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ORIGINAL ARTICLE

Is high platelet distribution width in the first hours of life can predict hemodynamically significant patent ductus arteriosus in preterm newborns?

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ABSTRACT

Aim: To determine whether there is any association between platelet indices within the first hours of life and hemodynamically significant patent ductus arteriosus (hsPDA) in preterm newborns.

Patient and methods: A total of 100 preterm infants, gestational age <32 weeks and birth weight <1500 g were analyzed in the study. Complete blood counts obtained within the first 6 hours of life were evaluated for platelet parameters and compared for patent ductus arteriosus (PDA) status.

Results: We included 50 infants with hsPDA and 50 controls. Mean gestational week of patients were 28.8 ± 2.4 weeks and mean birth weight of the patients were 1237.5 ± 406 g. Platelet distribution width (PDW) is higher in PDA group compared with the control group ($p = .023$). The cutoff value of PDW is 11.45 fL for hsPDA with 65% sensitivity and 66% specificity. The other blood parameters including platelet count, platelet mass, and mean platelet volume (MPV) were no statistically different between the two groups. Also, there was no association with the platelet count and the response to the medical therapy.

Conclusions: There is no association between hsPDA and the platelet count, platelet mass or MPV in the first day of life. We determined that hsPDA patency was significantly associated with a higher first day PDW level, which is a more specific indicator of platelet activation than other platelet parameters.

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Introduction

Patent ductus arteriosus (PDA) with significant left-to-right shunting may be an important problem for preterm infants in neonatal intensive care units (NICU) [1]. Preterm PDA is associated with a range of adverse outcomes, and clinical studies on PDA treatment have failed to show reduced incidence of most of those outcomes [2]. The association between PDA and neonatal morbidity, mortality and poor neurodevelopmental outcome has been a debate for years. Controversy still exists about determination of hemodynamically significant patent ductus arteriosus (hsPDA), criteria for treatment, and type of treatment and outcomes [3].

Left-to-right shunt results in lung volume overload and compromised organ blood flow and therefore PDA closure is indicated before significant left-to-right shunting occurs [4]. Closure of the ductus arteriosus at birth is a complex phenomenon being conditioned by antenatal events and progressing in preprogrammed steps. Functional at first, narrowing of the vessel is determined by two overlapping processes – removal of the blood oxygen tension. Structural closure follows the constriction through a remodeling process initiated antenatally with the development of intimal cushions and completed postnatally by a host of humoral and mechanical stimuli [5]. It was reported that low platelet count may increase the risk of PDA by preventing the thrombosis of ductal lumen [6–8]. In another study, platelet count and platelet distribution width (PDW) were found not to be risk factors for closure of hsPDA, but both high platelet mass and mean platelet volume (MPV) were determined to be independent risk factors for hsPDA [9]. Other platelet indices like PDW were also studied and one study showed that PDA was associated with high PDW [8]. The studies in this subject are very limited. In this

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study, we tried to find a platelet parameter that may be a marker to predict the hsPDA in preterm infants.

Materials and methods

We performed this retrospective study from the medical records of the infants with gestational age <32 weeks and birth weight <1500 g admitted to our NICU between January 2015 and March 2016. Infants with congenital heart disease, perinatal asphyxia, and placental insufficiency like preeclampsia or intrauterine growth retardation (IUGR) or small for gestational age were excluded from the study. Patient characteristics including gestational age, gender, birth weight, complications of prematurity like respiratory distress syndrome (RDS), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and sepsis were recorded.

Blood specimens were obtained from the patients within the first 6 hours of life. Blood samples were taken from the umbilical vein and collected in ethylenediamine tetraaceticacid (EDTA) tubes and within 1 h they were assessed for platelet count and indices (MPV, PDW, and plateletcrit [PCT]). Analysis were done by Coulter Counter model LH (Coulter Electronics, Hialeah, FL, USA). To calculate platelet mass, the formula, platelet count $\times$ MPV/10^3, was used.

