International Journal of Pharma Research and Health Sciences, 2021; 9 (1): 3286-3290
DOI:10.21276/ijprhs.2021.01.04
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CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

Original Article

Analysis of Low Dose Aspirin on Platelet Aggregation Percentage in High-Risk Pregnancy Hypertension

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ARTICLE INFO:
Received: 05 Feb 2021
Accepted: 14 Feb 2021
Published: 28 Feb 2021

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ABSTRACT:
Objective: Low dose aspirin (LDA) is one of platelet aggregation agents in high-risk pregnancy that is believed to prevent complication by inhibiting thromboxane A2 as a strong vasoconstrictor in platelet. It can inhibit platelet aggregation involved in pathophysiology of pregnancy hypertension. The aim of this study is to analyse the effect of LDA on platelet aggregation in pregnant patient with high-risk hypertension.
Material and methods: A prospective observational method was conducted in this study. It was approved by the Ethics Committee of Haji Teaching Hospital Surabaya. Data was collected from July to September 2018 involving 18 patients divided into three groups who have age of 35-39 years old in the majority. The range of gestational age in this study was 19-37 weeks. Platelet aggregations on plasma were measured before and 14 – 30 days after LDA use. The collected data were statistically analyzed by using a paired t-test.
Results: Platelet aggregation percentage using collagen agonists was an increase of 0.8% ($p > 0.05$) in the old patient group and followed by 6% ($p > 0.05$) in the group of patients who did not get LDA. Whereas in the group of new patients showed a decrease of 6% ($p > 0.05$). While ADP agonists showed that the group of new patients decreased by 17% ($p > 0.05$), followed by the group of patients who did not use LDA of 9% ($p > 0.05$) and the old patient group was 4% ($p > 0.05$).
Conclusions: Low-dose aspirin use did not affect a decrease in platelet aggregation values.

Keywords: high risk pregnancy, low-dose aspirin, platelet aggregation.

1. INTRODUCTION

Pregnancy in high-risk hypertension is a risk of complication in preeclampsia (PE) to eclampsia (E). PE is the secondary causes of maternal mortality that can occur in 1-8% of pregnant women in worldwide, one of the five causes of maternal mortality in developing countries [1-3].As the Indonesian Demographic and Health Survey (IDHS), the 2012 maternal mortality rate showed a significant increase from 228 to 359 maternal deaths per 100,000 live births. The proportion of hypertension in pregnancy (HP) as one of the biggest causes of maternal fatality in Indonesia increased significantly in 2013 [4].

HP shows an overview of endothelial dysfunction, the risk of thrombosis that triggers an imbalance between PGI2 (vasodilator) and TXA2 (vasoconstrictor) in utero-placental and systemic. This process continues until platelet hyperaggregation occurs due to platelet hyper activation and hypercoagulation [5-9]. Platelets have prominent role in the etiology of PE because of their involvement in the homeostasis and thrombosis processes [10-12]. In patients who are at high risk of PE, a decrease in PGI2 and an increase in TXA2 are seen at week 13 of gestation. One of the clinical manifestations of increased platelet aggregation in PE occurs after week 20 of gestation [13].

The prevalence and pathogenesis of the occurrence of PE underlie a particular treatment. Prevention or delay of PE can be done by providing prophylactic therapy, namely platelet anti-aggregation drugs [14]. The recommended anti-aggregation of platelets is LDA (75-162 mg / day) [15]. LDA can neutralize the TXA2 / PGI2 imbalance within 2 weeks in prothrombotic conditions [9]. A meta-analysis research conducted by Henderson-smart, et al. (2010) involving 59 trials showed that low-dose aspirin (75 mg) reduced the risk of PE by 17%, with a similar reduction in the risk of death in infants (14%) and a decrease in the risk of premature birth (8%). The use of LDA is used as a

prevention of blood clots because there is a blood clotting process that appears in preeclamptic conditions which can cause serious further complications [16].

This study aimed to analyze the effect of using low-dose LDA on the percentage of platelet aggregation by examining the ex vivo platelet response to various agonists. Platelet aggregation is the most useful in vitro test for platelet function tests today and is still the gold standard for detecting platelet disorders [17]. This study is expected to provide an overview of platelet activation or aggregation and information on the use of low-dose LDA in the prevention of PE in patients with high-risk pregnancy for hypertension so that it can be used as a clinical practice guide. In addition, giving low doses of LDA is expected to be effective in preventing PE during pregnancy by using the percentage marker of platelet aggregation.

