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How Much Do Routine Blood Tests Tell Us About Patent Ductus Arteriosus? Is the Red Cell Distribution Width to Platelet Count Ratio or/and Any Platelet Parameter Useful?

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Abstract

Objectives: In this observational study, to determine whether there is any association between red cell distribution width (RDW)/platelet count ratio (RPR) and hemodynamically significant patent ductus arteriosus (hsPDA) in preterms.

Materials and Methods: A total of 233 preterm infants, gestational age <34 weeks were analyzed in the study. Complete blood counts obtained at 24th h, 48th h, 72nd h and 7th days were evaluated for RDW, RPR, platelet parameters and compared for PDA status.

Results: Our study included 64 infants with hsPDA and 64 controls. The RDW at 48th h, 72nd h, and 7th day and the RPR at 24th h, 48th h, 72nd h and 7th day were significantly higher in the study compared to the control group; the PCT was lower. The RPR afforded 72.3-79.2% sensitivity and 82.3-89.2% specificity when used to predict hsPDA.

Conclusion: None of platelet count, PDW, mean platelet volume, or Platelet Mass index can be used to predict either hsPDA or treatment success, but a low PCT, and a high RDW and RPR, predict hsPDA but not treatment success.

Keywords: Patent ductus arteriosus, red cell distribution width, platelet count, ratio

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Introduction

The ductus arteriosus (DA), situated between the aortic arch and the pulmonary artery in the foetal circulation, closes within a few hours after birth; this is one of the most important changes required for the transition to extrauterine life[1-3]. A prolonged duration of DA patency increases left-to-right shunting, lung blood flow, and left ventricular volume loading, and decreases systemic perfusion. Although many studies on Doppler echocardiography (the principal PDA diagnostic method) have appeared, there is, as yet, no consensus on hsPDA diagnosis or how to predict morbidity and mortality[4-6]. Therefore, we sought new diagnostic methods identifying hsPDA prior to left-to-right shunting, increases in lung blood flow and left ventricular volume loading, and the decrease in systemic perfusion. Earlier, recognizing that platelets have important affects in many inflammatory events such as acute and chronic infection, malignancy, and wound-healing[7,8], Echtler et al.[9] studied the relationship between ductal closure and platelet levels in animals; this level correlated negatively with inflammation. Platelets played an important role in duct closure, becoming attached to the lumen of the DA a few minutes after birth. In the same study, the DA did not close (thus, remained permanently open) in animals in which platelet functions were compromised. Studies on premature infants followed. Mean platelet volume (MPV), platelet count, and platelet distribution width (PDW) were investigated; a low platelet count and a low PDW were risk factors for PDA[10-11]. No clear relationship was evident between the platelet mass index and ductal closure[12,13]. As the reported effects of platelet numbers were contradictory, other parameters that might aid hsPDA diagnosis were investigated. We hypothesized that inflammation might inhibit ductal closure. The red cell distribution width (RDW) and the RDW/platelet count ratio (RPR), a proven measure of inflammation in adults, would both be high in preterm infants with hsPDA[14,15].

Materials and Methods

Patients

This observational study was conducted between 2016 and 2018. We calculated total sample size of 128 in the study and 64 in the control group (d=0.5; power=80%; α=0.05)[16]. We examined the medical records of newborns admitted to our tertiary neonatal intensive care unit. Preterm infants of gestational age <34 weeks were included in the study; we calculated gestational age by reference to the mother's last menstrual date or on the basis of ultrasonography performed before 20 weeks. We excluded infants of unknown gestational age, those with conditions that might cause inflammation or affect platelet count and/or function and lack of data (Figure 1).