Routine echocardiography (ECHO) was performed to all infants included in the study between 3 and 5 days of life. hsPDA was defined as internal ductal diameter of $\geq$1.5 mm and/or with a left atrium (LA)/aortic root (AO) ratio >1.5 [8]. Signs of clinical significant PDA were presence of continuous murmur, tachycardia, hyperactive precordium, features of systemic hypoperfusion as low systemic blood pressure, low diastolic blood pressure, widened pulse pressure, metabolic acidosis and features of pulmonary hyperperfusion as tachypnea, respiratory distress, increased oxygen, or ventilation requirements.

Patients were placed on fluid therapy, starting with 70–80 cc/kg/day based on the postpartum day and weight, which was increased each day by 20 cc/kg/day according to physiologic weight loss until 150 cc/kg/day was reached. Oral ibuprofen therapy was started immediately after diagnosing hsPDA in case of no contraindication like renal insufficiency, platelet count <100 $\times$ 10^9/L or bleeding (first dose: 10 mg/kg/day; second and third doses: 5 mg/kg/day). At fourth day of after starting ibuprofen therapy, ECHO was repeated and patients who were determined to have persistent PDA, received a second course of therapy (three additional doses). Surgical ligation was performed on patients with hsPDA persisting after second course of therapy.

Our primary outcome was to determine the relationship between the platelet indices in the first hours of life and hsPDA.

The study was approved by the Ethics Committee of our Institution. Informed consent was obtained by the parents of the infants.

Statistical analyses

Statistical analyses were performed using the SPSS software (version 20, SPSS, Inc., Chicago, IL, USA). Descriptive analysis was performed for demographic and clinical characteristics of the patients. Student's t-test or Mann–Whitney U-test was used for comparison of numeric variables between two groups and chi-square test was used for comparison of ratios between the groups. In the descriptive analyses, variables with normal distribution were expressed as mean ± standard deviation. Multivariate regression analysis and Receiver Operating Characteristics (ROC) curve analysis were also performed. Statistical significance was set at $p<.05$.

Results

A total of 100 preterm infants were analyzed in the study, including 50 infants with hsPDA and 50 controls. The demographic properties of the patients are shown in Table 1. There were no differences between the groups in gender and other risk factors. Mean gestational week of patients with hsPDA was not significantly different from control group (28.1 ± 2.5 versus 28.5 ± 2.0, $p = .06$) and mean birth weight of the patients with hsPDA was also not significantly different from control group (1134 ± 432 versus 1241 ± 432, $p = .056$). The complications of prematurity are also shown in Table 1.

PDW is higher in hsPDA group compared with the control group (10.2 ± 0.7 versus 9.9 ± 0.1, $p = .026$;

Table 1. Demographic variables and complications of prematurity.

	PDA ($n = 50$)	Control ($n = 50$)	p
Gestational week	28.1 ± 2.5	28.5 ± 2.0	.06
Birth weight, g	1134 ± 432	1241 ± 432	.056
RDS	0.86 ± 0.35	0.76 ± 0.5	.082
ROP	0.06 ± 0.23	0.02 ± 0.14	.312
BPD	0.22 ± 0.41	0.08 ± 0.27	.051
IVH	0.62 ± 1.2	0.56 ± 0.68	.058
NEC	0.54 ± 0.81	0.42 ± 0.46	.075
Sepsis	0.34 ± 0.47	0.22 ± 0.41	.185

RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity; BPD: Bronchopulmonary dysplasia; IVH: Intraventricular hemorrhage; NEC: Necrotising enterocolitis; PDA: patent ductus arteriosus.

Table 2. Complete blood count of the patients.

