine the relationship of blood lead levels with nitric oxide (NO) levels in preeclampsia after controlling confounding variables (distance of residence, smoking status, and living environment).

Result

Based on the results of the frequency distribution test for blood lead levels and nitric oxide (NO) levels, the median, maximum and minimum preeclampsia ≤10 km and >10km are presented in the table below:

The result shows that the median blood lead level in preeclampsia ≤10 km is higher than the blood lead levels in preeclampsia >10 km. Meanwhile, the median nitric oxide (NO) levels in preeclampsia ≤10 km is lower than preeclampsia >10 km.

The results of statistical tests of the relationship between blood lead levels and nitric oxide (NO) levels in preeclampsia can be seen in the following table:

Table 2 Relationship of Blood Lead Levels with Nitric Oxide (NO) Levels in Preeclampsia Based on the Distance of Residence

	Nitric Oxide (NO) Levels
Preeclampsia ≤10km	
Blood Lead Levels	r = -0.601
	p < 0.001
	n = 33
Preeclampsia >10km	
Blood Lead Levels	r = 0.122
	p > 0.500
	n = 33

Since the value of r = -0.601 and p value <0.001 are obtained, it shows that the relationship between blood lead levels and nitric oxide (NO) levels in preeclampsia with a radius of ≤10 km is strongly correlate. Meanwhile, the relation is negative which means that the higher the blood lead level, the lower the nitric oxide (NO) levels in preeclampsia. In addition, the result shows that there is no relationship between blood lead levels and nitric oxide (NO) levels in preeclampsia with a radius of >10 km with a very weak correlation.

The results of statistical tests of logistic regression analysis of lead levels and nitric oxide (NO) levels in preeclampsia after controlling confounding variables (distance

Table 1 Median Distribution of Respondents with Preeclampsia Based on Distance of Residence ≤10km and > 10km from Semen Padang Factory

Variable	Median	Minimum	Maximum
≤10km			
Blood Lead Levels	26.23 µgr/dL	8.34 µgr/dL	31.04 µgr/dL
Nitric Oxide Levels	22.50 µmol/L	2.00 µmol/L	31.50 µmol/L
>10km			
Blood Lead Levels	23.52 µgr/dL	8.33 µgr/dL	28.95 µgr/dL
Nitric Oxide Levels	28.00 µmol/L	9.25 µmol/L	31.75 µmol/L

Table 3 Relationship of Blood Lead Levels with NO Levels in Preeclampsia after Controlling Confounding Variables (Distance of Residence, Smoking Status, and Living Environment)

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Distance	1.812	.585	9.602	1	.002	6.122
	Lead Level	.711	.581	1.498	1	.221	2.037
	Constant	-1.845	.552	11.188	1	.001	.158

of residence, smoking status, and living environment) can be seen in Table 3. The results of the bivariate selection of all variables resulted in p value < 0.25, smoking status and work environment with p value > 0.25. However, the variables of smoking status and work environment are analyzed using multivariate analysis since the substance of smoking status and living environment are very important variables related to nitric oxide (NO) levels.

The interpretation of the formed model is that the factors affecting nitric oxide (NO) levels are lead levels, distance from residence, smoking status, and living environment. Moreover, the greatest influence in reducing nitric oxide (NO) levels is the distance of residence. The risk of decreasing nitric oxide (NO) levels in preeclampsia living within a radius of ≤10 km from Semen Padang Factory is 6 times compared to those who lived in a radius of > 10 km from Semen Padang Factory with 95% CI (1.946-19258) after controlling blood lead levels, smoking status, and living environment.

The risk of decreasing nitric oxide (NO) levels in preeclampsia that have high lead levels is 2 times compared to preeclampsia with normal lead levels with 95% CI (0.652-6.362) after controlling for variables of residence distance, smoking status and living environment.

