

The role of platelet parameters in hemodynamically significant PDA

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ABSTRACT

Objective: Patent ductus arteriosus (PDA), a prevalent condition in neonates, is linked to multiple complications in premature infants. Although many studies have explored the relationship between platelet parameters and hemodynamically significant patent ductus arteriosus (hsPDA), a clear consensus has yet to be established. Our objective is to clarify the association between platelet parameters and hsPDA.

Material and Methods: This retrospective study was conducted at the neonatal intensive care unit (NICU) from January 2020 to January 2023. Premature infants (<29 weeks gestation) were grouped into “without hsPDA” (Group 1) and “with hsPDA” (Group 2). The first echocardiographic evaluations were performed within the first two days of life. When hsPDA was diagnosed, patients received either ibuprofen or paracetamol. Successful closure was defined by echocardiography performed 24–72 hours post-treatment. Demographic factors and platelet parameters were compared between the two groups.

Results: The study included 101 patients, with 45 in Group 1 (44.6%) and 56 in Group 2 (55.4%). Infants with hsPDA were significantly smaller in gestational age and birth weight. Patients with hsPDA had significantly lower platelet counts and platelet mass, along with higher MPV values within the first seven days. No significant differences were found in cord blood gas values (pH and lactate). Preterm infants with hsPDA had longer NICU stays.

Conclusion: Platelet parameters are significantly associated with the presence of hsPDA in premature infants. Lower platelet counts and platelet mass may be indicative of hsPDA.

Keywords: Neonate; patent ductus arteriosus; platelet mass; prematurity.

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Hemodinamik anlamlı PDA'da trombosit parametrelerinin rolü

ÖZET

Amaç: Patent duktus arteriyozus (PDA), yenidoğanlarda en sık görülen durumlardan biridir ve prematüre bebeklerde birçok komplikasyonla ilişkilidir. Trombosit parametreleri ile hemodinamik olarak önemli patent duktus arteriyozus (hsPDA) arasındaki ilişki birçok çalışmada araştırılmıştır, ancak kesin bir sonuca varılamamıştır. Bu çalışmada, trombosit parametreleri ile hsPDA arasındaki ilişkiyi açıklığa kavuşturmayı amaçlıyoruz.

Gereç ve Yöntemler: Bu retrospektif çalışma, Ocak 2020 ile Ocak 2023 tarihleri arasında yenidoğan yoğun bakım ünitesinde (NICU) gerçekleştirildi. Prematüre bebekler (<29 hafta), "hemodinamik anlamlı PDA'sı olmayan" (Grup 1) ve "hemodinamik anlamlı PDA'sı olan" (Grup 2) olarak gruplandırıldı. İlk ekokardiyografik değerlendirmeler yaşamın ilk iki günü içinde yapıldı. Hemodinamik anlamlı PDA tanısı konulduğunda hastalara ibuprofen veya parasetamol verildi. Başarılı kapanma, tedavi sonrası 24–72 saat içinde ekokardiyografi ile doğrulandı. Demografik faktörler ve trombosit parametreleri iki grup arasında karşılaştırıldı.

Bulgular: Çalışma, toplam 101 hastayı içermektedir. Grup 1'de 45 hasta (%44,6), Grup 2'de 56 hasta (%55,4) bulunmaktaydı. Hemodinamik anlamlı PDA'sı olan bebeklerde gebelik haftası ve doğum ağırlığı anlamlı olarak daha düşüktü. Ayrıca, ilk yedi gün içinde bu grupta anlamlı olarak daha düşük trombosit sayısı ve trombosit kütleleri, daha yüksek MPV değerleri saptandı. Kordon kan gazı değerlerinde (pH ve laktat) anlamlı bir fark bulunamadı. Hemodinamik anlamlı PDA'sı olan grupta NICU'da yatış süresi daha uzundu.

Tartışma: Trombosit parametreleri, prematüre bebeklerde hemodinamik anlamlı PDA varlığı ile önemli ölçüde ilişkilidir. Düşük trombosit sayısı ve trombosit kütleleri, hemodinamik anlamlı PDA için bir gösterge olabilir.

Anahtar Kelimeler: Patent duktus arteriyozus; prematürite; trombosit kütleleri; yenidoğan.