2. MATERIALS AND METHOD

This research is a prospective observational study with a longitudinal design that has been declared ethical clearance by the health research ethics committee of Surabaya Haji Hospital with the number: 073/10 / KOM.ETIK / 2018. The research sample with the criteria attached to Table 1 was carried out at the Obstetrical and Gynecology Clinic of the Haji Hospital and Wonokromo Primary Health Center, Surabaya in July-September 2018.

Table 1: Research Sample Criteria

Sample Criteria		
Inclusion	**Exclusion**	**Drop Out**
1. Pregnant women with high risk factors, both receiving or not receiving LDA therapy 1 x 80 mg / day orally. 2. New and old patients who have not received or have received LDA 80 mg / day orally. 3. Willing to follow and sign the research consent form	1. Patients on other anti-aggregation/anticoagulant therapy. 2. Patients with thrombocytopenia, heart disease, HELLP syndrome. 3. Patients on NSAID or cortico-steroid therapy	1. Patients who do not continue taking medication (LDA) or stop therapy suddenly. 2. The patient withdrew from the study.

In this study, 18 sample was divided into three groups, (1) new patient group is pregnant women at high risk of hypertension who did not taken acetosal 80 mg/ day, (2) old patient group that took acetosal 80 mg / day and (3) group patient who did not take acetosal 80 mg / day.

The patient's blood sample in the form of plasma will be observed the value of % platelet aggregation using Light Transmission Aggregometry (LTA) with the addition of collagen agonists as strong agonists and ADP as weak agonists through different platelet activation pathways. Plasma was collected twice, namely before and after using LDA within a period of 14-30 days. The% platelet aggregation data obtained will be analyzed statistically.

3. RESULTS

The study sample is 18 patients, divided into 3 groups, namely 4 new patients, 9 old patients and 5 patients who did not receive 80 mg / day LDA therapy. Patient characteristics are often found include (1) maternal age (35-39 years) with a mean gestational age of 28.944 ± 6.254 weeks, (2) a history of multiparity (1-3) with a mean of 1.611 ± 1.243 parity, (3) Body Mass Index (> 30 kg / m2), (4) signs of pregnancy risk (edema, proteinuria, and MAP), (5) other clinical features such as dizziness, pain in waist, and pain in neck, (6) duration of LDA therapy with a mean 5,667 ± 6,380 days at a dose of 80 mg / day, and (7) a history of contraception use including injections, pills, and IUD.

In this study, the % value of platelet aggregation was obtained against two agonists. Figure 1 shows the % platelet aggregation against collagen agonists has increased by 0.8% (from 69,556 ± 21,308 to 70,111 ± 21,115) in the old patient group and 6% (from 76,000 ± 20,322 to 80,400 ± 15,598) in the group of patients who did not get LDA, whereas in the new patient group it decreased by 6% (from 82,250 ± 19,568 to 78,000 ± 16,145). Distribution of % platelet aggregation to collagen agonists in three patient groups was in the hyperaggregation, normoaggregation, and hypoaggregation ranges.

The assessment of % platelet aggregation against ADP agonists is presented in Figure 2 show a decrease in the three groups, namely 17% (from 103,250 ± 7,932 to 85,500 ± 22,398) in new patients, 4% (from 86,111 ± 15,243 to 82,889 ± 22,740) in old patients, and 9% (from 100,000 ± 12,083 to 90,800 ± 11,367) of patients not receiving LDA. The distribution of the% value of platelet aggregation against ADP agonists shows a tendency to be in the hyperaggregation range.

Measurement of % platelet aggregation is important to determine the control of increased platelet aggregation. Statistical analysis of the % platelet aggregation observed before and after aims to determine the significance of the change in% platelet aggregation that occurs. The results of the analysis are listed in Figures 1 (Collagen Agonists), which shows that there is no significant difference in the % of platelet aggregation before and after in the new patient group ($p = 0.771$), old patients ($p = 0.889$), and patients who do not use LDA ($p = 0.578$). Whereas in Figures 2 (ADP agonists) there was no significant difference in the% platelet aggregation in the new patient groups ($p = 0.105$), old patients ($p = 0.698$), and patients who did not use LDA ($p = 0.237$).

