STUDY OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE ENZYME AND ISOPROSTANE ON PREECLAMPSIA WITH NIFEDIPINE, M ETHYLDOPA, AND MAGNESIUM SULFATE THERAPY

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ABSTRACT

Objective: The objective of this research is to measure erythrocyte glucose-6-phosphate dehydrogenase (G6PD) enzyme activity and isoprostane and to correlate enzyme activity of G6PD with proteinuria and isoprostane in pregnant with proteinuria after the administration of nifedipine, methyl dopa, and magnesium sulfate.

Methods: This cross-sectional study was held in Soewandi Hospital, Surabaya, East Java, Indonesia. This study used total sampling as much as 30 pregnant women with proteinuria who got nifedipine, methyl dopa, and magnesium sulfate administration. G6PD enzyme activity was measured from plasma by spectrophotometric method; plasma isoprostane was measured by competitive-ELISA method; and proteinuria urine spot was analyzed by urine dipstick from standardized laboratory of the hospital. Statistical analysis used in this study was Spearman’s correlation coefficient.

Results: In this research, the effect of proteinuria +1 (OR=0.056) is lower than proteinuria +3 level on the presence of high G6PD enzyme activity, and proteinuria +2 (OR=0.933) is lower than proteinuria +3 level on the presence of high G6PD enzyme activity in pregnant women with proteinuria. G6PD enzyme was positively correlated (p=0.08) with proteinuria, and the connection was statistically significant. There was no significant statistic correlation between G6PD enzyme activity and isoprostane concentration (p=0.797).

Conclusion: This study found correlations between the enzyme activity of G6PD and proteinuria as the marker of renal damage in pre-eclampsia (PE) with the administration of nifedipine, methyl dopa, and magnesium sulfate. However, it had no correlation with isoprostane as the marker of oxidative stress. This study suggests that there should be a concern about understanding the pathophysiology of proteinuria for possibility of drug target for individuals with PE.

Keywords: Preeclampsia, Glucose-6-phosphate dehydrogenase enzyme, Proteinuria, Isoprostane, Nifedipine, Methyldopa, Magnesium sulfate.

INTRODUCTION

Preeclampsia is an emergency case in pregnancy due to pregnancy-induced hypertension (systolic pressure >140 mmHg, diastolic pressure >90 mmHg) which develops after 20 weeks of gestation complemented by one or more of the new proteinuria onset, maternal organ dysfunction and uteroplacental dysfunction [1]. Pre-eclampsia is a major cause of maternal and perinatal morbidity and mortality, around 3–10% of all maternal deaths in the world [2]. The incidence of preeclampsia (PE) has risen in low socioeconomical status, it might be associated with increased prevalence of chronic hypertension, obesity, and diabetes [3]. Indonesia as a developing country also has pre-disposition of PE. In Dr. Kariadi Hospital, Semarang, Central Java, Indonesia, PE incidence was around 2.45% and the main cause of maternal death around 40% in 1999 [4]. In Dr. Soetomo Hospital, Surabaya, East Java, Indonesia from July 2012 to June 2013, severe PE patients were about 461 patients and 24 patients (7%) developed into hemolytic elevated liver enzyme low platelet count syndrome complication [5].

Preeclampsia is a unique disease in pregnancy and requires crucial attention because the etiology and pathophysiology are still underdetermined. A completely satisfactory and unifying hypothesis has not emerged. Schlembach (2003) calls this disease with the disease of theories, with one of the causes being oxidative stress [6]. Recent studies have investigated the association between PE and G6PD deficiency. The result showed that there were incident of G6PD deficiency in PE and normal pregnancy although the correlation is not statistically significant [7,8]. However, the study also demonstrated that there was normal G6PD enzyme activity in PE. Research on G6PD deficiency in PE was rarely conducted overseas and none yet in Indonesia.

G6PD enzyme deficiency is an enzyme disorder with the highest prevalence, estimated at around 470 million of the entire world population in mid-2007 (6.625 billion) (7.09%). The diagnosis of G6PD enzyme deficiency occurs when G6PD enzyme activity was <60% which will cause clinical signs. Prevalence deficiency of G6PD enzymes in Indonesia in men is 5.9% and in women is 3.6%. In this study, there were 11 cases (35.5%) of 31 patients with G6PD deficiency and a history of poor pregnancy with no known cause [9–12].

Glucose-6-phosphate dehydrogenase (G6PD) enzyme has a role as endogenous antioxidant enzymes and a key of enzyme of pentose phosphate pathway that forms a part of glycolysis. G6PD is an enzyme for producing reduced nicotinamide adenine nucleotide phosphate and plays a role as coenzymes and acts by reducing glutathione and stabilizing catalase. G6PD deficiency causes increasing production of reactive oxygen species (ROS) leading to imbalance between oxidants and antioxidants called oxidative stress. Some study hypothesized that
RESULTS AND DISCUSSION

Descriptive data are shown in Table 1. The results of the study obtained an average G6PD enzyme activity was 12.68 U/g Hb (normal reference 4.8-12.5), proteinuria was 1.85 (negative normal reference), body mass index (BMI) was 31.07 kg/m² (reference overweight: 25-29.9; obesity Grade I: 30-34.9; obesity Grade II: 35-39.9; and obesity Grade III: >40), isoprostane level was 11.2 pg/mL, Hb level was 11.2 g/dL (normal reference 11.7-15.5), systolic BP was 160.43 mmHg (normal <140 mmHg), and diastolic BP was 93.6 mmHg (normal <90 mmHg). From these data, it could be indicated that PE patients who had been administered by nifedipine, methylprednisolone, and magnesium sulfate therapy had normal G6PD activity with values of proteinuria, BMI, systolic and diastolic BP were still above normal values based on reference.

