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Original Article

Is the First Postnatal Platelet Mass as an Indicator of Patent Ductus Arteriosus?

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Abstract

Background: The aim of this study is to evaluate whether there is an association between the platelet mass and patent ductus arteriosus (PDA) closure in premature newborns.

Methods: Preterm infants (gestational age ≤33 weeks) with hemodynamically significant PDA (group 1, n = 178) and a control group of preterm infants without PDA (group 2, n = 211) were retrospectively evaluated between August 1, 2013 and July 30, 2015 in the neonatal intensive care unit (NICU). Platelet counts and platelet indices including mean platelet volume (MPV), and platelet mass (platelet count x mean platelet volume) in the first 24 hours of life, demographic findings and morbidities were recorded.

Results: No differences were observed in demographic findings between the study groups in terms of birth weight, gestational age, gender and maternal risk factors. The mean platelet count in the first postnatal hemogram in group 1 and group 2 were 189.43 ± 72.14 ($X10^3$ /mm^3) and 206.86 ± 70.11($X10^3$/mm^3), respectively ($P < 0.05$). The MPV were similar in both groups ($P > 0.05$). Platelet mass values were 1443.70 ± 572.40 fL/nL in Group 1 and 1669.49 ± 1200.42 fL/nL in group 2. There was a statistically significant difference in platelet mass values between the two groups ($P = 0.011$). Multivariable analysis including presence of thrombocytopenia, MPV and platelet mass showed that hemodynamically significant PDA was not independently associated with platelet count <150 000 (OR = 1.001, 95% CI 0.980–1.023; $P = 0.921$), MPV (OR = 0.967, 95% CI 0.587–1.596; $P = 0.897$) or platelet mass (OR = 0.999, 95% CI 0.997–1.002; $P = 0.681$). The optimal cut-off value of platelet mass for patients with PDA was ≤1530.8 fL/nL (area under the curve [AUC]: 0.580), with sensitivity of 58% and specificity of 56.2% ($P = 0.008$).

Conclusion: Our data suggest that platelet count, MPV, and platelet mass do not contribute to closure of PDA in premature newborns.

Keywords: Patent ductus arteriosus, Platelet count, Platelet mass, Preterm infant

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Introduction

In the intrauterine period, ductus arteriosus, located between the main pulmonary artery and the descending aorta, directs the right ventricular volume toward the aorta, since the lungs are collapsed. The shunt turns left to right in the postnatal period with the increased systemic vascular and decreased pulmonary vascular resistance. Patent ductus arteriosus (PDA) is physiologically evaluated within the first three days of life in preterm and term infants.[1] Its incidence is 57/100 000 in term infants, while PDA may be seen in 1/3 of preterm infants with a birth weight between 500–1500 g and half of infants under 1000 g.[2–5]

PDA affects the heart and lungs in the acute period. It may lead to myocardial dysfunction because of the 'ductal steal' phenomenon and the load on the left side of the heart. Effective systemic perfusion may not be maintained and organ blood flow may be compromised in time, resulting in intraventricular hemorrhage, necrotizing enterocolitis (NEC) and acute kidney failure. Because of the left-to-right shunt, increased capillary permeability in the lungs, increased interstitial and alveolar pulmonary edema and deterioration of lung compliance may lead to bronchopulmonary dysplasia (BPD).

Closure of PDA in the postnatal period occurs owing to numerous mechanisms. Intracellular calcium, which is increased with delivery, leads to phosphorylation in the light chain of myosin through Rho/Rho kinase, providing continuous vasoconstriction. Contraction of the smooth muscle cells of the ductus creates a hypoxic area, resulting in endothelial damage. Vascular remodeling occurs following the release of proinflammatory cytokines, adhesion molecules and transforming growth factor beta (TGF-β) which in turn leads to permanent closure.[6] The role of platelets in the closure of PDA was first reported in animal trials conducted by Echtler et al in 2010.[7] The authors reported that platelets caused aggregation in the closure process of the ductus and anatomical closure of PDA did not occur in mice with platelet dysfunction. A study conducted by Echtler et al on 123 preterm infants between 24 and 30 weeks of gestational age reported that PDA closure did not occur in the thrombocytopenic group and thrombocytopenia was an independent risk factor in the closure of the ductus.[7]