Discussion

The result of this study shows a significant relationship between blood lead levels and nitric oxide (NO) levels in preeclampsia who live within a radius of ≤10 km from Semen Padang Factory with p-value = 0.001. Furthermore, data analysis shows that the negative relationship's direction with the relationship's strength is in a moderate value (r= -0.601), which means that the higher the lead level, the lower the nitric oxide (NO) level. Meanwhile, preeclampsia living >10km radius of Semen Padang Factory has no relationship between blood lead levels and nitric oxide (NO) levels, and the correlation is very weak.

Lead is a hazardous environmental toxin because it produces reactive oxygen species (ROS) that may cause oxidative stress to anyone who inhales it. This oxidative stress can increase the possibility of preeclampsia. Indirectly, lead also binds to the antioxidant glutathione, which can cause stress due to changes in vasodilation caused by decreased nitric oxide (NO) production in the body. Increased levels of endothelial release from endothelin can also be caused by lead exposure. In addition, it can cause a decrease in production and trigger vasoconstriction.[5] There are suggestions that the renin-angiotensin-aldosterone system, effects on blood vessels and smooth endothelium, and stimulation of the sympathetic nervous system due to increased catecholamine production may be responsible for this occurrence.[9]

Inhibition of the Na-K ATPase pump may be due to lead exposure and its association with vasoconstriction. The association between lead and vasoconstriction can also lead to an increase in vasoconstrictor synthesis and a decrease in vasodilator synthesis (by increasing the production of endothelin and thromboxane and by inhibiting smooth muscle ATPase in blood vessels). In pregnancy, lead exposure may maintain vasodilation due to decreasing nitric oxide (NO) levels.[10]

One thing that affects the endothelium's function is nitric oxide (NO), which is a factor in the presence of endogenous relaxation derived from the endothelium. Under physiological conditions, the spread of nitric oxide (NO) in the fetal placental circulation can dilate the placental blood vessels and cause fetomaternal exchange.[11] In the case of a normal pregnancy, the mother's urethral spiral arteries undergo vascular remodeling. In the first 12 to 20 weeks of gestation, trophoblast cells invade the spiral arterioles and change the muscular walls of the mother's blood vessels. The muscular walls of these blood vessels will have low resistance, large holes, and large capacities.[12]

A critical mediator in the placentation process in the fetus is NO. Pathogenesis process endothelial dysfunction in preeclampsia is divided into two. Firstly, there is poor trophoblast invasion into the spiral arteries during the placentation process. In this case, failure to change the underlying placental artery from a high-low resistance vessel is likely. This case can lead to local ischemia, oxidative stress, and impaired reperfusion of the fetus. Secondly, local damage can disrupt the production process of angiogenetic and anti-angiogenetic factors. Disruption of this process will result in systemic inflammation, endothelial activation, changes in nitric oxide (NO) production, and systemic oxidative stress. If the activation and dysfunction of the vascular endothelium occur in the liver, kidneys, brain, and placenta, the clinical presentation of preeclampsia will appear.[13]

Wu et al. (2021) stated in their research that there is a linear relationship between blood lead levels and preeclampsia. The study showed a low level of lead exposure in the incidence of preeclampsia with a cut-off point of 4.2 g/dl. A significant increase in the risk of preeclampsia can occur with a marked increase in blood lead levels. If the lead level in the blood has exceeded 4.2 g/dl, the risk of preeclampsia increases by 105%.[14]

At the end of the first trimester, lead may be detected in the fetal brain after previous passive diffusion across the placenta. During pregnancy, there is an increase in bone reabsorption, which may lead to lead exposure to the fetus. In this situation, the bones will release more lead than the rest of the body. In addition, women with low calcium intake may also release higher amounts of lead. Lead exposure can enter easily and quickly. It is supported that the placenta cannot protect the fetus from lead exposure and the placenta is a pathway for lead to spread in the fetus. In recent years, there have been several cases of miscarriage, preeclampsia, premature birth, and infant death caused by lead exposure.[15]

However, Liu et al stated that there was no evidence of a link between lead and preeclampsia. Lead levels in the participants' blood were lower than in other studies, which are evidence of the unrelatedness between the two.[16] Tsoi et al argue that women's health can be compromised by lead exposure, even at low levels. Thus, the health effects caused by blood lead levels have become a significant focus of research in recent years.[17]

The result of this study shows that factors affecting nitric oxide (NO) levels are lead levels, distance from residence, smoking status, and living environment. The greatest influence in reducing nitric oxide (NO) levels is the distance of residence, in which the risk of decreasing nitric oxide (NO) levels in preeclampsia pregnant women living ≤10 km from Semen Padang Factory is 6 times compared to those living > 10 km from Semen Padang Factory with 95% CI (1.946-19258) after controlling blood lead levels, status variables, smoking status, and living environment.