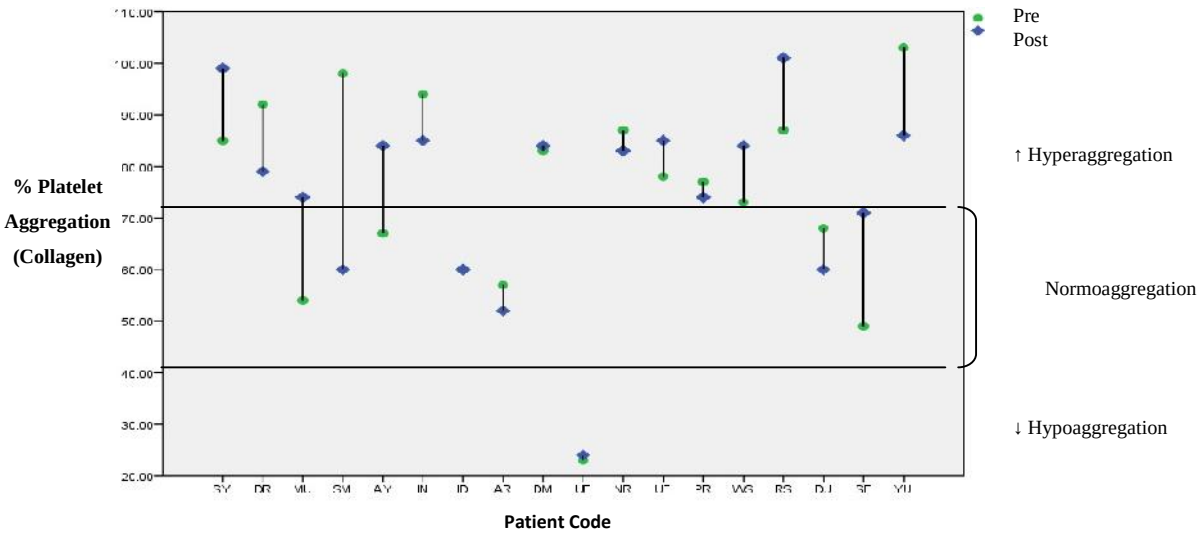

Fig 1: Platelet Aggregation Percentage (%) Profiling in Collagen

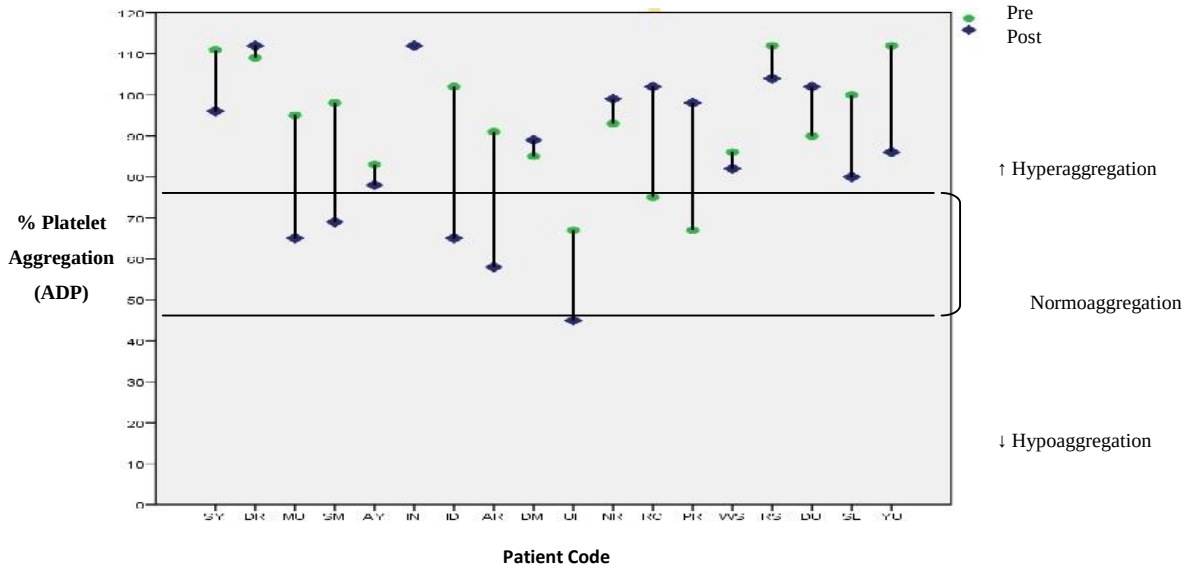

Fig 2: Platelet Aggregation Percentage (%) Profiling in ADP

4. DISCUSSION

Platelet hyperactivation and hypercoagulation conditions trigger the risk of thrombosis which is the basic mechanism for various pregnancy complications, such as PE [6]. Changing in the balance of PGI2 and TXA2 were seen at 13 weeks' gestation in patients at high risk of PE. A decrease in PGI2 and an increase in TXA2 production triggers utero-placental and systemic vasoconstriction as well as increased platelet aggregation and decreased uteroplacental blood flow [7-9]. One of the clinical manifestations of PE is that there is an increase in platelet aggregation at more than 20 weeks of age [13].

