COMPARISON OF COPPER LEVELS IN NORMAL PREGNANCY WOMEN AND SEVERE PREECLAMPSIA

Tia Reza[1]*, Ariadi[2], Yusrawati[3]

Departemen Obstetri dan Ginekologi Fakultas Kedokteran Universitas Baiturrahmah

*Email: dr.tiareza@gmail.com, 082388289411

ABSTRACT

Hypertension in pregnancy is one of the obstetric complications that cause a lot of morbidity and mortality in the field obstetrics, in addition to bleeding and infection. The incidence of severe preeclampsia is only 5-10% of all pregnancies but is a major cause of maternal and fetal death and is a major contributor to preterm labor. It is currently estimated that severe preeclampsia accounts for 50,000 deaths annually worldwide, in addition to the presence of this disease will increase the need for intensive neonatal care. The purpose of this research is to determine the difference in copper concentration in normal pregnant women with pregnant women with severe preeclampsia. This research is a diagnostic research with approach used is cross sectional study in maternity hospital room of Obstetrics and Gynecology Department of Faculty of Medicine Universitas Baiturrahmah since September 2016-March 2017. Obtained sample of 60 people who meet inclusion and exclusion criteria. The calculation is done by taking blood samples of patients and examined the level of copper. Data analysis was done univariant and bivariate by using T dependent test. there were significant differences in copper levels in patients with severe preeclampsia and normal pregnancy, where the p value <0.05, and the mean test with 95% confidence level was between 0.767-1.023 at 0.895. This means there is a significant difference in copper levels in severe preeclampsia and normal pregnancy. There were significant differences in copper levels in patients with severe preeclampsia and normal pregnancy.

Keywords: Copper, Preeclampsia.

INTRODUCTION

Hypertension in pregnancy is one of the obstetric complications that cause a lot of morbidity and mortality in the field obstetrics, in addition to bleeding and infection. The incidence of severe preeclampsia is only 5-10% of all pregnancies but is a major cause of maternal and fetal death and is a major contributor to preterm labor. It is currently estimated that severe preeclampsia accounts for 50,000 deaths annually worldwide, in addition to the presence of this disease will increase the need for intensive neonatal care.[1]

The incidence of severe preeclampsia in developed countries 4-5 cases per 10,000 live births. In developing countries the incidence of severe preeclampsia varies between 6-10% of cases per 10,000 live births. The incidence of severe preeclampsia in some hospitals in Indonesia is still quite high. In the hospital. M. Djamil Padang incidence of severe preeclampsia in 1998-2003 was 663 cases of 12034 deliveries (5.5%). Data from medical records of patients treated in Obstetrics and Gynecology Section RS M. Djamil Padang in 2010 was found severe preeclampsia patients in 113 cases from 1295 deliveries (8.7%), in 2011 about 119 cases from 1287 deliveries (9.2%) and in 2012 about 140 cases from 1301 deliveries (10.76%) (Madi J, 2003; Zilfira D, 2012). Based on the underlying pathophysiology of severe preeclampsia associated with failure in

trophoblast invasion of the spiral artery, it is necessary to understand the process of trophoblast invasion. The presence of placental developmental abnormalities that underlie the emergence of severe preeclampsia. Therefore, the risk of severe preeclampsia should be known by examination in the first trimester of pregnancy. This step allows obstetricians to take effective preventive intervention measures.[2]

One of the markers for the risk of severe preeclampsia is the increase in copper levels that act as free radicals which is one of the etiological theories of severe preeclampsia that can be found before other medical findings appear.[3] Copper can come from the food and water we consume. The provision of clean water for the benefit of the household such as for drinking water, bath water and for other purposes must meet the requirements set by the Government of the Republic of Indonesia. In accordance with the provisions stipulated in the Regulation of the Minister of Health of the Republic of Indonesia No. 492/MENKES/PER/IV/2010.[4]

Metals in certain levels in drinking water are needed by humans, but excessive levels can be detrimental to health. For example small amounts of copper are required by the body for metabolism. The maximum copper content in drinking water allowed is <2 mg / L.[5]

West Sumatera itself has a copper potential level of 0.2-12%, especially in Solok regency, Timbulun, Lubuk Selasih, Paninggahan and Sei Pagu.[6]