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In another study by Boo et al, thrombocytopenia was reported to be a risk factor for hemodynamically significant PDA and failed closure with indomethacin.[8] In their study, Dani et al reported that a platelet count less than 100 000/mm^3 was a risk factor for the incidence of hemodynamically significant PDA, although it did not change the response to ibuprofen therapy. They reported that MPV, as an indicator of the platelet activity, did not affect the incidence of hemodynamically significant PDA or response to treatment.[9] In a study by Sallmon et al. on 1350 premature infants, no correlation was observed between platelet count in the first 24 hours and the incidence of hemodynamically significant PDA (hsPDA) or the closure of PDA.[10] The inverse relationship between platelet size and platelet count in humans has prompted the development of platelet mass concept. Platelet mass has been proposed as a better predictor of production/regulation.[11]

In our study, we reviewed the platelet mass of preterm infants with hsPDA in the first 24 hours in the NICU and compared the findings to those without PDA to determine whether there is an association between platelet mass and PDA incidence.

Patients and Methods

This historical cohort study was conducted in a tertiary level neonatal intensive care unit (NICU) between August 1, 2013 and July 30, 2015. We included preterm infants with gestational age ≤ 33 weeks, birth weight <1500 g and echocardiographic evidence of hsPDA as well as premature newborns without PDA. Infants with incomplete data, severe asphyxia (5th-minute Apgar score of 3), structural cyanotic congenital heart disease, primary pulmonary hypertension, congenital anomalies, hydrops fetalis, inherited errors of metabolism and those with early sepsis were excluded.

Initially, a total of 461 inborn infants who were ≤33 weeks of gestational age were eligible for the study. A total of 178 premature infants with hsPDA and a total of 211 premature infants without PDA who fulfilled the inclusion criteria were included in the study. Echocardiogram was used to diagnose hsPDA (group 1: hsPDA; group 2: premature newborns without PDA).

Demographic and Clinical Data

Patient characteristics including gestational age, gender, birth weight, antenatal steroid, type of delivery, 5th-minute Apgar score**,** respiratory distress syndrome (RDS), maternal risk factors including preterm prolonged rupture of membranes, chorioamnionitis and preeclampsia were collected for all infants.

Diagnosis and Treatment of PDA

Hemodynamically significant PDA was diagnosed with echocardiographic examination. Echocardiographic Doppler ultrasound evaluation was performed routinely in very low birth weight (VLBW) infants at the age of 48 to 96 hours. Based on echocardiographic findings, hemodynamically significant PDA was defined as one with an internal ductal diameter ≥1.5 mm and/or with a left atrium (LA)/aortic root (AO) ratio ≥1.5. Two-dimensional color Doppler echocardiography examinations were performed with Philips EnVisor C HD ultrasound (Royal Philips Electronics, Amsterdam, The Netherlands). A multifrequency 12 MHz sector probe was used. Intravenous or oral ibuprofen (Pedea, Pedea®, Orphan Europe, Paris, France; or Pedifen, Pedifen® Atabay, Istanbul, Turkey) treatment was started for medical treatment in patients diagnosed with hsPDA. Successful response to COX inhibitor treatment was defined as absence of ductal shunt flow 24 to 48 hours after the end of pharmacotherapy. The groups were compared in terms of demographics, morbidities, and platelet measurements such as count, mean platelet volume (MPV), and platelet mass (platelet count × mean platelet volume).

Platelet Measurements

Complete blood counts were performed for the patients and controls during the first 24 hours. Samples for complete blood count were obtained by venous umbilical catheter, venipuncture, or rarely arterial puncture. Platelet count and MPV determinations were performed using the Coulter Counter model LH (Coulter Electronics, Hialeah, FL) and recorded. Platelet mass values were calculated by multiplying platelet count (×10^3/mm^3) by MPV (fL). In our study, low platelet count was defined as platelet count <150 × 10^3/mm^3.