	PDA ($n=50$)	Control ($n=50$)	p
Hemoglobin	16.7 ± 2.9	16.9 ± 2.0	.61
Hematocrit	48.7 ± 8.0	48.6 ± 6.0	.93
Leucocyte	13113 ± 1237	19877 ± 8482	.43
Platelet	216620 ± 65639	234210 ± 59925	.16
MPV	10.2 ± 0.7	9.9 ± 0.1	.078
Platelet mass	2208 ± 630	2314 ± 585	.382
PCT	0.22 ± 0.06	0.23 ± 0.05	.336
PDW	12.2 ± 2.1	11.2 ± 1.4	**.023***
MCH	38.4 ± 3.3	37.8 ± 2.4	.372
RDW	16.9 ± 1.7	16.9 ± 1.4	.927

MPV: Mean platelet volume; PCT: Plateletcrit; PDW: Platelet distribution width; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width.
Statistically significance was marked as bold.

Table 3. Standard multiple linear regression of PDW on gestational week, birth weight, sepsis, IUGR, and complications of prematurity.

Variables	*B*	Std. Error	Beta	*T* value	*p* value
Constant	8.069	4.849		1.664	.100
Gestational week	0.087	0.192	0.113	0.452	.652
Birth weight	0.000	0.001	0.054	0.237	.813
Sepsis	0.741	0.507	0.177	1.461	.148
NEC	0.139	0.305	0.051	0.456	.649
IVH	−0.071	0.236	−0.038	−0.301	.764
BPD	−0.033	0.677	−0.006	−0.049	.961
ROP	−0.795	1.184	−0.083	−0.671	.504
RDS	0.943	0.529	0.228	1.781	.078
IUGR	−0.181	1.988	−0.010	−0.091	.928

R = 0.263; R2 = 0.069; Adj. R2= −.025.

12.2 ± 2.1 versus 11.2 ± 1.4, $p=.023$, respectively). The other blood parameters including platelet count, platelet mass, and MPV were not statistically different between the two groups (Table 2). Higher PDW was an independent predictor of hsPDA by means of multivariate regression analysis, including gestational age, birth weight, sepsis, NEC, intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, respiratory distress syndrome, and IUGR ($p<.05$) (Table 3).

There is a significant association between higher PDW and hsPDA in ROC curve analysis ($p=.023$). The cutoff value of PDW is 11.45 fL, with 65% sensitivity and 66% specificity (Table 4) (Figure 1).

We compared the platelet parameters of patients with hsPDA who were treated with surgical ligation and those who responded to medical treatment. There was no statistically significant difference in the platelet parameters between this two groups. Also, there was no association with the platelet count and the response to the medical therapy.

Discussion

Closure of the ductus arteriosus at birth is a complex phenomenon being conditioned by antenatal events and progressing in preprogrammed steps. Functional

Table 4. ROC curve analysis for the association between higher PDW and hsPDA.

Area under the curve				
Test result variable(s): PDW				
			Asymptotic 95% Confidence interval	
Area	Std Error[a]	Asymptotic Sig.[b]	Lower bound	Upper bound
0.632	0.056	0.023	0.521	0.743

The test result variable(s): PDW has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
[a]Under the nonparametric assumption.
[b]Null hypothesis: true area = 0.5.

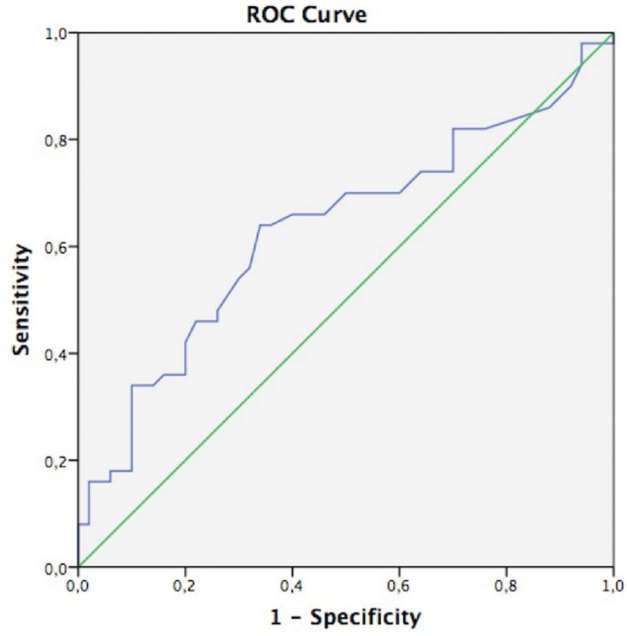

Figure 1. ROC curve analysis between hsPDA and PDW.

