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Platelet count and platelet indices in early life of infant with retinopathy of prematurity

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ABSTRACT

Background and objectives. Retinopathy of prematurity (ROP) is a complication of prematurity. Early detection of ROP is important because its management depends on prevention of severe ROP and its complications. Pro- and anti-angiogenic factors are involved in ROP pathogenesis. Platelet store and release these factors, but its role as predictor of ROP is still obscure. This study aimed to compare platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and platelet mass index (PMI) value between two age groups in early life of infant diagnosed with ROP.

Materials and methods. This study was retrospective study of medical record data of infants born at "dr. Soetomo" General Academic Hospital Surabaya during 2021-2023. The infants were divided into two groups, they who have complete blood count result (CBC) in 0-7 days old (group 1) and 8-28 days old (group 2). We evaluated platelet count, MPV, PDW, and PMI value from CBC data. These data were analyzed using suitable statistical test.

Results. Total of 126 infants were involved in this study. It consisted of 62 infants in group 1 and 64 infants on group 2. Platelet count was significantly different between groups (230.460±102.040/µL vs 313.664±182.890/µL, p=0,002). Value of MPV, PDW, and PMI were also significantly higher in group 2 (p<0.001). Frequency of thrombocytosis (>500.000/µL), high MPV (>10.05 fL), and high PMI (3640 fL/nL) were also significantly higher in group 2 (p<0.05).

Conclusions. Higher platelet count, MPV, PDW, and PMI value were observed in 8-28 days old infant with ROP. They also more likely to experienced thrombocytosis, high MPV, and high PMI value.

Keywords: retinopathy of prematurity, pathogenesis, platelet, platelet index

Abbreviations

CBC – complete blood count
IGF-1 – Insulin-like growth factor 1
MPV – mean platelet volume
PGDF – platelet-derived growth factor
PDW – platelet distribution width
PMA – post menstrual age
PMI – platelet mass index
ROP – retinopathy of prematurity
VEGF – vascular endothelial growth factor

INTRODUCTION

Retinopathy of prematurity (ROP) is a complication of prematurity. Enhanced neonatal care improves survival rates of preterm infant and may heighten the risk of prematurity such as ROP. The prevalence of ROP in various countries was ranged from 13.7-73% [1]. Its serious complication is blindness but it could be prevented through early and periodic screening of high risk infant. Abnormal proliferation of retinal vascular formation is the hallmark of retinopathy of prematurity. The pathogenesis consists of two phase; vascular regression phase (phase 1) and neovascularization phase (phase 2).

Platelet store and release pro- and anti-angiogenic factors and involve in ROP pathogenesis, but previous studies showed conflicting result of platelet role [2,3]. Thrombocytopenia (<100.000/µL) in first

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week of life was predictor of ROP [3,4], while another study found that thrombocytopenia in 2-6 weeks old was the predictor of ROP [5]. Conversely, Mendoza et al [6] found that thrombocytosis was the risk factor of ROP. Other different studies found no correlation between thrombocytopenia and ROP in early life [7-9]. This study aimed to investigate platelet count, MPV (mean platelet volume), PDW (platelet distribution width), and PMI (platelet mass index) value in early life of infant diagnosed with ROP.

MATERIALS AND METHODS

Over the period of January 2020 until December 2022, infant diagnosed with ROP at dr. Soetomo General Hospital Surabaya were included in this observational retrospective study. The infants were diagnosed as ROP by trained ophthalmologist. Infant with gestational age <37 weeks and have complete blood count (CBC) result in first month of life were included in this study. Infant with congenital anomaly and incomplete data was excluded. The infants were divided into two groups according to age when CBC was performed; 0-7 days old (group 1) or 8-28 days old (group 2). The Ethics Committee of the local hospital gave permission for this study (number 1174/LOE/301.4.2/XII/2022).

The data was retrospectively collected from medical record. Documentation was kept of the subject characteristic (sex, gestational age, birth weight and APGAR score) and CBC parameter (platelet count, MPV, and PDW value). Value of PMI was obtained by multiplying platelet count and MPV value. Data of platelet count, MPV, and PMI value was transformed into categorical data using cut off from previous study. Thrombocytopenia was defined as platelet value <100000/µl while thrombocytosis was platelet value >500000/µL [6]. High MPV was defined as MPV value >10.05 fL and high PMI was MPI value >3640 fL/nL [7,10].

Data presented as frequency and median ± interquartile range (minimal-maximal). Comparison test between two groups was performed using Mann Withney U test because all data were not normally distributed. Chi-square test was used to compare categorical data between two groups. Those parameters who reached p value < 0.05 were considered statistically significant.

RESULTS

In this study, total of 126 infants who met the inclusion criteria were involved. Group 1 consisted of 62 infants and group 2 consisted of 64 infants. Platelet value was collected from all subject, but MPV and PDW value just collected from 50 infants in group 1 and 55 infant in group 2, while PMI value collected from 50 infants in group 1 and 50 infants in group 2. Their gestational ages ranged from 25-27 months and birth weight ranged from 800-2900 grams. Table 1 showed subject characteristics (sex, gestational age, birth weight, and 1 minute APGAR score) of two age groups. No significant different was found on the parameters between two groups.