Copper metals include heavy metal essentials, so even though toxic but much needed by humans in small quantities. The toxicity of the new copper will work when it has entered the body of the organism in large quantities or exceeds the tolerance value of the related organism. Copper metal enters into the environmental order can occur naturally and as a side effect of human activities. Naturally, copper enters the water from erosion events, rock erosion or from the atmosphere brought down by rainwater. While from human activities such as industrial activities, copper mining, and industry is one of the pathways that accelerate the increase of solubility in the waters of copper. Copper metal is required by various systems in the human body. Therefore, copper must always be in the diet. To note is to keep the levels of copper in the body is not lacking and also not excessive.[7]

Heavy metals are generally toxic to living things, although some are needed in small quantities. Copper salts are also widely used in agriculture, for example as a "Bordeaux" solution containing 1-3% $CuSO_4$ to eradicate pests on farms. Through various intermediaries, such as air, food, or water contaminated by heavy metals, the metal can be distributed to parts of the human body and some will accumulate. If this condition persists, in the long term it can reach the amount that endangers human health.[9]

The concentration of copper in the human body can be assessed by blood examination. For severe preeclampsia many studies have shown that copper concentrations in blood are elevated in patients with severe preeclampsia, among others seen in the following research journals, but there are also studies.

METHOD

This research is a diagnostic research with approach used is cross sectional study. The research was conducted in RSUP M. Djamil Padang and RSUD M. Hanafiah Batusangkar which is one of Satellite Hospital of Obstetrics and Gynecology Department of Faculty of Medicine Andalas University of Padang. The study was conducted from September 2016 to March 2017. The population is all pregnant women who

control and treated at the Regional General Hospital RS M. Hanafiah Batusangkar and RS M Jamil Padang who meet the criteria of inclusion.

The inclusion criteria were normal pregnant women whose pregnancies were> 20

weeks, pregnant women> 20 weeks with severe preeclampsia, and patients willing to take the study and sign the informed consent sheet. Data analysis was done univariat and bivariate by using T dependent test.

RESULT

A study was conducted to determine differences in copper concentrations in normal pregnant women with pregnant women with severe preeclampsia conducted on 60 pregnant women. The subjects consisted of 30 pregnant

women with severe preeclampsia and 30 normal pregnant women. The study began in September 2016 until April 2017 in RSUD M. Hanafiah Batusangkar and RSUP M. Djamil Padang.

Table 1. Characteristics of study subjects based on severe preeclampsia, maternal age, and parity

Characteristic	Preeclampsia N=30	Normal N=30	P		
Age	31,93±6,627	29,70±5,867	0,172		
Parity					
- Primipara	7 (23,3%)	6 (20%)	0,759		
- Multipara	23 (76,6%)	24 (80%)	0,765		
Pregnancy aged					
- Preterm	12 (40%)	9(30%)	0,425		
- Aterm	18 (60%)	21(70)	0,427		
Blood pressure					
- Sistole	177,00±13,683	110,00±8,709	0,000		
- Diastole	110,33±9,643	73,00±6,512	0,000		
BMI	23,63±1,829			25,23±1,548	0,001
Hemoglobine	9,72±1,302			10,96±1,202	0,021
Leucosit	10.430±2915			9740±2115	0,310
Baby Weight	2328,33±693			3083±505	0,000

Table 1 shows the distribution of maternal characteristics for patients with severe preeclampsia and normal pregnancy, which were assessed for age, parity, gestational age, blood pressure, BMI, hemoglobin, leukocytes and birth weight. Characteristic data are then performed ststistic test.

Table 1 shows that statistical analysis of maternal characteristics was found to be p <0.05 for blood pressure and BMI characteristics. This showed significant differences between blood pressure and BMI characteristics between the severe preeclampsia and normal pregnancy groups.

The p> 0,05 values were obtained for maternal characteristics: maternal age, parity, gestational age, hemoglobin, leukocyte and birth weight, showed no significant differences in maternal age, parity, gestational age, hemoglobin, leukocyte and weight Infants born between heavy preeclampsia and normal pregnancy.

Prior to hypothesis testing, normality test was performed, obtained data of copper content with p 0.000 (p <0,05). Hypothesis test is done by t test. The differences in copper levels in patients with severe preeclampsia and normal pregnancy are shown in Table 2.