PDA Diagnosis

Echocardiography was performed on preterm infants at the time of clinical findings or within 24-72 h after admission. hsPDA associated clinical findings were

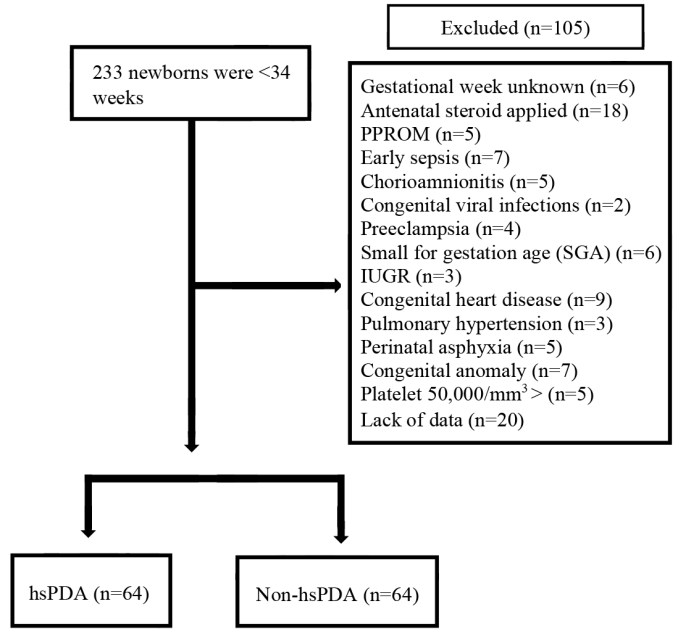

Figure 1. Flowchart of study group

PPROM: Preterm premature rupture of the membranes, IUGR: Intrauterine growth restriction, hsPDA: Hemodynamically significant patent ductus arteriosus

murmur, tachycardia, hypotension, oliguria, and increased respiratory distress. hsPDA's echocardiographic findings were ductal diameter ≥1.5 mm, left atrium/aortic root ratio ≥1.5, and/or diastolic flow failure or inverse flow in the abdominal aorta. Echocardiography was performed at the end of the medical treatment and the DA was classified as closed or open. The preterms were divided into two groups. Those with hsDPA who underwent ductus closure treatment constituted Group 1; those lacking hsPDA formed Group 2.

PDA Treatment

In our unit, we employ intravenous or oral ibuprofen to close the ducts of preterm infants exhibiting hemodynamically significant PDA. Intravenous or oral paracetamol are given if ibuprofen is unsuccessful or contraindicated[17,18]. Ibuprofen (Dolven 100 mg, Sanofi) was administered at 10 mg/kg on day 1, and at 5 mg/kg on days 2 and 3; paracetamol (Parol 10 mg/mL solution) was administered at 15 mg/kg every 6 h for 3 days. If DA was open, the second course was given.

Platelet Parameters

Blood samples taken from an umbilical venous catheter at the 24th, 48th and 72nd hours, and at day 7 were collected in ethylenediaminetetraacetic acid-containing tubes and blood counts performed via Coulter Counter (FL, USA). This yielded the platelet count and the MPV, PDW, PCT, and RDW. The Platelet Mass index was obtained from the platelet count (10^3/mm^3) and the MPV (fL); the RPR was the ratio of the RDW to the platelet count.

Data Collection

We recorded gestational age, birth weight, sex, mode of delivery, Apgar scores (at the first and fifth minute), 24th, 48th and 72nd hours, and at day 7 hemographic parameters, any surfactant requirement, ventilation history, the intraventricular hemorrhage, PVL, necrotizing enterocolitis, retinopathy of prematurity, and Bronchopulmonary dysplasia (BPD), duration of hospitalization and any death. The primary outcome was whether the RDW and/or RPR could be used to predict hsPDA diagnosis and treatment success.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0. The t-test and Mann-Whitney U test were used to compare. A p-value less than 0.05 was considered statistically significant. The cut-off value, sensitivity and specificity of the RPR were calculated using a receiver operator curve.

Results

Two hundred and thirty-three premature infants less than 34 weeks of gestational age were admitted to NICU and 105 premature infants were excluded from the study. The study group consisted of 64 hsDPA patients who underwent closure treatment and 64 with no hsDPA or a closed PDA constituted the control group (Figure 1). The demographic variables of the groups were shown in Table 1. Sixty-four premature infants with hsPDA were administered medical treatment, 51 premature infants' DAs were detected closed after the first course and 13 premature infants were required second course and none of premature infants required surgical closure. The hematological parameters of the groups were shown in Table 2. RDW values at the 48th h, 72nd h, and 7th day and RPR values at the 24th, 48th and 72nd hours, and at day 7 were significantly higher in the study group. We

Table 1. Comparison of demographic characteristics of the hsPDA and Non-hsPDA groups