Comparison of platelet count, MPV, PDW, and PMI value in two age groups were presented in table 2. Platelet count, MPV, PDW, and PMI value was higher in group 2 than group 1. Table 3 presented comparison of categorical data for each parameter between two groups. Frequency of thrombocytopenia was not significantly different between groups, but group 2 has significantly higher frequency of thrombocytosis, high MPV, and high PMI value.

TABLE 1. Subject characteristic of two age groups

Parameter	Group 1 (n=62)	Group 2 (n=64)	p
Sex*			
Boy	40 (64,5)	45 (70,3)	–
Girl	22 (35,5)	19 (29,7)	
Gestational age (week)**			
(25-37)	32±2		0.748
(26-37)	32±2.25		
Gestational age (week)*			
34-<37	8 (13)	5 (7,8)	0,434
32-<34	27 (43,5)	31 (48,4)	
28-<32	24 (38,7)	21 (32,8)	
<28	3 (4,8)	7 (11)	
Birth weight (gram)**			
(800-2900)	1400±300		0.225
(800-2600)	1400±412.5		
Birth weight (gram)*			
≥2500	3 (4,8)	2 (3,1)	0,848
<2500	24 (38,7)	23 (36,0)	
<1500	29 (46,8)	30 (46,9)	
<1000	6 (9,7)	9 (14,0)	
APGAR score (1 min)*			
7-10	20 (32,25)	16 (25,0)	0,649
4-6	22 (35,5)	24 (37,5)	
0-3	20 (32,25)	24 (37,5)	

Data presented as: *n (%) **median ± interquartile range (min-max)

TABLE 2. Comparison of platelet count and platelet indices value between two groups

Parameter	Group 1 (n=62)	Group 2 (n=64)	p
Platelet (/µL)	239000 ± 123750 (20000-541000)	294500 ± 232750 (6000-895000)	0.002*
Parameter	**Group 1 (n=50)**	**Group 2 (n=55)**	**p**
MPV (fL)	10.30 ± 1.15 (8.3-13.0)	11.50 ± 1.80 (9.3-45.2)	<0.001*

PDW (%)	10.7 ± 2.7 (8,2-18.1)	13.10 ± 4.32 (9.1-23.2)	<0.001*
Parameter	**Group 1 (n=50)**	**Group 2 (n=50)**	**p**
PMI (fL/nL)	2484 ± 1343,55 (220-5090)	3625,4 ± 3089,25 (76.8-30900)	0.001*

Data presented as median ± interquartile range (min-max), *p<0,05

TABLE 3. Comparison of categorical data between two groups

Parameter	Total	Group 1 (n=62)	Group 2 (n=64)	p
Thrombocytopenia	13 (1,03)	7 (11,2)	6 (9,3)	0,724
Thrombocytosis	11 (8,73)	1 (1,6)	10 (15,6)	0,005*
Parameter	**Total**	**Group 1 (n=50)**	**Group 2 (n=55)**	**p**
High MPV	78 (74,3)	30 (60,0)	48 (87,2)	0,001*
Parameter	**Total**	**Group 1 (n=50)**	**Group 2 (n=50)**	**p**
High PMI	28 (28,0)	4 (8,0)	24 (48,0)	<0,001*

Data presented as n (%), *p<0,05

DISCUSSION

This retrospective study showed that subject characteristics between two age groups were not different on sex, gestational age, birth weight, and APGAR score. Our main result in this study was different with majority of previous study result. Our study found that platelet count of 8-28 days old infant was significantly higher than 0-7 days old infant and thrombocytosis was frequently found in 8-28 days old infant. While majority of previous study found that ROP was associated with thrombocytopenia.

Previous study was found that thrombocytopenia either in first week of life or more than 1 week old was associated with ROP. Thrombocytopenia in post menstrual age (PMA) >30 weeks (phase 2 ROP) also associated with severe stage of ROP who required laser photocoagulation therapy [11,12]. Thrombocytopenia (<100.000/µL) in first week of life was also associated with more severe ROP such as type 1 ROP and aggressive ROP [3]. This result was supported by another study that found platelet value in first day of life was significantly lower in infant with ROP than control [4].

Study in mice model of oxygen-induced retinopathy found that whole platelet transfusion decreased retinal VEGF mRNA expression and inhibited retinal neovascularization. Transfusion of degranulated platelet in same mice model did not showed the same result. This phenomenon showed that platelet α-granules stored and released anti-angiogenic factor. Platelet stores both pro-angiogenic factor such as vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-1, IGF-binding protein 3, platelet-derived growth factor (PDGF), and anti-angiogenic factor such as platelet factor 4 and endostatin in its α-granules [12]. Release of αgranules contents are controlled by various signaling pathway. Adenosine diphosphate promotes VEGF release, while thromboxane A2 promotes release of endostatin [13]. Different role of platelet on angiogenesis could possibly a result of different micro environment condition [12]. For example, in acute phase of endothelial injury, platelet clot is formed and activate protease-activated receptor (PAR1) signals to release pro-angiogenic factors. In the late phase, the clot is crosslinked to factor XIII then activate PAR4 to release anti-angiogenic factors [2].