The risk of decreasing nitric oxide (NO) levels in preeclampsia that have high lead levels is 2 times compared to preeclampsia with normal blood lead levels with 95% CI (0.652-6.362) after controlling variables of residence distance, smoking status and living environment.

The wind will carry cement dust emissions up to 10 km from the cement plant. The large dust particles settle within 3 to 4 km from the cement plant, and the small ones have carried 8 to 10 km from the cement plant.[18] These data differ from the results of research by Novirsa and Achmadi. The study shows that an area in industrial area can be said to be safe for residential use by the community if it is more than 2.5 km from the operating industrial center.[19]

Cement factories are important emission source of organic and inorganic chemical pollution. Besides, they produce metals, one of which is lead. This industry produces lead which is highly toxic and harmful to humans. Even the chemical cement dust can spread through wind and rain in low concentrations. Moreover, the dust released by the factory into the air will be carried by the wind so that it will expand the exposure range. The industrial waste will be accumulated into the air and it will be influenced by wind speed. However, the source is not moving, so that the surrounding environment receives the highest risk of pollution impacts.[20]

The result of research conducted by Khairiah et al showed that the further the house from the cement factory, the lower the dust content. Distance greatly affects the concentration of dust. Furthermore, dust originating from the activities of cement factory can be spread up to 3000 m and it will be reduced the further the distance from the industry. People living near industrial areas in a distance of less than 3000 meters have a greater risk than people living at a distance of more than 3000-5000 meters of decreased lung function capacity.[21]

The environment around the Semen Padang factory contains heavy metals exceeding the threshold. Moreover, the heavy metals in the sample are estimated coming from PT Semen Padang factory emissions. Most of the heavy metals in residential areas have exceeded the threshold, one of which is lead. The results of the research conducted by Martha and Budiman showed that the five test samples contained one of the heavy metals, lead, which exceeded the threshold. Based on the relationship between magnetic susceptibility values and heavy metal concentrations in the five test samples, it can be concluded that almost all samples taken around Semen Padang Factory contained heavy metals exceeding the threshold.[22]

The higher the concentration of lead particles in the air and the longer the exposure lasts, the greater the number of particles that settle in the body. The severity of lead effects depends on the process of lead exposure that is continuous or intermittent exposure. Continuous exposure will have a more severe effect than intermittent exposure. Lead poisoning through inhalation is 10 times more likely to occur than poisoning through the digestive tract. It is because the inhaled lead will be carried by the bloodstream and pumped directly throughout the body thereby stimulating a toxic effect.[23]

Industrial emissions exposure for a long duration has detrimental effects on various organ systems including the reproductive system in humans. Industrial emission poisoning is a public health problem faced by both developed and developing countries. Despite the fact that the exact pathophysiology of this multisystem disorder is still unclear, oxidative stress is one of the mechanisms involved in preeclampsia. Environmental toxicants that can produce reactive oxygen species (ROS) causes oxidative stress. Moreover, oxidative stress increases the proliferation and transformation of vascular smooth muscle cells and disrupts nitric oxide homeostasis. Nitric oxide (NO) plays a role in blood vessel walls that are endothelial vasodilation, inhibition of platelet activity and smooth muscle cell proliferation and migration. If the homoseity of nitric oxide (NO) is disturbed due to lead in the blood, vasodilation will be disrupted so that the diameter of the endothelium cannot widen, resulting in narrowing of the endothelium which will cause atherosclerosis.[24]

Conclusion

Based on the result of this study, there is a relationship between blood lead levels and nitric oxide (NO) levels in preeclampsia.

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