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Platelet counts and C-reactive protein in preterm infants with patent ductus arteriosus

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Abstract

Introduction: Patent ductus arteriosus (PDA) is a common disorder in premature infants which causes heart failure. Platelets and C-reactive protein (CRP) play an important role in closure.
Objectives: The purpose of this study was to evaluate serum CRP and plasma platelet count in preterm infants with PDA compared to infants without PDA.
Patients and Methods: This case-control study was conducted on premature infants with PDA admitted to Imam Khomeini hospital in Ahvaz, Iran (2020-2021). A group of 120 infants with inclusion criteria was selected and divided into two groups of 60 subjects. The preterm infant with PDA and without PDA was defined as the case and control group, respectively. Platelet count, serum CRP, and an echocardiogram were assessed in all infants. The subjects were matched by gender, gestational age, and birth weight.
Results: The mean platelet count was 194.67±74.03 ($\times 10^3/mm^3$) in the neonate with PDA, and it was significantly lower than in neonate without PDA (P=0.04). The mean of serum CRP was significantly different in neonates with PDA (11.62±5.96 mg/L) compared to neonates with closed arterial ducts (8.52±3.97 mg/L; P=0.002). Additionally, PDA was associated with high platelet distribution width (PDW).
Conclusion: The findings of this study revealed that PDA is associated with a low-number of platelets and high serum levels of CRP in preterm neonates. It is suggested that further studies with a higher sample size on platelet count and/or function be performed in PDA patients to understanding more about the cause of PDA and to discover novel and beneficial aims in these cases.

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Introduction

The ductus arteriosus is the connection between the aorta and the pulmonary artery and is necessary for the fetus survival (1). After birth, this duct must be closed due to changes in the fetal to neonatal blood circulation (2). Ductal closure failure in premature babies is a mystery that infants have confronted for a long time, while the pathophysiological and scientific consequences have not yet been resolved (3-5).

The exact mechanism of ductal constriction remains controversial (6). Patent ductus arteriosus (PDA) is the main challenge in preterm infants in neonatal intensive care units (7). Additionally, the endurance of PDA in premature infants causes severe hemodynamic modifications that sometimes result in death(8).

Several previous studies suggested that inflammation plays a critical function in the pathogenesis of PDA (9, 10). It has been shown that serum C-reactive protein (CRP) levels are higher in preterm infants with PDA (9). Moreover, several studies have reported that impaired platelet linkage or transgenic failings in its biogenesis lead to determine of ductus arteriosus (7).

Echtler et al showed an essential role of platelets in postnatal ductus arteriosus closure in a mouse model. They also reported that thrombocytopenia may have a critical role in rising the risk for failure of ductus arteriosus closure in premature newborns(11). There is few human studies on the association of CRP and platelet levels with PDA (1).

Key point

Patent ductus arteriosus (PDA) is one of the most common congenital heart diseases that causes serious hemodynamic changes and sometimes leads to death in preterm neonates. Based on our findings, PDA is associated with a low number of platelets and high levels of C-reactive protein in preterm neonates.

Objectives

Considering the importance of this disease, we decided to conduct this study with the

aim of assessing the CRP and platelet count in preterm infants with PDA compared to neonates without PDA.

Patients and Methods

Study design

This case-control study was performed at Imam Khomeini hospital in Ahvaz in 2020-2021. A group of 120 infants with inclusion criteria was selected and divided into two groups of 60 subjects. The preterm infant with PDA and without PDA was defined as the case and control group, respectively. A detailed questionnaire was completed by medical records, which contain the demographic data and laboratory parameters.

Inclusion criteria were defined for cases who were 34 weeks of gestational age and have low- birth weight (less than 2000 g). Moreover, infants conducted a blood test and an echocardiogram on day of 3 ± 1 days and accordingly 7±1 days after birth by an ACUSON Sequoia 512 (Siemens, Erlangen, Germany) Doppler echocardiography device. Exclusion criteria were considered for cases who had died before day 7 and also had congenital heart defects, fetal abnormalities, life-threatening infections, small for gestational age, evidence of bleeding, neonatal sepsis, maternal preeclampsia, and liver failure. Matching was conducted based on gender, gestational age, and birth weight for all the cases. In order to measure the platelet count and serum CRP, 2 mL of blood sample was taken from each neonate. Analyzing the blood specimens was conducted with an automated hematology analysis system (Sysmex XE-2100, Japan).