Other study found a possibility that thrombocytopenia indirectly associated with ROP. Platelet value of infant with ROP who observed weekly over 2-6 weeks significantly lower than control, but the different became insignificant after adjustment with confounding variable such as sepsis, blood transfusion, and bronchopulmonary dysplasia [5]. Sepsis could promote platelet activation, endothelial injury, and bone marrow suppression, while bronchopulmonary dysplasia causes ventilation–perfusion mismatch and hypoxia. Thrombocytopenia may be a sign of other conditions, such as intrauterine growth retardation, neonatal sepsis, or necrotizing enterocolitis [14].

Our study found that thrombocytosis (>500.000/µL) frequently found in infant with ROP age 8-28 days. This result supported by previous study that very preterm infant with ROP was associated with thrombocytosis after first week of life, even after adjustment with gestational age, sepsis, and oxygen supplementation [6]. Thrombocytosis frequently found in preterm infant with low birth weight, and correlate with high concentration of thrombopoietin caused by low expression of its receptor on infant platelet <1 month old. High concentration of thrombopoietin promotes megakaryocyte to produce more platelet [15].

High platelet value is associated with serum VEGF concentration, but there is no evidence shows its effect on retinal VEGF concentration [16]. Previous study found that VEGF was not main mediator of angiogenesis. Blockage of VEGF receptor in endothelial cell inhibit 15% angiogenesis process, while aspirin inhibit VEGF release from platelet granules, endothelial proliferation, and tubule formation [13,17]. Effect of aspirin shows that platelet promotes neovascularization possibly through thromboxane-A2 pathway [18]. Thromboxane-A2 is produced by ischemic retinal tissue. It promotes expression of p-selectin glycoprotein ligand-1 (PSGL-1) that triggers platelet adhesion and endothelial cell activation [19]. This explanation possibly explained the different result of our study on thrombocyte

role during ROP pathogenesis.

Platelet indices consist of MPV, PDW, and MPI. The parameters reflect platelet activation and associates with systemic inflammation. They are better reflects platelet activity than platelet count alone. Bigger MPV value shows higher platelet activity because it contains more granules. Our study found significantly higher MPV value in 8-28 days old infant with ROP. This result was supported by previous study that found higher MPV value in both 3 days old and 1 month old ROP infant than control [20]. Infant with severe ROP who require laser photocoagulation also had higher MPV on 7 days old [7]. Infant with MPV value more than 10.05 fL in PMA >36 weeks old experienced higher stage of ROP (≥3) [10]. Our study result also found that 8-28 days old infant with ROP frequently had MPV value >10.05 fL than 0-7 days old infant. High MPV shows high activity of VEGF during phase 2 of ROP pathogenesis. Despite, another study found no significant difference of MPV value in infant with PMA >38 weeks between severe and mild ROP (9.12 ± 1.52 vs 8.74 ± 0.81) [9].

Platelet distribution width shows size variation of platelet. It also reflects platelet activity. Its role in ROP is still not widely studied. Our study found that PDW value was higher in 8-28 days old infant. The result supported previous study that PDW value was higher in 1 month old infant with ROP than control [20]. There was no study investigated PDW value cut off in infant with ROP. Another study found an opposite result that there was no significant different in PDW value between 1 month old infant with ROP and control [21].

Platelet mass index shows overall platelet mass. It is considered as a novel platelet parameter that reflects platelet activity better than platelet count and MPV value. It also provides information about VEGF concentration and platelet-endothel interaction that promotes neovascularization. Previous study found that PMI value in 1, 7, and 10 days old was associated with ROP [22]. Our study also found that 8-28 days old ROP infant experienced high PMI value (>3640 fL/nL) more than 0-7 days old ROP infant. The result supported by Korkmaz et al [7] study that found PMI value significantly different between infant with severe and mild ROP.

Several limitation of our study needs to consider. This study was retrospective, single-centered, relatively small sample, and wide range of gestational age may cause demographic bias. Complete blood count examination was influenced by several factors such as acute stress, systemic inflammation, infections, drugs, and storage condition of blood sample.

Management of ROP in developing country is more complicated than developed country because better care in neonatal intensive care unit allows higher percentage of preterm infant survive. Oxygen monitoring is not routinely observed because limitation on human resources and monitoring tools in developing country, therefore infant with older gestational age and larger birth weight could have ROP [23]. Coordination of pediatrician and ophthalmologist, better neonatal care, early and routine screening are important to prevent severe ROP and its complication. Identification of ROP risk factor could raise screening program success because early screening would find ROP from mild stadium. Our study result provides potential predictor of ROP from complete blood count result in early life of preterm infant.

CONCLUSION

In conclusion, significantly higher platelet count, MPV, PDW, and PMI value were found among 8-28 days old infants with ROP. Higher frequency of thrombocytosis, high MPV and high PMI were also frequently found in 8-28 days old baby with ROP.

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