Characteristics	hsPDA (n=64)	Non-hsPDA (n=64)	p value
GA, week (mean ± SD)	29.4±3.6	30.1±4.2	0.166
BW, g (mean ± SD)	1226±109	1317±168	0.104
Male, n (%)	37 (57.8)	33 (51.5)	0.092
C/S, n (%)	29 (45.3)	18 (28.1)	0.077
Apgar score, medians (min–max)			
First minute	6 (4-8)	7 (4-8)	0.144
Fifth minute	7 (5-9)	8 (5-9)	0.168

GA: Gestational age, SD: Standard deviation, BW: Birth weight, g: Gram, CS: Caesarean section, hsPDA: Hemodynamically significant patent ductus arteriosus

Table 2. Comparison of the hematological parameters of the hsPDA and Non-hsPDA groups

Parameters	DOL 1			DOL 2			DOL 3			DOL 7		
	PDA	Non-hsPDA	p value	PDA	Non-hsPDA	p value	PDA	Non-hsPDA	p value	PDA	Non-hsPDA	p value
RDW (%)	16.3±0.87	16.4±0.83	0.145	17.5±2.12	16.8±1.02	**0.002**	17.2±0.95	16.4±1.58	**0.044**	18±1.56	16.7±1.38	**0.000**
Platelet count (x10^3/mm^3)	198.7±35.6	220.1±45.8	0.092	186.1±69.6	222±63.3	0.066	158.7±41	251.6±72	0.113	215±82	289±69.3	0.088
RPR (%)	0.086±0.024	0.066±0.019	**0.000**	0.091±0.023	0.067±0.018	**0.000**	0.098±0.033	0.070±0.027	**0.000**	0.096±0.03	0.069±0.027	**0.000**
PDW (%)	18.1±2.72	17.4±1.86	0.166	18±2.29	18.1±1.98	0.097	18.6±2.87	18.3±2.61	0.073	18.4±1.74	18.5±1.88	0.114
PCT (%)	0.123±0.023	0.175±0.042	**0.000**	0.109±0.055	0.193±0.076	**0.000**	0.086±0.035	0.303±0.213	**0.000**	0.250±0.83	.333±0.88	**0.000**
MPV (fl)	8.13±1.47	8.47±2.33	0.156	9.67±1.89	8.45±1.43	0.213	11.2±2.14	9.81±2.97	0.181	7.76±2.83	8.73±2.79	0.098
Platelet Mass index	1609±291	1760±310	0.144	1715±105	1653±196	0.078	1798±72	1960±288	0.193	1868±247	1944±354	0.067

DOL: Day of life, RDW: Red cell distribution width, RPR: Erythrocyte distribution width/platelet count ratio, PDW: Platelet distribution width, PCT: Platocrit, MPV: Mean platelet volüme, Platelet mass index: the platelet count (10^3/mm^3) X MPV (fL); hsPDA: Hemodynamically significant patent ductus arteriosus

calculated cutoff value, sensitivity and specificity, positive and negative predictive values of RPR (Table 3). RPR afforded 72.3-79.2% sensitivity and 82.3-89.2% specificity when used to predict hsPDA. However, there was no difference between the groups in the hematological parameters of the preterm infants with closed DAs and the 13 preterm infants with open DAs after the first treatment. In other words, none of the RPR, RDW, or platelet count could be used to predict the response to treatment (Table 4). When the complications of prematurity of the groups were compared, surfactant requirement, pulmonary hemorrhage, steroid requirement to treat BPD, total duration of ventilation, and the BPD were detected more frequently in the study group (Table 5).