Table 2. Differences in Copper Rate in Patients Severe Preeclampsia and Normal Pregnancy

Variabel	Average Difference	CI 95%	P
Copper (µg/L)	0,895	0,767-1,023	0,000

Table 2 shows significant differences in copper levels in patients with severe preeclampsia and normal pregnancy,

DISCUSSION

Table 1 shows that statistical analysis of maternal characteristics was found to be p <0.05 for blood pressure and BMI characteristics. This showed significant differences between blood pressure and BMI characteristics between the severe preeclampsia and normal pregnancy groups. The p> 0,05 values were obtained for maternal characteristics: maternal age, parity, gestational age, hemoglobin, leukocyte and birth weight, showed no significant differences in maternal age, parity, gestational age, hemoglobin, leukocyte and wight Infants born between heavy preeclampsia and normal pregnancy.

P <0.05 in blood pressure statistics test also obtained the same result in previous research that is Murat et al's study, 2015 which reported the mean of sistole blood pressure in severe preeclampsia patient 170 mmHg, and in normal pregnancy 120mmHg, with p value <0.001, as well as for diastole blood pressure value in severe preeclampsia 105 mmHg, in normal pregnancy 72.5 mmHg with p value <0.001. But Murat et al, 2015 does not have a check on BMI. [9.] P <0.05 in blood pressure statistics test also found the same results in previous research that is Bargale et al., 2011 study which reported the mean of sistole blood pressure in patients with severe preeclampsia 162.23 ± 8.73 mmHg, and in pregnancy Normal value is 116,26 ±

where the p value <0.05, and the mean test result with 95% confidence level was between 0.767-1.023 at 0.895.

4,35mmHg, with p value <0,001, so also for diastole blood pressure value in heavy preeclampsia 104,61 ± 5,25 mmHg, normal pregnancy 75,33 ± 4,37 mmHg with p value <0.001. But similar to Murat et al, 2015, Bargale et al, 2011 there is no examination on BMI.

P <0,05 in BMI statistic test showed the same result in previous research that is Kanagal et al, 2014 which reported the result of BMI average in severe preeclampsia patient 27,07 ± 3,07, and in normal pregnancy 24,9 ± 2.32, with a value of p <0.001. Tests on BMI also appear in a study reported by Golmohamad et al, 2008, where the p> 0,05 is 0.84, this is different from the results of this study obtained p value 0.001. The insignificant BMI results were also obtained from Rafeeina et al, 2014 and Ziae et al, 2008.[3,10-13]

A p value of 0.05 was obtained for maternal age characteristics, found in Rafeeina et al's study, 2014 p value 0.44 and Ugwuja et al. 2010, p value of 0.076 showed no significant difference in maternal age characteristics between the severe preeclampsia group and Pregnant normal, but p <0,05 was found in Alghazali 2014 study p value <0oo6.[3,13,14]

A p value of 0.05 was obtained for maternal characteristics: parity, found in the Ugwuja et al, 2010 study of p value 0.134, it showed no significant difference of parity characteristics between the severe

preeclampsia and normal pregnant group, but the p value <0.05 was found in Research Alghazali 2014 value p <0.008. The p> 0,05 was obtained for maternal characteristics: gestational age, found in the Ugwuja et al, 2010 study p value of 0.873 and Ziaei et al, 2008 states insignificant, Golmohamad et al., 2008 p value 0.84, A significant difference in the characteristics of gestational age between the severe preeclampsia and normal pregnant groups, but the p <0.05 score was found in Kanagal et al's study, 2014 p value <0.001.[13-15]

A p value of 0.05 was obtained for maternal characteristics: hemoglobin, found in the Ugwuja et al, 2010 study of 0.444 p value showed no significant difference in hemoglobin levels between hepatic preeclampsia and normal pregnancy. A p value of 0.05 was obtained for maternal characteristics: leukocytes, found in the Ugwuja et al, 2010 study of 0.255 p value showed no significant difference in leukocyte characteristic between the severe preeclampsia and normal pregnant groups. The p> 0,05 was obtained for maternal characteristics: infant weight, but in Kanagal et al, 2014 and Bakacak et al, 2015 the p <0.001 study showed significant differences in the characteristics of infant weight born between the severe preeclampsia group and Pregnant normal.[9,13,14]

