Relationship between Mean Platelet Volume and Bronchopulmonary Dysplasia and Intraventricular Hemorrhage in Very Low Birth Weight Neonates

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Abstract: Background and Objective: Mean platelet volume (MPV) may be considered as an indicator of platelet function and it may have an association with adverse neonatal outcome. Thus, we hypothesized that high MPV could represent a risk factor for the development of bronchopulmonary dysplasia (BPD) and intaventricular hemorrhage in very low birth weight neonate (VLBW). **Patient and Method**: 134 very low birth weight neonates were enrolled, they were stratified into BPD (n=20), IVH (n=36), and non BPD non IVH control group (n=78), MPV was demonstrated during the first 24-48 hours of life. **Results**: Platelet counts were similar in the BPD, IVH and control groups but MPV was significantly higher in BPD than in non-BPD groups (12.3±1.4 versus 9.6±1.2 fl, p=0.001). MPV in IVH was significantly higher than non- IVH group (11.6±2.0 versus 9.6±1.2 fl, P<0.001). MPV size > 11 fl was significantly higher in RDS (48.0%) compared to non-RDS (0%) groups (P<0.001). MPV size > 11fl was associated with higher mortality rate (72.7%) compared to MPV size <11fl (33.3%). **Conclusion:** Our data support the hypothesis that changes in MPV value at 24-48 hours of life could represent an easy and early biomarker for identification of neonates at higher risk for the development of BPD and IVH.

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1. Introduction

Blood platelets in the newborn demonstrate several activities both in physiological and pathological conditions including; haemostasis, the integrity of blood vessels, transportation and phagocytosis (1). In preterm newborns, blood platelet count is found to be decreased depending on birth weight and gestational age (2). There is some evidence that the functions of blood platelet are related to gestational age (3).

Platelet counts in full-term are not different compared to preterm neonates and within the normal range for adult of 150-450×109 /L (4). The mean platelet volume (MPV) averages 7to 9 fl for both full-term and preterm neonates (5). Previous studies reporting that mean platelet volume was greater in term than in preterm neonates (6).

MPV has been recognized in the adult as an important cardiovascular pathology risk factor (7&8)). Larger platelets are more reactive and associated with a shortened bleeding time. Thus, MPV is predictive of stroke, acute myocardial infarction and restenosis of coronary angioplasty (9). MPV has been poorly investigated in preterm neonates. MPV was found similar or lower in preterm than term neonates (5&10). Changes in MPV may be a marker of platelet production as well as an indicator of change in severity of diseases such as respiratory distress syndrome (RDS) and neonatal sepsis (11).

Bronchopulmonary dysplasia (BPD) is the product of complex interactions between several factors that adversely affect the lung in the neonatal period (12). High MPV could represent a risk factor for the development of BPD in preterm neonates by two different mechanisms. First, because of the more frequent need for mechanical ventilation and the following ventilation induced lung injury. Second due to the marked reactivity of large platelet which could favor the pathological deposition of fibrin in the lung microcirculation and alveolar spaces of preterm neonates with respiratory distress syndrome (RDS) through activation of the coagulation system and/or concomitant insufficient fibrinolysis (13).

Intraventricular hemorrhage (IVH) is a major complication of the prematurity. The etiology of IVH is multifactorial and is primarily attributed to the intrinsic fragility of the germinal matrix vasculature and disturbances of cerebral blood flow (14). Coagulation and platelet function are important in the pathogenesis of IVH. Prolonged bleeding time, prothrombin time, partial thromboplastin time, lower platelet count and distributed platelet function have all reported as risk factors for the development of IVH (15).

The aim of this study is to assess the possible relationship between MPV and the occurrence of BPD and intracranial hemorrhage (IVH) in very low birth weight preterm neonates.

2. Material and Methods

This is a prospective study carried out at intensive care unit (NICU) of Kasr Elaini Hospital, Cairo University over 10 month period starting from November 2010 to August 2011. Data confidentiality was preserved according to the Revised Helsinki Declaration of Bioethics (16).

