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C-reactive Protein and Platelets Changes in Preterm Neonates with Patent Ductus Arteriosus

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Abstract

Introduction: This study aimed to investigate CRP and platelet count changes in preterm neonates with Patent Ductus Arteriosus on the seventh day of birth compared to the third day.

Methods: This longitudinal study was conducted on fifty neonates with PDA complications in Afzalipour hospital in 2017-2018. All neonates underwent repeated echocardiography before the closure of their arterial duct and 2 cc of blood sample was taken from each neonate and was sent to the laboratory for platelet and CRP count test.

Result: The mean of platelet was 296.17±18.08 on day 7, and it was significantly different compared to day 3 (195.49 ± 10.49). The arterial ducts of 15 neonates out of 50 patients with PDA were closed on the seventh day. The mean of CRP was significantly different in neonates with PDA (35.70) compared to neonates with closed arterial ducts (2.32) on day 7.

Conclusions: The results of this study revealed that PDA is associated with a low number of platelets and high level of CRP in preterm neonates.

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Introduction

Ductus Arteriosus connects the pulmonary artery to the aorta. During prenatal development, due to high pressure in the lungs, blood is shunted from the pulmonary artery to the descending aorta. In the 6th week of pregnancy, the amount of blood that flows into the artery is about 50 to 60% of the total cardiac output. Prostaglandins are potent vasodilators that keep the artery patent in the uterus. In the normal state after birth and under the influence of oxygen and respiratory, the resistance of the pulmonary vessels gradually decreases. Blood enters the pulmonary circulation and takes the prostaglandins to the lungs, where they are metabolized and removed from circulation. Oxygenated blood plays an important role in arterial duct closure (1,2). The normal blood circulation of the fetus depends on the presence of placenta and patent Ductus Arteriosus and after the birth (2).

With arterial duct closed during the first few days after birth, all of the right ventricle output enters the pulmonary

artery. If the duct remains patent after birth and pulmonary vascular resistance decreases, blood will flow from the aorta to the pulmonary artery through this duct. Of course, this flow continues throughout the cardiac cycle. This duct is closed in most neonates on the first day of life, but occurs anatomically at the end of the first week. It is abnormal for arterial duct to remain patently permanently. In premature neonates, ductal susceptibility to the effects of incessant potent prostaglandin-induced duct is greater and it decreases with aging. This duct remains patent in 30 to 60% of neonates with very low birth weight (less than 1500 grams). 3 The permanent self-closure of the duct occurs only in one third of neonates who weigh less than 1000 g in the first four days of life (3,4).

Patent Ductus Arteriosus (PDA) is one of the common disorders in premature neonates and many studies indicate that platelet levels play a significant role in its closure, and thrombocytopenia can play a predictive role in this regard. A large number of studies conducted on animals have shown that the adhesion caused by platelet activity in the lumen of the arterial duct occurs within a few minutes after birth, which can help close the arterial duct and fibrin formed in small vessels can activate the process of coagulation and close this duct (5). CRP (C-reactive protein) is a protein found in human and animal plasma and serum due to tissue injuries, necrosis, inflammation, infections, surgeries or cancers during the acute phase which vary in amount. Most of these proteins play a role in reducing the inflammatory lesions in the tissues, but in some cases they also exacerbate inflammatory lesions (6).

The inflammation plays a very important and decisive role in the pathogenesis of the patent Ductus Arteriosus and it has been shown in a study that platelet level is lower and CRP level is higher in premature neonates with patent Ductus Arteriosus, respectively (7).

Unfortunately, there is no human research considering the relationship between C-reactive protein amount, platelet level and arterial duct and most of studies have been conducted on animals. Also, considering the prevalence and importance of this disease, we decided to investigate CRP and platelet count changes in preterm neonates with Patent Ductus Arteriosus on the seventh day of birth compared to the third day.

Material and Methods

Sample

This longitudinal study was undertaken at Afzalipour Hospital in Kerman in 2017-2018. After receiving the ethical code document (IR.KMU.REC.1396.1731) and informed consent, 50 preterm neonates with PDA complications were selected through convenience sampling.