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INTRODUCTION

The fetal ductus arteriosus functions as a vascular conduit between systemic and pulmonary circulations, facilitating the pulmonary circulation during intrauterine life (1). The process of ductus arteriosus closure is a critical step in the postnatal adaptation of the circulatory system. Patent ductus arteriosus is a congenital heart defect that can lead to significant neonatal complications, including pulmonary overcirculation, edema, and hemorrhage (2, 3). Patent ductus arteriosus, a frequent complication in premature infants, has prompted recent studies into the role of platelets in its closure (4). Evidence from animal models, particularly murine studies, has shown that platelets play a crucial role in ductal closure. Activated platelets adhere to the ductal endothelium, forming a platelet plug that contributes to the closure of the ductus arteriosus, leading to thrombus formation, which undergoes remodeling and results in the permanent closure of the DA (2, 5). Although animal research has demonstrated that platelets play a vital role in the closure of the patent ductus arteriosus (PDA), the clinical implications for preterm infants remain a topic of debate (6). This research sought to enhance the academic literature by examining the correlation between platelet parameters and the closure of the patent ductus arteriosus (PDA).

MATERIAL AND METHODS

A retrospective study was conducted at the Health Sciences University, Ümraniye Training and Research Hospital, Neonatal Intensive Care Unit, İstanbul, from January 2020 to January 2023. Approval for this study was obtained from the hospital ethics committee on 23.02.2023, with reference number B.10.1.TKH.4.34.H.GP.0.01/66. The study complied with the principles of the Declaration of Helsinki.

Data of premature infants born with a gestational age <29 weeks during the study period were extracted from the digital records of the hospital database. Demographic characteristics of the patients and laboratory findings within the first week of life were recorded. Infants with congenital heart defects, multiple congenital anomalies, chromosomal disorders, and those who died within the first week of life were excluded.

Echocardiographic evaluation was performed by an experienced pediatric cardiologist for all infants within the first two days of life or whenever clinically indicated, according to our NICU protocol. The hemodynamic significance of PDA was determined by a ductus diameter >1.5 mm, a left atrial inner diameter to aortic root ratio (LA/AO) >1.4, and the presence of a left-to-right shunt as observed via echocardiography (1).

Table 1. The demographic characteristics of the patients

	Group 1 without hsPDA (n=45)			Group 2 with hsPDA (n=56)			p
	Mean±SD	n	%	Mean±SD	n	%	
Gestational age, week	26.5±1.6			25.6±1.5			*0.003
Body weight, g	923.5±293.8			789.1±206.3			*0.016
Head circumference, cm	24.2±3.1			23.4±2.3			*0.049
Gender							**0.343
Male		23	51.1		35	62.5	
Female		22	48.9		21	37.5	

SD: Standard deviation; hsPDA: Hemodynamically significant patent ductus arteriosus; *: Mann-Whitney U test; **: Chi-square.

Table 2. Comparison of baseline characteristics between groups

	Group 1 without hsPDA Mean±SD	Group 2 with hsPDA Mean±SD	p*
Lowest platelet count in the first 7 days, (10 ⁹ /L)	190.5±75.4	142.2±73.5	0.002
MPV value (fL)	9.8±0.9	10.4±1.1	0.021
Platelet mass (fL/nL)	1865.6±747.3	1452.8±728.9	0.005
Cord pH	7.3±0.1	7.26±0.2	0.740
Cord lactate	3.9±2.7	4.4±3.2	0.327
Length of stay (day)	69.6±48.4	93.9±72.3	0.015

SD: Standard deviation; hsPDA: Hemodynamically significant patent ductus arteriosus; MPV: Mean platelet volume; *: Mann-Whitney U test.

Premature infants were divided into two groups based on Doppler echocardiography assessments: Group 1, without hsPDA, and Group 2, with hsPDA. When hsPDA was diagnosed, patients received ibuprofen (10 mg/kg followed by 5 mg/kg after 24 and 48 hours) or paracetamol (15 mg/kg/6h for 3 days). The criteria for successful PDA closure included the absence of a PDA shunt, as verified by echocardiography within 24–72 hours post-treatment (1, 7). Successive echocardiographic assessments were performed, and patients with hemodynamically significant PDA received medical therapy and/or underwent surgical ligation.

Infants' characteristics were collected, including gestational age (GA), birth weight (BW), head circumference, length, gender, mean platelet volume (MPV), platelet mass, minimum platelet count in the first seven days, cord pH, lactate levels, and hospitalization time. Platelet mass was determined by multiplying the platelet count by the MPV. Demographic factors, platelet count, MPV, and platelet mass were compared between the two groups of patients.