The study group included 134 very low birth weight neonates (VLBW) weighting less than 1500 gm. Enrolled neonates were divided into three group; BPD group (n=20), IVH group (n=36), non BPD-non IVH; the control group (n=78). Neonates with thrombocytopenia,congenital malformations, fetal hydrops, or inherited error of metabolism were excluded.

The following data were collected for each neonate: gestational age (GA), birth weight (BW), gender, Apgar score at 5 minutes, mode of delivery, maternal diseases as preeclampsia, antenatal steroids, oxygen therapy and highest value of fraction of inspired air (FIO2), RDS occurrence, surfactant administration, need for mechanical ventilation (MV), complications as patent ductus arteriosus, sepsis, BPD and IVH occurrence. BPD was defined as oxygen requirement at 36 weeks of postconceptional age (17). Grading system for IVH into four grades was adapted from **Papile et al (18).**

Blood sample were drawn from patients by venipuncture during the first 24-48 hours of life for complete blood count (CBC). Hematological tubes with K2-EDTA were used to collect blood samples. Platelet count and MPV determination were performed using the Coulter Counter (Coulter Electronics, Hialeah, FL).

Statistical Methods

Data management and analysis were performed using Statistical Package for Social Sciences (SPSS) version 17.

The t-test was used to compare the means of the groups. Comparisons between the three groups with respect to numerical data were done using one analysis of variance or Kruskal-Wallis test for non - normal distributed variables. Comparisons between categorical data were performed using the chisquare test. Because of the multiple comparisons, p-values were adjusted using the Bonferroni corrections. To measure the strength of association between MPV and platelets, the Pearson's correlation coefficient was calculated. To study the independent effect of the different prognostics on BPD or IVH, a stepwise logistic regression was performed (19). All p-values are two-sided. P-values ≤0.05 were considered significant.

3. Results

Tables (1) demonstrates that neonates with BPD had statistically significant difference with the following parameters; lower birth weight (P=0.004), Apgar score at 5 minute (P=0.022), as well as, higher need of oxygen therapy (P=0.034), mean FIO2 (P<0.001), need of mechanical ventilation with longer duration on ventilation (P<0.001), PDA (P<0.032), RDS (P<0.001) and sepsis (P<0.004) than the non- BPD group. Similarly, neonates with IVH had statistically significant difference with the control group regarding; lower gestational age (P=0.003), lower birth weight (P<0.001), Apgar score at 5minute (P<0.001), higher oxygen therapy (P<0.002), mean FIO2 (P<0.001), need of mechanical ventilation (P<0.001), PDA (P=0.032), higher occurrence of RDS (P<0.001) and sepsis (<0.006).

Platelet counts were similar in the BPD, IVH and control groups (Figure 1), but MPV was significantly higher in BPD than non-BPD group (12.3±1.4 vs 9.6±1.2 fl, p=0.001). MPV in IVH group was significantly higher than non- IVH group (11.6±2.0 vs 9.6±1.2 fl, P<0.001). (Figure 2).

Table 1: Demographic, clinical and laboratory data of the studied groups.

	BPD (n=20)	IVH (n=36)	Non BPD non IVH (n=78)	P
Gender Male female	 12(60%) 8(40%)	 12(33.3%) 24(66.7%)	 45 (57.7%) 33(42.3%)	 0.852[a] 0.003[b] 0.038[c]
GA (wk) 27-30 31-34	 14 (70%) 6 (30%)	 26 (72.2%) 10 (27.8%)	 33 (42.3%) 45 (57.7%)	 0.054[a] 0.003[b] 0.003[c]
GA (wk)	29.8±4.2	29.6±3.2	30.7±3.0	0.074[a] 0.004[b] 0.003[c]
Mode of delivery Vaginal (n=41) Cesarean section (n=93)	 2(10%) 18(90%)	 12 (33.3%) 24(66.7%)	 27 (34.6%) 51(65.4%)	 0.061[c]

