ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/cardiosci.2018-62380

The Fate of Patent Ductus Arteriosus is not Affected by Platelet Count and Mean Platelet Volume in Premature Infants < 32 Gestational Weeks

32 Gebelik Haftasından Küçük Prematüre Bebeklerde Patent Duktus Arteriyozus Trombosit Sayısı ve Ortalama Trombosit Hacminden Etkilenmemektedir

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Received: 07.08.2018
Accepted: 27.08.2018
Available online: 28.09.2018

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ABSTRACT Objective: There have been controversial data regarding the effect of platelet count and functions on spontaneous and medical closure of patent ductus arteriosus (PDA) in preterm infants. Our aim was to investigate the relationship between platelet count and mean platelet volume (MPV) and the medical and spontaneous closure of PDA in premature infants of <32 weeks of gestational age. **Material and Methods:** Patients were cathegorized as (1) those with a hemodynamically significant PDA (HSPDA) at 12 to 24 hours of age and (2) those in whom PDA was small or closed spontaneously. Patients with a HSPDA were further divided into two subcathegories: Patients achieved ductal closure with medical treatment and those needed surgical closure. **Results:** Seventy-five patients were included into the study population: 46 patients had a HSPDA, while in 29 ductus arteriosus closed spontaneously by the first 24th hour of life. Platelet count and MPV were similar between patients with and without a HSPDA (p>0.05). Of the 46 patients with a HSPDA, 38 achieved a successful PDA closure after medical treatment, while 8 needed surgical ligation. Again, there was no significant difference regarding platelet count and MPV between patients responded to medical therapy and those did not. **Conclusion:** Although platelet count and MPV may play a role in physiologic mechanisms of ductal closure; there has been insufficient and controversial clinical data regarding the effect of platelet count and functions on the fate of PDA in preterm infants. Prospective studies in this regard are warranted.

Keywords: Patent ductus arteriosus; platelet count; mean platelet volume; prematurity

ÖZET Amaç: Trombosit sayısı ve fonksiyonlarının, prematüre bebeklerde, patent duktus arteriyozusun (PDA) spontan veya medikal olarak kapanmasına etkisi üzerine çelişkili yayınlar bildirilmiştir. Çalışmamızda; 32 gebelik haftasından küçük prematüre bebeklerde, trombosit sayısı ve ortalama trombosit hacmi (OTH) ile PDA' nın kapanması arasında ilişki olup olmadığını araştırmayı amaçladık. **Gereç ve Yöntemler:** Hastalar (1) yaşamlarının 12-24. saatinde hemodinamik olarak önemli PDA'sı olan ve (2) PDA'sı kapanmış veya hemodinamik olarak önemsiz olan olarak 2 gruba ayrıldı. Hemodinamik olarak önemli PDA'sı olan hastalar iki alt gruba ayrıldı: Medikal tedavi ile PDA'sı kapanan hastalar ve cerrahi kapatmaya ihtiyaç duyan hastalar. **Bulgular:** Çalışmaya 32 gebelik haftasından küçük 75 prematüre bebek alındı: 46 bebekte hemodinamik olarak önemli PDA mevcuttu. Yaşamının 12-24. saatinde hemodinamik önemli PDA'sı olan ve olmayan prematüre hastalar arasında, trombosit sayısı ve OTH açısından istatistiksel olarak anlamlı bir fark saptanmadı (p>0.05). PDA'sı olan hastalardan 38'inde PDA medikal tedavi ile kapanırken, 8 hasta cerrahi kapatmaya ihtiyaç duydu. Aynı şekilde, medikal tedaviye cevap veren ve cerrahi ihtiyacı olan hastalar arasında, trombosit sayısı ve OTH açısından istatistiksel olarak anlamlı bir fark saptanmadı (p>0.05). **Sonuç:** Trombosit sayısı ve OTH, PDA'nın kapanmasında etkili fizyolojik mekanizmalarda rol oynasa da; bu konuda prematüre bebeklerde şimdiye kadar yapılan çalışmalar birbiriyle çelişmektedir ve bu etkiyi ortaya koymakta yetersiz kalmıştır. Bu konuda ileriye dönük çalışmalar yapılması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Patent duktus arteriyozus; trombosit sayısı; ortalama trombosit hacmi; prematürite

Premature infants with hemodynamically significant patent ductus arteriosus (HSPDA) has been associated with a low survival rate. Furthermore, these infants were found to be more prone to have significant sequelae namely; Respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and necrotising enterocolitis (NEC), when compared to premature infants without a HSPDA.[1-4]

Previous research showed that the closure of patent ductus arteriosus (PDA) is a two-step process including the constriction of surrounding smooth muscles and the anatomic remodelling with cellular proliferation. Although, platelet count and functions, local and systemic cytokines and hormones have been suggested to affect the closure of PDA. The exact mechanisms that play a role in these processes after birth remains to be elucidated.[2,5]