Table 2 shows that there was a significant relationship between G6PD enzyme activity variables with proteinuria, proteinuria with BP, and BP with the occurrence of PE in patients who had been treated with nifedipine, methylprednisolone, and magnesium sulfate. However, there was no significant relationship between isoprostane with G6PD or proteinuria. From the correlated data, the regression test was continued so that the results of causal relationships between variables could be found which can be seen in Table 3 and Fig. 1. The results showed that the relationship between G6PD enzyme activity and PE was hypothesized through variable proteinuria and BP (systolic and diastolic). G6PD activity correlates directly with systolic BP, systolic BP correlates directly with diastolic BP, and diastolic BP correlates directly with PE (Fig. 1).

The aim of this study was to correlate between G6PD enzyme activity, proteinuria, isoprostane, and BP in preeclamptic patients with nifedipine, methylprednisolone, and magnesium sulfate therapy. The result from this study showed that there was positive correlation between G6PD enzyme activity and proteinuria due to the production of ROS by hypertension (Table 2). Hypertension is strongly associated with increased oxidative stress and reduced PO2 in the kidney, as a result, the risk for development of progressive kidney dysfunction will be increased. Furthermore, there is increasing evidence that oxidative stress contributes to and accelerates hypertension. Other studies indicate that BP induces ROS formation dependent on ANG II. ANG II increases arterial BP elevation and increases mitochondrial oxidative stress [17,20]. However, mitochondrial nitric oxide (NO) production increases as O2 is reduced [13], which results in elevated levels of ONOO- , the end product reaction between O2 and NO [21,22].

Some studies suggest that in PE patients, there is a large concentration of ROS in the placental and maternal circulation, and the antioxidant capacity is lower than the normal placenta, which causes oxidative stress. ROS production causes impaired remodeling, platelet aggregation, loss of vasodilation, inflammation, and endothelial dysfunction [13]. One of the markers of oxidative stress is measuring the level of membrane lipid damage products, isoprostane [23]. Isoprostane is produced by the lipid peroxidation process. The result in this study was not showing correlation between G6PD enzyme activity with isoprostane [23]. The administration of the drug combination nifedipine, methylprednisolone, and magnesium sulfate in pregnant women with hypertension and proteinuria was recommended to be done immediately at least 20 weeks of gestational age, as hypertension and proteinuria may cause long-term complications for both mother and child. The results of this study showed that PE patients who had been treated with nifedipine, methylprednisolone, and magnesium sulfate had normal G6PD activity with values of proteinuria, BMI, systolic and diastolic BP were still above normal values based on reference. The results of this study showed that PE patients who had been treated with nifedipine, methylprednisolone, and magnesium sulfate had normal G6PD activity with values of proteinuria, BMI, systolic and diastolic BP were still above normal values based on reference.
Table 2: Statistical analysis; Spearman correlation between G6PD, proteinuria, isoprostane, and pre-eclampsia

| Variable 1 | Variable 2 | Spearman correlation (p) |
|------------|------------|--------------------------|
| G6PD       | Proteinuria| p=0.008*                  |
| Proteinuria| Systole    | p=0.021*                  |
| Proteinuria| Diastole   | p=0.001*                  |
| Systole    | Diastole   | p=0.0001*                 |
| Proteinuria| BMI        | p=0.036*                  |
| Systole    | PE         | p=0.017*                  |
| Isoprostane| G6PD       | p=0.797                   |
| Isoprostane| Proteinuria| p=0.99                   |

*Significant. G6PD: Glucose-6-phosphate dehydrogenase, PE: Pre-eclampsia

Table 3: Statistical analysis; regression analysis between significant correlation variables

| Variable 1 | Variable 2 | (p)  | B          |
|------------|------------|------|------------|
| G6PD       | Proteinuria| 0.0001* | 0.534     |
| Proteinuria| Systole    | 0.019*  | 0.396      |
| Systole    | Diastole   | 0.0001* | 0.665      |
| Diastole   | PE         | 0.0037* | 0.336      |

*Significant. G6PD: Glucose-6-phosphate dehydrogenase, PE: Pre-eclampsia

CONCLUSION

The present study found that there were correlations between the enzyme activity of G6PD and proteinuria as a marker of kidney damage in preeclamptic patients with nifedipine, methyldopa, and magnesium sulfate therapy. This study suggested that there was no association between G6PD enzyme activity and isoprostane as a market of stress oxidative in preeclamptic patients with nifedipine, methyldopa, and magnesium sulfate therapy. However, there is still more possibility to do further studies on any drug target for PE by reducing risk factors of becoming eclampsia, reducing proteinuria and isoprostane. The present study suggests conducting further research by taking samples after the use of the drugs in PE.

CONFLICTS OF INTEREST

All authors declared that there were not any conflicts of interest in this study.

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