antenatal steroids (n=16)	4(20%)	6(16.7%)	6(7.7%)	0.188[c]
Preeclampsia (n=24)	6(20%)	6(16.7%)	12(15.4%)	0.307[c]
BW(gm) <1245gm (n=68) >1245gm (n=66)	1161.9±368.0 16 (80%) 4(20%)	1090.5±414.4 28(77.8%) 8(22.2%)	1304.2±333.2 24(30.8%) 54(69.2%)	0.004[a] <0.001[b] <0.001[c]
Apgar score (5min) <8 (n=76) ≥8 (n=58)	 14(70%) 6(30%)	 32(88.9%) 4(11.1%)	 30(38.5%) 48(61.5%)	 0.022[a] <0.001[b] <0.001[c]
RDS (n=98)	20(100%)	36(100%)	42 (53.8%)	<0.001[a] <0.001[b] <0.001[c]
Surfactant use (n=21)	4(20%)	8(22.2%)	9(11.5%)	0.292[c]
O_2 therapy (n=116)	20(100%)	36(100%)	60 (76.9%)	<0.034[a] <0.002[b] <0.001[c]
MV (n=70)	20(100%)	26(72.2%)	24 (30.8%)	<0.001[a] <0.001[b] <0.001[c]
Sepsis (n=63)	14(70%)	22 (61.1%)	27 (34.6%)	<0.004[a] <0.016[b] <0.003[c]
PDA (n=64)	12(60%)	28 (77.8%)	24 (30.8%)	<0.032[a] <0.001[b] <0.001[c]
Cord PH	7.3±0.2	7.2±0.2	7.3±0.2	0.169[c]
Duration of ventilation(d)	34.0±7.0	8.5±4.0	8.5±3.4	<0.001[a] 0.998[b] <0.001[c]
Platelet count ($x10^3/mm^3$)	242.5±118.8	278.5±99.8	263.4±142.4	0.136[c]
MPV (fl)	12.3±1.4	11.6±2.0	9.6±1.2	0.004[a] <0.001[b] <0.001[c]
MPV (fl) ≤11 (n=78) >11 (n=47)	 0 20	 12(33.3%) 24(66.7%)	 75 (96.2%) 3 (3.8%)	 0.001[a] <0.001[b] <0.001[c]
Outcome Discharge (n=65) Death (n=69)	 8 (40%) 12 (60%)	 12(33.3%) 24 (66.7%)	 45 (57.7%) 33 (42.3%)	0.214[a] <0.016[b] <0.038[c]

a BPD vs controls
b IVH vs controls
c Overall P value

Table-2: MPV size among neonates with or without RDS

	RDS(n=98)	Non RDS(n=36)	P
MPV≤11fl (n=87)	51 (52.0%)	36 (100%)	<0.001
MPV>11fl(n=47)	47 (48.0%)	0 (0%)	

Table (2) shows that MPV size >11flwas significantly higher in RDS compared to non-RDS groups (P<0.001).