Discussion

The principal factors of the DA continuity in intrauterin life are decreased oxygen concentration, increased prostaglandin and nitric oxide. After birth, increased oxygen concentration and decreased prostaglandin enable DA's functional closure[19]. Moreover, various suggestions have been made about DA closure physiology. The discussion began when Echtler et al.[9] showed that platelets were attached to the lumen of the closed DA and confirmed this experimental finding via a retrospective study of preterm births. After this animal study, various hypotheses about the role played by platelets in duct closure in newborns have been proposed. The most accepted hypothesis is that platelets affect on DA contraction, decreasing the blood flow in the venous lumen and vasa vasorum cause hypoxia in the vessel wall which occurs immediately after birth in term neonates; in preterm neonates, the cells of the ductus vessel wall are fed by the vessel lumen because of the absence of a vasa vasorum. As the ductus vessel wall is thin, contraction is inadequate, and hypoxia causes endothelial damage and platelet aggregation. Therefore, it was speculated that platelet functions were important regarding of DA closure in preterm infants[20,21]. Despite that, this hypothesis is not sustained in some studies. These studies have reported that platelet transfusion does not reduce the frequency of the PDA in preterm infants with immune thrombocytopenia[22,23]. In our study, no difference was found between the platelet counts of the groups. In addition, there was no difference between the platelet counts of patients who did and did not fail treatment. In conclusion, the platelet count was

Table 3. ROC curve analysis of the RPR between hsPDA and non-hsPDA groups

Parameters	Cut-off value	AUC %	Sensitivity %	Specificity %	LR+	PPV %	NPV %
RPR at 24.hours	0.735	0.746	72.3	82.3	4.08	80.3	74.8
RPR at 48.hours	0.735	0.779	74.6	85.4	5.10	83.6	77.1
RPR at 72.hours	0.795	0.786	79.2	89.2	7.35	88	81.1
RPR at 7th day	0.830	0.789	76.2	91.5	9	89.9	79.3

RPR: Erythrocyte distribution width/platelet count ratio, AUC: Area under curve, LR+, Likelihood ratio, PPV: Positive predictive value, NPV: Negative predictive value, ROC: Receiver operating characteristic

Table 4. Comparison of study groups in terms of hematological parameters before and after treatment

Parameters	Closed PDA (n=51)	Open PDA (n=13)	p value
RDW %	17.1±3.67	17.8±4.12	0.137
Platelet count (x10^3/mm^3)	223±56	198±44	0.099
RPR %	0.091±0.026	.096±0.03	0.114
PDW %	18.3±3.17	19.1±4.26	0.235
PCT %	0.185±0.041	0.138±0.037	0.086
MPV (fl)	7.84±2.23	7.13±1.98	0.134
Platelet mass index	1765±437	1629±383	0.185

RDW: Red cell distribution width, RPR: Erythrocyte distribution width/platelet count ratio, PDW: Platelet distribution width, PCT: Platocrit, MPV: Mean platelet volume, Platelet mass index: the platelet count (10^3/mm^3) x MPV (fL)

not a predictor of hsPDA diagnosis or treatment success. The results of our study contradict those of the two major meta-analyses conducted by Simon et al.[24] and Mitra et al.[25], but support the cohort study of Sallmon et al.[26].

Shah et al.[11], Kahvecioglu et al.[13], Fujioka et al.[27], Bekmez et al.[28], Bas-Suarez et al.[29], Murphy et al.[30] and Brunner et al.[31] reported that platelet count was not related to PDA diagnosis or treatment success. On the other hand, Echtler et al.[9], Kulkarni et al.[32] and Meinarde et al.[33] reported that a low platelet count increased the hsPDA frequency. In some studies performed after these contradictory studies, it was reported that large platelets create a greater potential risk of prothrombotic reactions; large platelets are more aggregated than small and normal platelets given the greater number of receptors such as thromboxane A2-B2 and glycoproteins IIb-IIIa on the surfaces of large platelets. It was suggested that the increased metabolic and enzymatic activities of dysfunctional thrombocytes, rather than the platelet count, were associated with PDA[34-38]. We sought to identify parameters related to platelet function associated with PDA. These remain controversial; all of MPV, PDW, PCT, and platelet mass index have been associated with cardiovascular diseases in adults[39-44]. In addition, in a limited number of studies on neonates, the MPV and PDW were shown to be associated with prematurity complications such as RDS and BPD[45-47]. In our study, the difference between the PCT levels of the hsPDA and control groups was statistically significant. The MPV and platelet mass index values were similar in both groups. Thus, we conclude that the PCT can be used to predict hsPDA but not treatment success. Demirel et al.[48] reported that the PDW was higher in preterm infants with hsPDA than in control groups. Bekmez et al.[28] reported that a low PCT increased the hsPDA incidence. Demir et al.[49] found a high MPV and a low platelet mass in the hsPDA group. In contrast, none of MPV, platelet mass, PDW, or PCT differed between the hsPDA and control groups of many studies[13,14,30,46,50]. Inflammation caused by hypoxia and oxidative stress plays an important role in DA closure; inflammation inhibited platelet aggregation by increasing cyclooxygenase activity and prostaglandin synthesis[51]. However, Olsson et al.[52], in a study on 47 preterms 22-27 weeks of gestational age, found that BNP, NT-proBNP, PDGF, IL-6, IL-8, and IL-10 levels were high in hsPDA patients and an inflammatory indicator could be used to predict hsPDA persistence and treatment failure. In addition, it has been suggested that the RDW and the RPR, which have been associated with hypoxia and inflammation, may be useful markers of PDA[51-54].