There have been controversial data regarding the effect of platelet count and functions on spontaneous and medical closure of PDA in preterm infants. Some studies suggested that platelet count and functions play an important role in the closure of ductus arteriosus, while some others did not find any relationship between the ductal closure and platelet count and functions.[6-8]

High platelet count and mean platelet volume (MPV) have been shown to support ductal closure by promoting thrombosis inside the lumen of arterial duct. Large platelets are known to be more active. MPV has been suggested as a marker of thrombopoiesis and platelet function. Some studies reported that high MPV was associated with higher rates of ductal closure in premature infants possibly by supporting the formation of fibrin deposits inside the arterial duct.[2,3,6-8]

The aim of the study was to investigate the relationship between platelet count and MPV and the medical and spontaneous closure of PDA in premature infants less than 32 weeks of gestational age.

MATERIAL AND METHODS

STUDY DESIGN AND POPULATION

We retrospectively evaluated the medical records of all premature infants with a gestational age of < 32 weeks followed in our hospital's neonatal intensive care unit (NICU) in the past two years. We did not evaluate premature infants with a gestational age 32 weeks or above to keep the effect of maturity on the PDA and platelet parameters to a minimum. One hundred and five premature infants of <32 weeks gestational age were followed in our NICU in the last two years. The patients with insufficient data, major congenital malformation, severe pulmonary hypertension, and those deceased within the first five days of life, were excluded from the study. Patients' data regarding birth weight, gestational age, gender, delivery type, and mechanical ventilation type were noted. The occurence of respiratory distress syndrome, necrotising enterocolitis, sepsis, and retinopathy of prematurity were investigated. Patients were cathegorized as those with a hemodynamically significant PDA at 12 to 24 hours of age and those in whom PDA was small or closed spontaneously. Patients with a HSPDA were further divided into two subcathegories: Patients achieved ductal closure with medical treatment and those needed surgical closure. The study was compatible with the Declaration of Helsinki and approved by the hospital administration.

ECHOCARDIOGRAPHY

The diagnosis of PDA was made echocardiographically. PDAs with an internal diameter above 1.5 mm on colored Doppler evaluation and/or with a left atrium to aortic root ratio above 1.5 was deemed to be hemodynamically signicant.

LABORATORY DATA

Complete blood counts of patients at 0-24 hours and 24-72 hours of age were obtained from a computerized patient database. Platelet count and MPV of the patients were recorded. Blood samples were drawn from the umblical or a peripheral vein and kept in ethylene diamine tetra acetic acid tubes.

Samples were analyzed in a standard blood count analyzer within four hours after collected.

STATISTICAL ANALYSES

Data was analyzed and processed with SPSS 18.0 statistical package programme (SPSS Inc., Chicago, Illinois, USA). The distribution pattern of data was assessed by the Kolmogrov-Smirnow test. Quantitative variables were demonstrated as mean ± standard deviation for normally distributed data or as median and minimum–maximum for the others. The Chi-square test or Fisher's exact test were employed to compare the qualitative data. The differences between the quantitative groups with normal distribution were analyzed with Student's t-test. The Mann-Whitney U test was used for abnormally distributed data. P value of < 0.05 was considered as statistically significant.

RESULTS

The number of the premature infants of < 32 weeks gestational age followed in our hospital's NICU between January 2016 and April 2018 was one-hundred and five. After exclusions, seventy-five patients were included into the study population. The mean gestational age and birth weight of the study population were 28,5±2,4 weeks and 1180 ± 406 grams, respectively.

Of the patients included into the study 46 patients had a HSPDA, while in 29 ductus arteriosus closed spontaneously by the first 24th hour of life. Gestational age and birth weight were significantly lower in patients with HSPDA. The need for oxygen and mechanical ventilation, the rate of NEC, sepsis and all grade IVH were higher in patients with HSPDA (Table 1). Nonetheless, gender, delivery type, the rate of antenatal steroid administration, RDS, and ROP were similar between groups. Moreover, the groups did not differ in terms of platelet counts and MPV (p>0.05).

Of the 46 patients with a HSPDA, 38 achieved a successful PDA closure after medical treatment using either ibuprofen or parasetamol, while 8 needed surgical ligation. A successful closure with medical treatment occured after one course of therapy in 26 patients, two courses in 5, and three

TABLE 1: Demographic and clinical characteristics of the patients with and without patent ductus arteriosus.