Statistics Analysis

Statistical analyses were performed using the SPSS software (version 16, SPSS, Inc, Chicago, Illinois, USA). To test the normal distribution of variables, visual (histogram and probability graphics) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests) were used. Clinical characteristics of infants are described by mean values and standard deviation, or rates and percentage. Univariate statistical analysis was performed using the Student *t* test for continuous variables with normal distribution, Mann-Whitney U test for continuous data with no normal distribution, and Fisher exact test or chi-square test for categorical variables. To determine the optimal cut-off value for platelet mass measured in PDA, the receiver operating characteristic (ROC) curve analysis was used. Logistic regression analysis was carried out to determine the most probable independent variables affecting the development of hsPDA. A *P* value < 0.05 was considered statistically significant.

Results

After exclusion of some infants for various reasons, the

study protocol was eventually completed for 389 patients. There were 178 preterm infants in group 1 and 211 preterm infants in group 2. Patient characteristics are shown in Table 1. Groups were similar in terms of features such as gestational weeks, birth weight, gender, preeclampsia and chorioamnionitis. Median gestational age and birth weight of patients were respectively 29 weeks and 1025 g in group 1, and 30 weeks and 1080 g in group 2 (Table 1).

The mean platelet count in the first postnatal hemogram was 189.43 ± 72.14 × 10^3/mm^3 in group 1 and 206.86 ± 70.11 × 10^3/mm^3 in group 2. Median thrombocyte count was significantly lower in the PDA group compared to the control group (P = 0.040) (Table 2). The median values of MPV in group 1 and group 2 were 7.4 fL and 7.7 fL, respectively. MPV values were similar between the two groups (P = 0.327).

Platelet mass values (obtained by multiplying the platelet count by MPV) were 1443.70 ± 572.40 fL/nL in group 1 and 1669.49 ± 1200.42 fL/nL in group 2. There was a statistically significant difference in the platelet mass values of the two groups (P = 0.011) (Table 2).

The optimal cut-off value for platelet mass was ≤1530.8 fL/nL (area under the curve [AUC]: 0.580) for patients with PDA, with a sensitivity of 58% and specificity of 56.2% (P = 0.008) (Figure 1).

Multivariable analysis including presence of thrombocytopenia, MPV and platelet mass showed that hemodynamically significant PDA was not independently associated with platelet count <150 000 (OR = 1.001, 95% CI 0.980–1.023; P = 0.921), MPV (OR = 0.967, 95% CI 0.587–1.596; P = 0.897) or platelet mass (OR = 0.999, 95% CI 0.997–1.002; P = 0.681) (Table 3).

Discussion

In this study, we investigated the correlation between platelet mass and the incidence of PDA. We could not find a correlation between platelet count, MPV and platelet masses of the hsPDA group and the group without PDA.

Experimental studies suggest that platelet-triggered ductal sealing is critically involved in definite ductus arteriosus closure. Whether thrombocytopenia contributes to persistently PDA in humans is controversial. The correlation between platelets and closure of the ductus arteriosus was first described by Echtler et al. It was reported in their animal trial that besides endothelial damage, platelets also play a role in the closure of the ductus and that the closure did not completely occur in cases which developed platelet dysfunction.[7] In a study by Alyamac Dizdar et al which compared 154 cases of hsPDA in the premature group and 207 cases in the group without PDA, thrombocytopenia and high PDW were reported to be correlated with hsPDA, but not with MPV. The same study reported that platelet number did not affect medical closure of the ductus.[12] Similarly, it was stated in a study by Dani et al that platelet count <100 (×10^3/mm^3) at the time of delivery increased the incidence of PDA by 4.5 folds and constituted an independent risk factor, but it did not change the response to ibuprofen therapy.[9]