Results in Tables 1 and 2 showed significant differences in copper levels in patients with severe preeclampsia and normal pregnancy, where the p value <0.05, and the mean test with 95% confidence were between 0.767-1.023 at 0.895. This means there is a significant difference in copper levels in severe preeclampsia and normal pregnancy. This is consistent with the results of the study by Prasad et al. Reffeina et al. P <0.0001, Al Ghazali et al, 2014 p <0.001 and Murat et al 2014 showed a significant difference between normal pregnant copper levels and severe

preeclampsia, but Research conducted by and Basima et al, Emmanuel et al in 2010, Deep Kanagal 2014 showed levels of copper did not increase in severe preeclampsia.[3,11,14,15]

Micronutrient deficiency is usually found in pregnant women. Deficiency of some elements can make women susceptible to severe preeclampsia, because some elements can regulate the balance between free radicals and antioxidants. Some elements such as copper, zinc contribute in the development of several diseases such as severe preeclampsia Copper is an important mineral in humans and animals. Copper derived from food is reduced to Cu and in small absorption in the stomach and mostly in the duodenum passively and actively at 1.5-4 mg / day. Cu enters into the apical membrane of intestinal enterocytes with carriers such as Ctr1 (copper transporter) and DMT1. Copper transport to the liver mainly uses the means of transport of albumin and trankuprein. Copper is incorporated into cell proteins (including enzymes), but most copper is released from the basolateral membrane of the intestinal cells into the portal blood. The deposits of copper in the liver are metalotionein or ceruloplasmin. Further copper is transported throughout the body by ceruloplasmin and transkuprein. Total body copper is about 75-150 mg, and is found in some body tissues, with the highest expression in the liver, heart, brain, pancreas as well as intermediate expression in the gut. Copper is also removed from the liver as part of the bile. In the gastrointestinal tract, copper can be reabsorbed or removed from the body depending on the body's needs. Expenditure through bile increases when there is excess copper in the body. A little copper is released through urine, sweat and menstrual blood. Copper can be reabsorbed by the kidneys when the body needs it. Unabsorbed copper is removed through the feces. The loss of copper is about 2-3 mg / day. Inside the human body are separated three forms of oxidation ie Cu0,

cuprous (Cu1 +) with cupric (Cu2 +). Cupric form the most in the body that play a role in the biological system. Copper is one of the major minerals needed by the human body, although in small quantities. The distribution of copper in the adult human body is estimated to be 70 - 80 mg. 24.7% were in skeletal muscle, 15.3% in the skin, 14.8% in bone marrow, 19% in bone, 8.0-15% in the liver and 8% in the brain. In patients with severe preeclampsia, copper will produce high reactive hydroxyl radicals. Copper reacts with H2O2 to produce a radical OH. [17]

Copper participates as an electron in a reduction oxidation reaction that will catalyze free radicals including hydroxyl radicals that contribute to oxidative stress which is one of the causes of severe preeclampsia.[18] This radical can initiate the process of lipid peroxidation that can cause cellular damage as described in the above chapter that reacts with "polyunsaturated fatty acids" (PUFA) in cell membranes and lipoproteins in the plasma that make up lipid peroxide which will cause cell endothelial damage. Many studies have shown that copper concentrations increase in severe preeclampsia compared with normal pregnant women. Serum copper concentrations also increased when compared with mild and severe preeclampsia. Possible causes of this change are related to hormonal, metabolic, enzyme from severe preeclampsia and copper carrier proteins.[3,11,14-16]

This study has some limitations, the design of this study is cross sectional study, preferably copper levels assessed at the time of conception and followed by the process of pregnancy whether the patient will become severe preeclampsia or not.

CONCLUSION

A study was conducted to determine differences in copper concentrations in normal pregnant women with pregnant women with severe preeclampsia, and the result were significant, whereas p < 0,05.

Authors may suggest: examination of copper levels from preconception can be made to assess the risk of severe preeclampsia and further research is needed on the association of copper levels assessed at conception and followed by the process of pregnancy whether or not the patient will become severe preeclampsia.

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