at first, narrowing of the vessel is determined by two overlapping processes – removal of the blood oxygen tension. Structural closure follows the constriction through a remodeling process initiated antenatally with the development of intimal cushions and completed postnatally by a host of humoral and mechanical stimuli [5,10–12]. As platelets play a key role in many inflammatory, allergic and immune processes *via* interaction with endothelial cells, platelet count, and parameters are also studied to understand ductal closure mechanisms [13–15]. Recent studies in this aspect suggest that platelets may play a key role during ductal closure *via* interaction with endothelial cells [8,9,16]. It was reported that low platelet count may increase the risk of PDA by preventing the thrombosis of ductal lumen. Other platelet indices like PDW were also studied and shown that hsPDA was associated with high PDW [8]. The studies on this subject are

very limited. In this study, we tried to find a platelet parameter that may be a marker to predict hsPDA in preterm infants. Our study showed that in preterm infants there is no association between hsPDA and the platelet count, platelet mass or MPV in the first hours of life. We determined that hsPDA patency was significantly associated with first day PDW level, which is higher in patients with hsPDA. The cutoff value of PDW for hsPDA is 11.45 fL, with 65% sensitivity and 66% specificity.

PDW is an indication of variation in platelet size which can be a sign of active platelet release. To obtain a larger surface platelets change in shape during activation, MPV and especially PDW increase during platelet activation. PDW seems to be a more specific indicator of platelet activation than MPV since it was not elevated during single platelet distention caused by platelet swelling. The combined use of MPV and PDW could predict activation of coagulation more efficiently [17]. There are few studies about ductal closure and platelet parameters, which have various results. Dizdar et al. [8] evaluated platelet indices of preterm infants with PDA and compared with control group and found that PDA was associated with low platelet count and higher PDW, whereas other platelet indices were not different between the two groups. They could not show an association between platelet counts and persistence or closure after medical treatment. They suggested that further studies should be performed in this area.

Demir et al. [9] evaluated whether or not platelet mass contributes to closure of PDA in premature newborns. They compared 115 newborns with hsPDA and 120 control patients and found that platelet count and PDW were not risk factors but high platelet mass and MPV were independent risk factors for closure of hsPDA. As the results of those studies are different, Olukman et al. [16] also evaluated the relationship between platelet parameters and patency of ductus arteriosus in preterm infants. Unlike other studies, they stated that none of the platelet parameters had an influence on ductal closure after medical treatment. Sallmon et al. [18] provided further evidence for an association between low platelet counts during pharmacological therapy for symptomatic PDA and treatment failure while platelet counts before initiation of therapy did not affect treatment outcome.

Recently, Kahvecioğlu et al. [19] searched the effect of platelet functions on the spontaneous closure of ductus arteriosus in prematurity. They found that longer collagen-ADP duration is identified as a risk factor of ductal closure.

In conclusion, our study showed that in preterm infants there is no association between hsPDA and the platelet count, platelet mass, or MPV in the first day of life. We determined that hsPDA patency was significantly associated with higher first day PDW level, which is a more specific indicator of platelet activation than other platelet parameters. We suggest that PDW levels in the first day of life may predict hsPDA and can be used in combination with other markers. Previously reported studies have different outcomes. Further studies are needed to explain the role of PDW on the development of PDA.

Disclosure statement

No potential conflict of interest was reported by the authors. The authors have no financial relationships relevant to this article to disclose.

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