Table 1. Demographic and Perinatal Characteristics of the Study Infants

	Group 1 (n = 178)	Group 2 (n = 211)	95% CI	*P*
Gestational week, wk[a]	29 (24–33)	30 (23–32)	0.00–1.01	0.092
Birth weight, g[a]	1025 (320–2020)	1080 (440–1940)	-49.96–84.59	0.154
Male gender, No. (%)[b]	95 (53.4)	96 (45.5)	-0.18–0.02	0.122
Cesarean delivery, No. (%)[b]	135 (75.8)	169 (80.1)	-0.04–0.13	0.312
Premature rupture of membranes, No. (%)[b]	39 (21.9)	62 (29.4)	-0.01–0.16	0.094
Preeclampsia, No. (%)[b]	47 (26.4)	41 (19.4)	-0.15–0.01	0.101
Antenatal steroid, No. (%)[b]	123 (69.1)	135 (64)	-0.21–0.16	0.094
APGAR scores at 5th min[a]	8 (3–9)	8 (4-9)	0.25–0.78	0.159
RDS, No. (%)[b]	163 (91.6)	94 (44.5)	-0.55–-0.38	**0.001***
BPD, No. (%)[b]	81 (45.5)	34 (16.1)	-0.38–-0.21	0.001*
NEC, No. (%)[b]	6 (3.4)	1 (0.5)	-0.15–0.01	0.032*
Pneumothorax, No. (%)[b]	12 (6.7)	4 (1.9)	-0.09–-0.01	0.017*
Duration of hospitalization, days[c]	52.83 ± 38.34	33.20 ± 23.47	-25.11–-12.69	0.001*

Abbreviations: NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia.
*P < 0.05; [a]median (minimum-maximum), Mann-Whitney U test; [b] No. **(%)**, chi-square or Fisher exact test; [c]Mean ± standard deviation, independent student t test.

Table 2. Comparison of Groups in Terms of Platelet Count, Mean Platelet Volume and Platelet Mass

Parameters	Group 1 (n = 178)	Group 2 (n =211)	95% CI	*P*
Platelet count, (X10^3/mm^3)	189.43 ± 72.14	209.86 ± 70.11	1.90–32.14	0.040*
Platelet mass, fL/nL	1443.70 ± 572.40	1669.49 ± 1200.42	13.56–438.02	0.011*
MPV, fL	7.4(5.5–12.9)	7.7(5.5–13.8)	-0.12–0.37	0.327

Abbreviation: MPV, mean platelet volume.
*P < 0.05, P values are from the independent student t test and Mann-Whitney U test, as appropriate.

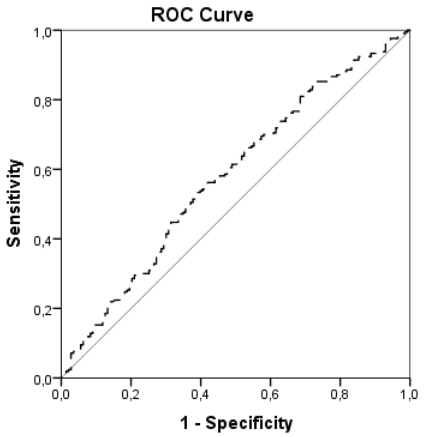

Figure 1. ROC Curve for Platelet Mass. Area under the curve [AUC]: 0.580, with a sensitivity of 58% and specificity of 56.2% and $P = 0.008$.

On the other hand, some studies in the literature report contrary views. A large retrospective study by Salmon et al, with 1350 VLBW (<1500 g) infants, including 592 extremely low birth weight (<1000 g) infants, reported that thrombocytopenia in the first 24 hours after birth is not associated with PDA.[10] Bas-Suárez et al reported that in a cohort of preterm VLBW infants, the median platelet count nadir and the rate of mild, moderate or severe thrombocytopenia – within the first 2 days of life – were not significantly associated with the presence of hsPDA on day 3. Moreover, low platelet counts in the first 7 days of life were not significantly associated with the rate of response to treatment with indomethacin or ibuprofen.[13] Fujioka et al found similar results, indicating no association between thrombocytopenia and incidence of PDA.[14]

There is an inverse relationship between platelet size and platelet count in the literature. Reported data show platelet mass as a better predictor of production/regulation coagulation.[15] Zisk et al reported that it is feasible to use platelet mass, rather than platelet count, as platelet transfusion trigger in the NICU.[11] Transfusion recommendations according to platelet mass are based on the young platelets being larger and of better quality.