Statistical Analysis

A comparative analysis between the groups was undertaken using the t-test and/or the Mann-Whitney U test for independent samples with non-parametric continuous variables. The data were presented as mean±standard deviation for continuous variables. The chi-square test was used for categorical parameters. Statistical analysis was conducted using

the Statistical Package for Social Sciences (SPSS) version 15 for Windows (SPSS Inc., St. Louis, MO), with statistical significance determined at a two-tailed p-value of 0.05.

RESULTS

The study was carried out from January 2020 to January 2023. A total of 101 patients were included and divided into two groups: without hsPDA and with hsPDA. In Group 1, there were 45 patients (44.6%), and in Group 2, there were 56 patients (55.4%). The demographic characteristics of the 101 infants are shown in Table 1. Infants with hsPDA were significantly smaller in gestational age and birth weight (Table 1).

When comparing the two groups, it was found that patients with hsPDA had significantly lower platelet counts and platelet mass and significantly higher MPV values within the first seven days (p=0.002, 0.005, and 0.021, respectively). There were no significant differences in cord blood gas values between the two groups. It was observed that preterm infants with hsPDA had longer NICU stays (p=0.015) (Table 2).

DISCUSSION

The role of platelet parameters in the closure of PDA in preterm infants has been a significant research topic in recent years. In our study, 101 preterm infants with a gestational age<29 weeks were examined. The hsPDA cases in Group 2 had significantly lower

body weight and were born at earlier gestational ages, indicating that the degree of prematurity increases the risk of hsPDA. Additionally, the longer NICU stays in Group 2 suggested that hsPDA negatively affects clinical outcomes in preterm infants.

Experimental studies have reported that platelets, activated immediately after birth, adhere to the ductal wall, contributing to thrombus formation and subsequent ductal closure and vascular remodeling (5). This finding is supported by retrospective studies in preterm infants, emphasizing the role of platelets in PDA closure. Retrospective studies have provided varying outcomes on whether thrombocytopenia contributes to failed spontaneous ductal closure and if it is a risk factor for unsuccessful closure with cyclooxygenase inhibitors (6). A meta-analysis assessing the relationship between platelet indices and PDA demonstrated that low platelet counts in the first three days of life are associated with PDA development in preterm infants (8). Clinical studies have shown that the risk of PDA is significantly increased in infants with low platelet counts in the early days. Specifically, a platelet count $<150 \times 10^9/L$ increases the PDA risk by 1.58%, and a count $<100 \times 10^9/L$ increases the risk by 1.61%. This suggests that platelet count can be used as an important biomarker for PDA development (9). In our study, the lowest platelet count measured within the first week in Group 2 was $142.2 \pm 73.5 \times 10^9/L$, and this value was significantly lower than that of Group 1, which was $190.5 \pm 75.4 \times 10^9/L$.

Platelet mass, an indicator of platelet production and regulation, is calculated by multiplying the platelet count by the mean platelet volume (MPV). It has been proposed to be potentially associated with hemodynamically significant patent ductus arteriosus (hsPDA) (8). Larger thrombocytes exhibit higher enzymatic activity compared to their smaller counterparts. Suboptimal platelet and endothelial function may result in platelet plug formation being more heavily influenced by platelet mass than by platelet count, as larger platelets can create a more effective platelet plug (10). Four studies included in the meta-analysis demonstrated that platelet mass was significantly lower in the hsPDA group (8). Similarly, Demir et al. (11) found that while platelet count is not a risk factor in the closure of hsPDA in premature newborns, low platelet mass is associated with hsPDA patency. In contrast, Akar et al. (12) found that platelet mass is not a risk factor for hsPDA in premature infants. However, studies differ in patient characteristics, diagnostic strategies, and treatment protocols. Furthermore, some studies indicate that impaired platelet function, rather than platelet count, is critically involved in ductus arteriosus closure failure (6). Our study supports these findings, as platelet mass was significantly lower in Group 2 (1452.8 ± 728.9) compared to those without hsPDA (1865.6 ± 747.3).

CONCLUSION

This study demonstrates that platelet parameters play an important role in hsPDA in preterm infants. It was found that the risk of hsPDA is increased in infants with low platelet counts and platelet mass, negatively affecting clinical outcomes. Future research should further investigate the mechanisms by which platelets contribute to PDA closure, and these findings should be considered in treatment strategies.

Ethics Committee Approval: The Health Sciences University, Ümraniye Training and Research Hospital, Ethics Committee granted approval for this study (date: 23.02.2023, number: B.10.1.TKH.4.34.H.GP.0.01/66).

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