Statistical analysis

In the current study, descriptive statistics were presented as mean ± standard deviation (SD) for quantity values and frequency (percentage) for qualitative values. To compare the variables, the independent *t* test and chi-square test were employed.

The associations between PDA and other variables were determined using the logistic regression analysis; significant variables from the univariate analysis were entered into the logistic regression analysis model. Moreover, odds ratios (ORs) and related 95% confidence intervals (CIs) were estimated. A *P* value less than 0.05 (2-sided) was considered as significant. All the statistical analysis was performed with SPSS version18.

Results

The current case-control study consists of 120 eligible infants. By considering included and excluded criteria and matching, each group consists of 60 infants. The mean birth weight for all the participants' was1248.33 ± 234.91 g (range; 850-1970 g) with a mean gestational age of 29.99 ± 1.76 weeks (range 27-34 weeks). The mean age for all the mothers was estimated 25.57 ± 6.64 years (range: 15-42 years).

Demographic and laboratory features of PDA infants versus infants without PDA were; the mean of birth weight in the PDA group was estimated 1228.33 ± 203.37 g, since this variable was 1268.33 ± 262.93 g in the non-PDA group (P=0.35). Furthermore, the gestational age did not differ between the two groups (*P* = 0.44). It was estimated 29.87 ± 1.67 weeks and 30.12 ± 1.86 weeks in the case and control groups, respectively. This study showed serum CRP, platelets, platelet distribution width (PDW), and qCRP (quantitative C-reactive protein) were significantly different between infants with and without PDA. Our study showed that the mean of serum CRP, qCRP, and PDW was higher in infants with PDA. While the mean platelet count in neonates with PDA was 194.67 ± 74.03 ($\times 10^3/mm^3$) and was significantly lower than neonates without PDA (*P* = 0.04). More details are provided in Table 1.

Logistic regression was conducted to assess the outcome of significant variables on PDA. As it is indicated in Table 2, only CRP was significantly and independently associated with PDA (OR: 1.54 (95% CI: 1.23-1.99). This means that plasma CRP level is 1.54-fold more in the PDA infants in compare with non-PDA group.

Moreover, there was no significant correlation between weight, gestational age and platelet counts with CRP serum concentration. More details are seen in Table 3.

Discussion

To investigate whether platelet and CRP levels generally affect the threat of PDA, we surveyed the relation between PDA, platelet count, and serum CRP levels in preterm infants with a case-control study at Imam Khomeini hospital in Ahvaz (affiliated to Ahvaz Jundishapur University of medical sciences). Our current study indicated that PDA was linked to high CRP levels and low-platelet count in preterm infants. In addition to small level of platelet, other related factors such as PDW had a

Table 1. Demographic and laboratory characteristics of infants

Variables	PDA infants (n=60)	Non-PDA infants (n=60)	*P* value
Birth weight (g)	1228.33 ± 203.37	1268.33 ± 262.93	0.35
Gestational age (wk)	29.87 ± 1.67	30.12 ± 1.86	0.44
Mother's age (y)	23.97 ± 6.47	27.17 ± 6.47	0.008
CRP (mg/L)	11.62 ± 5.96	8.52 ± 3.97	0.002
Platelets ($\times 10^3/mm^3$)	194.67 ± 74.03	222.25 ± 74.45	0.04
PDW (%)	15.42 ± 2.65	13.35 ± 1.94	<0.001

CRP, C-reactive protein; qCRP, quantitative C-reactive protein; PDW, platelet distribution width.

Table 2. Univariate logistic regression analysis

Variables	OR (95% CI)	*P* value
Mother's age (y)	1.063 (0.99-1.13)	0.055
CRP (mg/L)	1.54 (1.23-1.99)	0.03
qCRP (mg/L)	1.99 (1.27-7.02)	0.26
Platelet (× 10^3/mm^3)	1.004 (0.99-1.009)	0.19
PDW (%)	1.74 (0.79-3.86)	0.17

CRP, C-reactive protein; qCRP, quantitative C-reactive protein; PDW, platelet distribution width.