MPV is one of the four platelet parameters (platelet count, MPV, platelet distribution width and plateletcrit), which indicates the activation of platelet. In previously published reports, no statistically significant correlation was found between MPV and hsPDA, although MPV was reported to be higher in hsPDA groups.[9,12] In our study, mean platelet count was significantly lower in the group with hsPDA, while MPV values were similar in both groups. No significant correlation was found between hsPDA and MPV and platelet count in logistic regression analysis.

Although there are many studies evaluating the correlation between platelet count and PDA, to our knowledge, only a few studies have so far evaluated the correlation between platelet mass and PDA. The correlation between platelet mass and PDA was first reported in the literature by Demir et al. In a retrospective study on 115 preterm newborns with hsPDA, platelet count and PDW were found not to be risk factors for closure of hsPDA, and high platelet mass and MPV were determined to be independent risk factors for hsPDA. In conclusion, they reported that platelet mass may be a more significant indicator than platelet count regarding closure of hsPDA.[16] Similarly in our study, the mean platelet count and platelet mass were also significantly lower in the group with hsPDA. However, platelet mass was not an independent factor for hsPDA in logistic regression analysis. We believe that impaired platelet function, due to immaturity and critical illness, rather than platelet number, might play a role in PDA.

In our study, the higher rates of RDS, BPD, NEC, incidence of pneumothorax and duration of hospitalization in group 1 might be a result of smaller preterm infants included in our study. Similarly, lower platelet count and

Table 3. Effects of Variables on the Presence of hPDA in Multivariable Logistic Regression Analyses

Parameters	OR	95% CI for OR		*P* Value
Gestational week, wk	1.13	0.96	1.33	0.154
Birth weight, g	1.00	0.99	1.00	0.301
Male gender, No. (%)	1.22	0.72	2.09	0.475
Cesarean delivery, No. (%)	0.37	0.18	0.74	0.005
Premature rupture of membranes, No. (%)	1.81	0.28	1.08	0.082
Preeclampsia, No. (%)	1.37	0.68	2.77	0.385
Antenatal steroid, No. (%)	1.00	0.74	1.36	0.992
APGAR scores at 5th min	0.95	0.77	1.18	0.650
RDS, No. (%)	14.54	6.76	31.33	0.001
BPD, No. (%)	1.86	0.77	4.49	0.169
NEC, No. (%)	1.63	0.82	3.23	0.163
Pneumothorax, No. (%)	3.64	0.92	14.34	0.065
Platelet count <150.000 ($\times 10^3/mm^3$)	1.00	0.98	1.02	0.921
Platelet mass, fL/nL	0.99	0.99	1.00	0.681
MPV, fL	0.97	0.59	1.60	0.897

Abbreviations: MPV, mean platelet volume; NEC, necrotizing enterocolitis; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia.

platelet mass could be attributed to the lower birth weight. However, logistic regression analysis revealed that these parameters were not risk factors.

Our study has several limitations: the study was retrospective in design, we could not rule out drugs such as furosemide and gentamicin which are thought to be effective on PDA, and we could not determine platelet dysfunction.

In conclusion, according to our findings, platelet count, MPV and platelet mass are not risk factors for hsPDA in premature infants. Further studies are needed to determine the factors that affect the closure of PDA because of the contradictory and insufficient information on this topic in the literature.

Authors' Contribution

SA performed the research; TG, GK and FO designed the research study; AT collected data; ST and HOK contributed essential reagents and tools; SA, EO analyzed the data; SA wrote the paper.

Conflict of Interest Disclosures

None.

Ethical Statement

This retrospective study was approved by the institutional review board and strictly followed the institution's ethical guidelines.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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