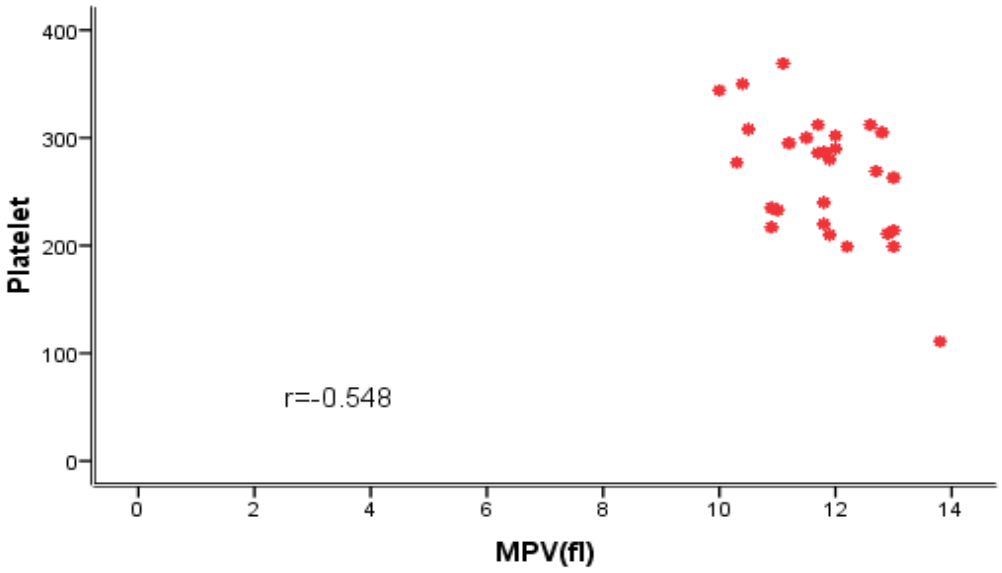

Figure 1: Relationship between platelet count and MPV in BPD and IVH groups.

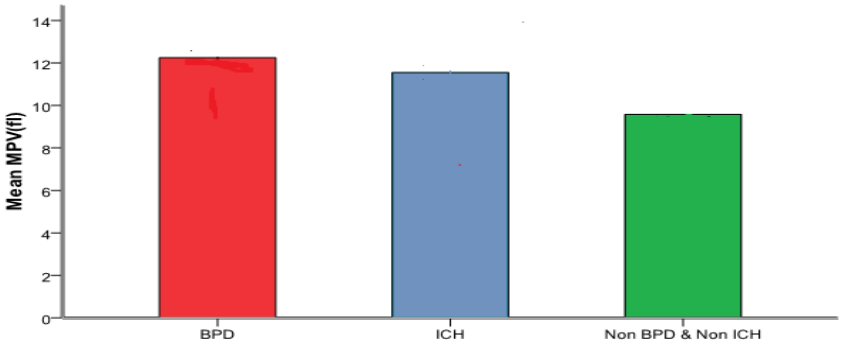

Figure 2: MPV distributions among the studied groups.

Table- 3: MPV size and outcome among studied groups.

	Discharge(n=20)	Death(n=36)	P
MPV≤11fl (n=12)	8(66, 7%)	4(33.3%)	0.012
MPV>11fl(n=44)	12(27.3%)	32(72.7%)	

Table (3) demonstrates that MPV size > 11fl was associated with significantly higher mortality rate (72.7%) compared to MPV size <11fl (33.3%) (P=0.012).

Table -4 Multivariate stepwise logistic regression analysis of selected variables in infants who developed BPD

		95% C.I. for OR		
	OR	Lower	Upper	P-value
Birth weight <1250 g	8.7	2.5	29.5	0.001
Apgar score <8 at 5 min	3.5	1.1	11.1	0.031

Multivariate analysis (table-4) demonstrated that birth weight<1250gm and Apgar score <8 at 5 minutes were independent risk factors increasing the risk of developing BPD (P=0.001 and 0.031respectively) with odds ratios 95%.

Table -5 Multivariate stepwise logistic regression analysis of selected variables in infants who developed IVH

		95% C.I.for OR		
	OR	Lower	Upper	P-value
Gender (male)	9.6	1.2	75.3	0.031
MV	12.0	1.9	76.0	0.008
Birth weight <1250 g	9.0	1.7	47.0	0.009
Apgar score <8 at 5 min	11.4	1.8	72.7	0.010
MVP >11 fL at 24–48 h of life	65.6	8.2	525.7	<0.001

Multivariate analysis among cases of IVH (table-5) demonstrated that male gender (P=0.031), need of MV (P=0.008), birth weight<1250 gm (P=0.009), Apgar score <8 at 5 min (P=0.010) and MPV >11 fl (<0.001) were independent risk factors increasing the risk of developing IVH (P=0.031, 0.008, 0.009, 0.010, <0.001 respectively) with odds ratio 95%.

4. Discussion

The aim of this study is to detect possible relationship between MPV and occurrence of BPD and IVH in very low birth weight preterm neonates.