Table 5. Comparison of the prematurity complications of the hsPDA and non-hsPDA groups

Characteristics	hsPDA (n=64)	Non-hsPDA (n=64)	p value
Respiratory outcome			
Received surfactant, n (%)	49 (76.5)	37 (57.8)	**0.012**
Pulmonary hemorrhage, n (%)	7 (10.9)	2 (3.1)	**0.023**
Pneumothorax, n (%)	3 (4.6)	2 (3.1)	0.122
Duration of mechanical ventilation, days (mean ± SD)	40.8±4.6	25.1±5.3	**0.014**
Postnatal steroid use for BPD, n (%)	14 (21.8)	4 (6.2)	**0.003**
Clinical outcome			
IVH, Grade 3-4, n (%)	7 (10.9)	6 (9.3)	0.162
NEC, Grade 2-3, n (%)	9 (14)	6 (9.3)	0.092
BPD, n (%)	9 (14)	3 (4.6)	**0.011**
ROP, n (%)	5 (7.8)	3 (4.6)	0.214
Duration of hospitalization (mean ± SD)	66.3±9.5	51.2±4.4	**0.033**
Death, n (%)	3 (4.6)	1 (1.5)	0.124

hsPDA: Hemodynamically significant patent ductus arteriosus, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, SD: Standard deviation, n: Number

The primary aim of our study was to investigate whether the RDW and the RPR predicted PDA. In our study, the RDW and RPR values were significantly higher in hsPDA patients than in the control group. Bekmez et al.[28] reported that although no RDW difference was evident between the study and control groups, the RPR was higher in the study group. Strengths of our study are that we calculated the required sample size using a statistical program, applied rigid exclusion criteria and tried to homogenize our sample group. We excluded infants with sepsis because this might affect platelet count and function, and might trigger erythropoiesis caused by inflammation and cytokine release[51,54]. We also excluded patients who received ibuprofen as ductus closure therapy because of potential effects on platelet count and functions. Infants born to mothers with prior preeclampsia, which affects platelet count and ductal flow because of the increased placental resistance, were also excluded[55-57]. We also excluded infants with perinatal asphyxia associated with an increased PDA, thrombocytopenia, and platelet dysfunction[58-60]. Newborns whose mothers had earlier received steroids were excluded because of possible effects on the platelet count. We thus excluded all pathologies that may affect platelet count and function and induce inflammation. We evaluated platelet count and function of preterms before and after the medical treatment. We diagnosed hsPDA according to both echocardiographic and clinical findings because of significant numbers of hsPDAs close spontaneously.

Study Limitations

We believe that our results are reliable and contribute significantly to the literature. However, there are some limitations of the study. The first is its retrospective nature. Although we excluded sepsis, simultaneous disease caused by inflammation may have affected the results of the study. The third limitation is that gestational age of preterm infants included in the study were <34 weeks, it was not less.

Conclusion

None of platelet count, PDW, MPV, or platelet mass index can be used to predict either hsPDA or treatment success, but a low PCT and a high RDW and RPR predict hsPDA but not treatment success.

Ethics

Ethics Committee Approval: This study is observational and retrospective nature.

Informed Consent: This study is observational and retrospective nature.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: B.K., A.Ş., Design: B.K., A.Ş., Data Collection or Processing: B.K., A.Ş., Analysis or Interpretation: B.K., A.Ş., Literature Search: B.K., A.Ş., Writing: B.K., A.Ş.

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