Table 3. Association between baseline characteristic and clinical information in PDA infants (n=60)

Variables	CRP (mg/L)	Platelet (×10^3/mm^3)
Weight (g)		
W < 1000 (n= 8)	12.25 ±4.20	176.25 ± 68.85
1000 ≤ W < 1500 (n=47)	11.79 ± 6.24	192.13 ± 68.75
W ≥ 1500 (n=5)	9.00 ±5.91	248.00 ± 117.77
P value	0.58	0.42
Gestational age (wk)		
GA < 28 (n=13)	13.08 ± 4.46	181.54 ± 58.71
GA ≤ 28 < 32 (n=42)	11.48 ± 6.35	192.38 ± 71.53
GA ≥ 32 (n=5)	9.00 ±5.91	248.00 ± 117.77
P value	0.42	0.221

PDA, patent ductus arteriosus; CRP, C-reactive protein.
Significant level is considered as 0.05.

statistically significant relation to PDA threat in preterm infants.

In line with our results, Meinarde et al in the PDA infants observed that platelet count was decreased and the CRP had increasing trend, and the platelet count associated oppositely with CRP (9). Furthermore, Dizdar et al declared that PDA was associated with low count of platelets and higher levels of PDW (7).

The extent of platelet distribution was shown the activeness of platelets. High levels of PDW were seen in cases with fatal thrombocytopenia. The finding of Dizdar et al study is entirely similar to our research (7). Boo et al also noted that it is possible to predict PDA based on platelet counts, which the low levels will show increasing the defeat in PDA after using the indomethacin (12). A study by Dani et al examined the correlation between the level of platelet and PDA, and they revealed that low-platelet counts elevate the risk of PDA (13). Moreover, Hillman et al found that PDA is related to decreasing the levels of platelets and increasing the levels of CRP in preterm infants (1). The results of the study by Hillman et al, like current findings, indicate the prominent role of platelets in arterial duct closure. The logical association between low-platelet counts and PDAs is due to platelet adhesion, and accumulation is the main stage in duct closure after initial contraction (14).

In contradiction to our results, the reported study by Fujioka et al showed no significant association between platelet counts and ductus arteriosus closure in Japanese premature infants (8). Shah et al demonstrated that the closure of the arterial duct was not associated with the platelet counts in preterm infants (15). These results are inconsistent with our findings. Shah et al asserted that decreasing in rotatory of platelet level was not accountable for insistent PDA in neonates, considering that infants with Wiskott-Aldrich syndrome or autoimmune thrombocytopenia close their ducts naturally, even though they have severe thrombocytopenia. Hence, platelet accumulation does not play a prominent role in duct closure in term infants (15).

In addition, it has been suggested that impaired platelet function may be associated with PDA rather than platelet counts (16). Echler et al have shown DA closure is impaired in neonates with malfunctioning platelet adhesion or aggregation or with defective platelet biogenesis (11).

In the current research, the association between CRP and PDA was considered. We found a remarkable difference in the level of CRP between the neonate with and without PDA. Similar to our finding, in the studies of Hillman et al and Meinarde et al, the level of CRP was higher in PDA infants than infants without PDA (1, 9). Based on the findings of previous studies, we interpreted that systemic inflammation due to oxidative stress may be involved in the pathogenesis of PDA (17). This inflammation can increase the expression of cyclooxygenase 1 and 2, followed by an increase in prostaglandin E2 and prostacyclin, which finally keeps the duct becomes extensive and stopping the platelet accumulation (18). High serum CRP value may indicate an inflammatory index or may be involved in inflammatory reactions, pathways, and platelet dysfunction. (19). Prenatal efforts to target inflammation may help close the duct.

Conclusion

Overall, we concluded that the current research delivers more documents regarding the relationship between decreasing level of platelet and higher levels of CRP and the threat of emerging PDA in neonates.

Limitations of the study

Further studies with a higher sample size on platelet count and/or function are necessary in PDA patients to understand the cause of PDA and to discover novel and beneficial aims in these cases.

Authors' contribution

MRR and MRSH were the principal investigators of the study. MRR, AM, MHZ, MD and MRSH were included in preparing the concept and design. MRR revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript and have read and approved the content of the manuscript.

Conflicts interest

The authors report no conflicts of interest.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The

Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences approved this study (IR.AJUMS.REC.1398.679). Moreover, written informed consent was obtained from parent's patients or legal guardians. This study was extracted from the residency thesis of Mohammad Rostami Shahrebabaki at department of neonatal intensive care unit, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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