In the current study, we found that the preterm neonates who developed BPD were more significantly affected by RDS, higher need of oxygen therapy, higher mean FIO2, with longer duration on mechanical ventilation as compared to the non-BPD group. These findings are in agreement with **Dani et al (20)** who found that preterm neonates with BPD had higher incidence of RDS, need of mechanical ventilation and significantly higher oxygen therapy and mean FIO2 (P<0.001).

Lower birth weight and Apgar score at 5 minutes are independent risk factors for BPD occurrence in this study. **Merritt et al (21)** described that the risk factors of BPD included; fetal and neonatal infection, abnormal stretch of the developing airways and alveoli, altered expression of surfactant proteins (or genetically altered proteins), polymorphisms of genes encoding for vascular endothelial growth factors and reactive oxygen species result in impaired gas exchange in the developing lung.

MPV > 11fl was significantly higher in BPD than non-BPD groups (P=0.001).This is also similar to **Dani et al (20)** who observed that MPV >11fl was significantly higher in BPD group (P=0.033) compared to the control group.

In our study, MPV was significantly higher in RDS than non-RDS groups. This is in accordance with **Canpolat et al (21)** who found that neonates with RDS had significantly higher MPV than neonates without RDS (P=0.00029).

Disruption of alveolocapillary membrane integrity in RDS results in leakage of coagulation factors into alveolar spaces. High levels of activated procoagulant factors and insufficient fibrinolysis leads to alveolar fibrin deposition and hyaline membrane formation in neonates with high MPV (22). Fibrinogen and related products are known to be potent inhibitors of surfactant. Thrombin and plasmin that accumulate in the alveolar spaces induce chemotaxsis and aggregation of platelets and neutrophils. Increased levels of procoagulants (e.g.plasminogen activator inhibitor-1) may induce pulmonary damage and local platelet activation (23). Therefore, high MPV may favor BPD development by worsening RDS through surfactant inhibition (20).

In addition, treatment of RDS including oxygen therapy and mechanical ventilation may represent the main risk factors of BPD development because of the related ventilation-induced lung injury and oxidative damage (21).

In this study, we observed that MPV at 24-48 hours of life was significantly higher in preterm neonates with IVH than non-IVH group and MPV>11fl was an independent risk factor for IVH development. This is against a study reported by **Dani et al (20)** who found that MPV was similar in preterm neonates with or without IVH (P=0.256).

Other independent risk factors for development of IVH in this study included; male gender, lower birth weight and Apgar score at 5 minute, and need of mechanical ventilation. In a study reported by **Linder et al (24)** independent risk factors for development of intraventricular hemorrhage in very low birth weight included; fertility treatment (P=0.023), pneumothorax (P=0.024) and early sepsis (P=0.049).

In the current study, platelet counts were similar in BPD, IVH and control groups and there was negative relationship between MPV and platelet count. **Canpolat et al (21)** and **Aliberti et al (25)** found an inverse relationship between platelet count and MPV in preterm neonates. In the light of their study, MPV may be a marker of platelet production.

In a study done by **Wasiluk et al (10)** Platelet count was significantly lower in preterm neonates in comparison with full-term neonates (P=0.0001), they considered MPV as a marker of platelet production. **Sola-Visner (26)** explained the underlying mechanism of neonatal thrombocytopenia and suggest that neonatal megakaryocytes are smaller and of lower ploidy and fewer platelet. The

megakaryocyte diameter is 15.3µm in neonates, whereas it is 19.4 µm in adults. Similarly, **Arad et al (5)** observed that platelet count and MPV increase in term neonates.

The limitations of this study are the small size of the study groups and inability to evaluate MPV with BPD stages and IVH grades.

In several conditions, increased platelet count was associated with decrease in MPV values such as inflammatory bowel disease and rheumatoid arthritis or an increase in MPV may accompany a lower platelet count such as hyperthyroidism (27).

5. Conclusion

MPV value at 24-48 hours of life could represent an easy and early biomarker for identification of neonates at higher risk for the development of BPD and IVH. Larger platelet can induce worsening of RDS and consequent inflammatory and oxidative damage due to the greater need of mechanical ventilation and oxygen therapy.

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