The inclusion criteria for neonates with a gestational age between 30 to 34 weeks was the nineties birth weight less than or equal to 2000 g or being diagnosed with the disease after undergoing echocardiography or taking blood tests during days 3±1 and 7±1.

The exclusion criteria were as follows: fetal abnormalities, death before the seventh day of birth, neonatal sepsis, maternal chorioamnionitis including maternal fever, purulent discharge, amniotic fluid, vaginal discharge caused by uterine tenderness, maternal leukocytosis, shock, twin, small for gestational age, maternal preeclampsia, maternal autoimmune disease, and congenital heart disease with the exception of arterial duct.

Procedure

All neonates underwent echocardiography using HMG70A-Sumsung echocardiography instruments made in South Korea. Echocardiography was repeated to follow up neonates with patent Ductus Arteriosus until the duct was closed and surgery was performed on neonates if the arterial duct was not closed. Echocardiography was performed by only one pediatric cardiologist.

To measure the amount of CRP and platelet count, 2 cc of blood was taken from each neonate. Then, using the selectra-XL and sysmex-KX-21N kits, these two variables were measured.

Statistical analyses

Data were analyzed using independent and paired sample T test. All analyses were conducted using SPSS software version 20.

Results

Sample characteristics

Fifty preterm neonates including 28 boys and 22 girls entered into the study. The mean weight was 1754.28 ± 423 and 1650± 307 for boys and girls, respectively. The mean age of mothers was 29± 6.62. Thirty five neonates were born through cesarean section, and intubation was done for 10 neonates.

A significant change was observed in the mean of platelet on day 7 compared to day 3. The mean difference of CRP on day 7 compared to day 3 was 2.59, but it was not significant (Table 1).

Table1. Comparison of platelet and CRP on day 7 compared to day 3

	Day 3		Day 7		
	Mean	SE	Mean	SE	P-value
Platelet	195.78	10.49	296.17	18.08	<0.001
CRP	9.08	2.46	11.67	3.01	0.44

The arterial ducts of 15 neonates out of 50 patients with PDA were closed on the seventh day (14.9%). The mean of platelet in patients with PDA was 300.88 in neonates with Closed Ductus Arteriosus compared to Patent Ductus Arteriosus (285.46), but no statistical significance was observed between the two groups. The mean of CRP was significantly different in neonates with PDA (35.70) compared to neonates with closed arterial ducts (2.32) (Table 2).

Table 2. Comparison of platelet and CRP in neonates with closed and patent Ductus Arteriosus on day 7.

	Closed Ductus Arteriosus		Patent Ductus Arteriosus		
	Mean	SE	Mean	SE	P-value
platelet	300.8	17.57	285.46	45.90	0.702
CRP	2.32	0.52	35.70	7.67	<0.001

Discussion

Patent Ductus Arteriosus is a common problem in premature neonates (5). In recent years, the relationship among platelet count and C-reactive protein levels and the patent Ductus Arteriosus has been taken into account. Our study showed that patent Ductus Arteriosus is associated with a lower platelet count and a higher level of C-reactive protein in premature neonates. In 15 neonates with PDA, the duct was

closed after 7 days. Different studies have been done in this area in which a number of researches are consistent with the results of the present study.

Echtler et al. presented a new insight into the arterial duct closure mechanism. Due to the role of endothelial cell injury in the arterial duct closure, platelets may play a role in this process. By studying the mice, it was concluded that platelets help in the arterial duct closure after birth. In newborn mice with platelet aggregation, adhesion or defective platelet production, arterial duct was not closed. 8 This study, like our study, concluded that platelets play a role in arterial duct closure.

The arterial duct closure mechanisms are different in premature and mature neonates. In mature neonates, contraction of the arterial duct after birth causes a decrease in blood flow into the lumen of ductus and vasa vasorum which leads to hypoxia in the vascular wall. The platelet aggregation affects the closure of the arterial duct. On the other hand, the arterial duct in the premature neonates is much thinner, lacking vasa vasorum, and obtains the required oxygen from the lumen. Therefore, contraction of the arterial duct in the premature neonates is not enough to close the arterial duct and hypoxia and platelet aggregation are necessary (9).