	Patients with PDA (n: 46)	Patients with Spontaneous Closure (n:29)	p value
Gestational age (wk)[a]	27.7 ± 2.3	29.6 ± 2.0	<0.001
Birth Weight (g)[a]	1083 ± 343	1335 ± 452	0.008
Male gender[b]	26 (57)	16 (55)	0.9
Antenatal steroid use[b]	8 (17)	5 (17)	0.98
Cesarean Section[b]	36 (78)	25 (86)	0.54
RDS[b]	33 (72)	17 (59)	0.31
Maximum FiO_2[a]	58.1 ± 23.9	44.2 ± 22.8	0.015
Mechanical Ventilation[b]	34 (74)	11 (38)	0.03
NEC[b]	7 (15)	0 (0)	0.039
Sepsis Occurence[b]	33 (72)	9 (31)	0.01
ROP Occurence[b]	4 (9)	1 (3)	0.64
IVH (all grades)[b]	18 (39)	1 (3)	<0.001
Platelet count (0-24 hour) x $10_3/mm^3$ [a]	218.0 ± 76.0	222.5 ± 68.0	0.79
Platelet count (24-72 hour) x $10_3/mm^3$ [a]	187.9 ± 102.7	209.9 ± 81.5	0.33
MPV (0-24 hour) (fl)[a]	8.55 ± 0.6	8.6 ± 0.7	0.77
MPV (24-72 hour) (fl)[a]	9.03 ± 0.8	8.84 ± 0.8	0.33

[a]Data are expressed as mean±SD; [b]Data are expressed as numbers with percentage in parantheses.

PDA: Patent ductus arteriosus; **wk:** week; **g:** grams; **RDS:** respiratory distress syndrome; **NEC:** necrotizing enterocolitis; **ROP:** retinopathy of prematurity; **IVH:** intraventricular hemorrhage; **MPV:** mean platelet volume; **fl:** femtoliter.

courses in 6 cases. One patient received four courses of medical therapy to achieve the successful closure. Again, there was no significant difference regarding platelet count and MPV between patients responded to medical therapy and those did not.

DISCUSSION

In this study, we demonstrated that platelet count and MPV were not associated with the occurence of PDA, and neither with its response to medical therapy in premature infants with a gestational age <32 weeks.

There has been accumulating controversial data reported after Echtler et al.[9] demonstrated that mice pups with a defective platelet adhesion and production was more vulnerable to develop persistent PDA even after treatment with indomethacin. They also reported that low platelet count was an independent predictor of HSPDA in preterm infants of < 30 weeks gestational age.

Some clinical studies showed that platelet count and functions were associated with the closure of arterial duct in premature infants after birth: Ahamed et al. in their study, showed that higher platelet count was a predictor of successful ductal closure after indomethacin therapy with an odds ratio of 1.5 in premature infants of <32 weeks gestational age.[1] Dani et al. found that thrombocytopenia at birth was associated with the occurrence of PDA.[2] However, they also showed that MPV values did not influence the fate of PDA in preterm infants. Dizdar et al. showed that the occurence of PDA was associated with platelet count but not with MPV.[5] They could not demonstrate an association between platelet parameters and the response of PDA to medical therapy. Kahvecioglu et al. found that decreased platelet function was associated with the persistence of ductus arteriosus in premature infants and suggested that impaired platelet function might play an important role in the pathogenesis of PDA in this subgroup of patients.[7] However, they could not show an association between platelet count, MPV and HSPDA in the same cohort.

On the other hand, Shah et al.[10] found that low circulating platelet counts was unrelated to the fate of PDA, mentioning that term infants born with severe thrombocytopenia secondary to inherited or alloimmune disease do not have a higher incidence of PDA. Again, similar to our results, Olukman et al. in their study, where 824 premature infants of < 34 weeks of gestational age were retrospectively analyzed showed that neither low platelet count nor MPV was associated with the persistence of HSPDA.[3] Simon et al. in their systematic review and meta-analysis, where they evaluated eleven cohort studies involving 3,479 preterm infants with a gestational age <32 weeks, found a marginal yet significant assocciation between low platelet count in the first days of life and the persistence of ductus arteriosus.[11] They concluded that this association needs to be investigated in prospective studies. The discrepancy among these studies may be explained by differences in the mean gestational age, male to female ratio, the rate of sepsis and respiratory problems in study populations.[2,3]

CONCLUSION

We did not find any relationship between platelet count, MPV and the medical and spontaneous closure of PDA in preterm infants. Although platelet count and MPV may play a role in physiologic mechanisms of ductal closure. There has been insufficient and controversial clinical data regarding the effect of platelet count and functions on the fate of PDA in preterm infants. Prospective studies on this issue are warranted.

LIMITATIONS

Relatively small sample size was the main limitation of the study. Retrospective design of the study was another drawback. We did not evaluate the platelet functions using elaborate hematologic tests, which may significantly affect the fate of ductus arteriosus.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Yazar Katkıları

Idea / Concept: *Mehmet Küçük;* ***Design:*** *Mehmet Küçük, Onur Bağcı;* ***Supervision / Consultancy:*** *Mehmet Küçük, Mahir İğde;* ***Data Collection and / or Processing:*** *Mehmet Küçük;* ***Analysis and / or Interpretation:*** *Mehmet Küçük, Onur Bağcı, Mahir İğde;* ***Resource Scanning:*** *Mehmet Küçük;* ***Writing of the Author:*** *Mehmet Küçük;* ***Critical Review:*** *Onur Bağcı, Mahir İğde;* ***Resources and Funding:*** *Mahir İğde.*

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