Measurement of % platelet aggregation in this study used two agonists, namely collagen and ADP. Collagen is a strong agonist that directly induces platelet aggregation, TXA2 synthesis, and secretion of platelet granules. Based on theory, the aggregation method using collagen agonists is more sensitive in evaluating the effects of acetosal [18]. While ADP is a weak agonist that induces platelet aggregation without causing secretion of platelet granules [12].

The different agonists indicate the location of the injured blood vessel wall and play a role in the overall platelet adhesion process. The platelet adhesion process begins with exposure to the matrix components (collagen and vWF) on

the blood vessel walls with receptors on the platelet surface membrane. Platelet activation occurs after the agonist binds to its receptors. Collagen agonists bind to the GPVI receptors and α2β1 integrin, while ADP agonists bind to the P2Y12 and P2Y1 receptors on the platelet surface [19].

Changing in the % value of platelet aggregation was tested by statistical analysis to determine the significance of changes before and after that occurred. Statistical analysis used for data processing in each group used the Wilcoxon signed rank test. The results of statistical analysis, there was no significant difference in this study, showed that the value of % platelet aggregation in the group of patients who received therapy (new patients and old patients) was influenced by one factor of the time to start LDA therapy which varied. In this study, the initiation of LDA therapy was from weeks 12 of gestation to weeks 37. The meta-analysis reported that of 45 randomized control trials, low-dose acetosal started after 16 weeks of gestation showed a moderate reduction in preeclampsia, whereas use before weeks 16 showed a significant reduction in severe preeclampsia and foetal growth restriction. Meanwhile, another meta-analysis stated that the decrease only occurred in the group who started LDA therapy before 16 weeks of gestation at a dose of 100 mg or more [20].

Several supporting studies gave results that platelet aggregation increased significantly from the first to the third trimester in response to collagen agonists ($P < 0.001$) and arachidonic acid ($P < 0.001$). Arachidonic acid acts via the COX TXA2 pathway to induce platelet aggregation. Platelets showed increased reactivity to arachidonic acid in the second and third trimesters of this study. Increased aggregation of arachidonic acid explains that in the condition of pregnancy there is a picture of a prothrombotic condition. The results provide evidence that platelet reactivity during pregnancy changes when compared to nonpregnant conditions and these changes depend on gestational age and agonist compounds to activate platelets [11].

Another study is a prospective study gave results that the effect of collagen agonist compounds, arachidonic acid, and epinephrine on platelet activation in the aspirin group and the group that did not receive aspirin showed a significant difference ($P < 0.0001$). The difference in agonist compounds affected the results of the percentage of aggregation obtained, namely for the ADP compound 83.8%, collagen 74.8%, arachidonic acid 77.9%, and epinephrine by 72% in the group that did not get aspirin. This study used a pharmacodynamic effect using low-dose acetosal (81 mg) which targets platelet function during pregnancy [21, 22].

Limitations in this study included the small sample size, limited study time, different types of risk factors, comorbid or complicated complications, disease severity, varying gestational age and initiation of LDA therapy and the level of adherence for each patient. This is because the average patient has entered a sufficient gestational age, LDA that has been given in previous health facilities, so that these factors cannot be controlled during the study. The number of samples is too small and the homogeneity of patient characteristics causes the results of the data analysis to be insignificant, so it is suggested that further research can be done with a larger sample size and can be done at a younger gestational age to see the progress of the disease and the effectiveness of LDA therapy given.

5. CONCLUSION

This study confirmed the use of low-dose acetosal as a preventive therapy in high-risk pregnant women does not affect the decrease in the platelet aggregation percentage value for either patients who have not taken acetosal yet or patients who have received it.

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CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

SOURCE OF FUNDING: None.

AVAILABILITY OF DATA AND MATERIALS: Not applicable.

CONSENT FOR PUBLICATION: Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: 073/10 / KOM.ETIK / 2018.