Boo et al. examined 60 premature neonates with PDA symptoms. In their study, low platelet count was a predictor of failure in the treatment of indomethacin. The high levels of platelet cause thrombosis and therefore luminal obstruction works better when closing the patent arterial duct (10). Compared to this study, Shah et al. examined a large group of premature neonates treated with indomethacin. They found that the closure of the arterial duct was not related to the platelets count in premature neonates, and concluded that the low platelet count does not affect the patent Ductus Arteriosus in human neonates. However, they found that in neonates whose platelets were not less than 230×10^9 liters, the prevalence of PDA was at its lowest level on their 3rd and 7th day after birth. In the present study, the average level of blood platelet in neonates with PDA was 150×10^9 liters. This amount was in mild range of thrombocytopenia (11). Also, there was no relationship between the platelet level and patent Ductus Arteriosus in the studies conducted by Fujioka et al. and Sallmon et al (12,13). These studies are not consistent with the results of the present study due to their low sample size, different birth weight and gestational age.

It should be noted that platelet adhesion did not occur in the arterial duct lumen of animals on the first days after delivery and was seen in a few neonates during that period. Therefore, platelet aggregation in mature neonates has no significant role in the closure of the arterial duct (14,15).

In a study conducted by Meinarde et al. with the aim of determining the association among CRP, platelet count and the prevalence of PDA, there was a significant difference between platelet and CRP levels in the two groups. It was concluded that low platelet levels and high levels of C-reactive protein are associated with patent Ductus Arteriosus and have a significant contribution to the closure of the arterial duct (7). This finding is completely consistent with the results of our study.

In another study by Kulkarni et al. with the aim of determining the association between thrombocytopenic complications in preterm neonates and delayed arterial duct closure, it was emphasized that platelet count below 100,000 at the first 24 hours after birth is related to delayed closure of arterial duct and this is one of the specific homodynamic risk factors of this complication in the first week of birth (5). This result is also consistent with our study.

A study by Dani et al. examined the association between platelet count and spontaneous or treated closure and they concluded that low platelet count increases the risk of patent Ductus Arteriosus (16).

In a new study, Dizdar et al. investigated hospitalized premature neonates with patent Ductus Arteriosus and found that the average amount of platelet was lower in the group with PDA in comparison to those without PDA. In addition, platelet count in patients became the same as the platelet level in neonates who did not have a patent Ductus Arteriosus after treatment with Brufen (17). The results of this study are completely in line with the present study.

Hillman et al., in another retrospective study, investigated the relationship between CRP and patent Ductus Arteriosus. Similar to our study, the average level of C-reactive protein in patients with PDA was higher than those with closed arterial duct and this difference was statistically significant (18).

Conclusion

With respect, many studies have not done about this on human being, our study evaluates the number of platelets and the amount of CRP in relationship among closure of patent ductus arteriosus at the same time, and we have decided to do so. Our data showed that patent Ductus Arteriosus is associated with low level of platelets and high level of C-reactive proteins in premature neonates. The study demonstrates that increasing the level of CRP that is an inflammation factor and also decreasing platelet count that has an important role in formation of clotting process and formation of thrombosis. The study concludes that in case we prevent from the occurrence of problem that can cause inflammation in premature neonates, we can prevent from patent ductus arteriosus. In addition to these, by prevention of procedures that can cause decreased platelet the study can lead to, we also the same result. Our study showed that in addition to the prophylactic treatment with NSAIDS for patent ductus arteriosus closure in premature neonates. All of these drugs have many contraindications and side effects during usage or use of low risk procedure. One of the strength of this study is its retrospective nature as well as the provision of the same nursing conditions for all neonates. Besides, a pediatric cardiologist at our center was present to visit the neonates as needed.

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