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Does platelet mass influence the effectiveness of ibuprofen treatment for patent ductus arteriosus in preterm infants?

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Abstract

Objective: The aim of this study is to evaluate whether the platelet mass in the first 24 h of life is effective on closure of patent ductus arteriosus (PDA) or not.

Study design: Preterm infants with a gestational age of <32 weeks, hospitalized at a tertiary neonatal intensive care unit (NICU) and requiring medical treatment (intravenous or oral ibuprofen) for hemodynamically significant PDA (hsPDA) were enrolled in this study. The patients were divided into two groups after first course of pharmacologic treatment according to closure of PDA (Group 1: PDA closure, Group 2: PDA without closure). Groups were compared in terms of demographics findings, morbidities, platelet measurements like counts, mean platelet volume (MPV) and platelet mass (platelet count x mean platelet volume).

Results: The study included 77 preterm newborns in Group 1, and 30 preterms in Group 2. There were no differences in birth weight, gestational age, gender and maternal risk factors between the study groups. The mean platelet count in the first postnatal blood count was in Group 1: 211.3 ± 89.2 × 10³/mm³ and in Group 2: 216.5 ± 26 × 10³/mm³, respectively (p = 0.783). The mean platelet volumes (MPV) were similar in both groups (p = 0.535). No statistically significant difference between platelet mass values was detected (Group 1: 1811 ± 884 fl/nl, Group 2: 1868 ± 717 fl/nl) (p = 0.753).

Conclusion: Our data suggest that platelet count, MPV and platelet mass did not affect the closure of hsPDA with ibuprofen.

Keywords

Patent ductus arteriosus, platelet mass, prematurity

Introduction

Patent ductus arteriosus (PDA) is one of the most common problems in newborns, especially in extremely low birth weight (ELBW < 1000 g). The delay in closure has an important role in the morbidity of preterm infants [1]. Patency of the ductus arteriosus (DA) increased the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and death in preterm infants [2]. Almost 60–70% of preterm infants with a gestational age of <28 weeks require medical or surgical treatment for PDA [3,4]. The primary mode of treatment is pharmacologic closure using by cyclooxygenase (COX) inhibitors with a closure rate of 70–80% [5].

Several molecular pathways, such as nitric oxide (NO), vascular endothelial growth factor (VEGF), cyclooxygenase/prostaglandins, are known to be involved in DA sealing, but the molecular mechanisms contributing to DA closure remains poorly understood. It is known that postnatal increase in oxygen and decrease in prostaglandin levels have an important role in the closure of PDA. Affecting factors on closure and relationship between PDA and platelet count are being investigated. Recent studies reported a role in the closure of PDA with platelet counts [6]. Boo et al. showed that hsPDA is associated with low platelet count and predicted a high failure in the closure of DA after indomethacin treatment [7]. Opposite results are also reported in the literature. Shah et al. could not demonstrate an association between low platelet count and permanent PDA or ductus reopening [8]. The inverse relationship between platelet size and platelet count in humans has prompted the development of platelet mass concept. Platelet mass has been proposed as a better predictor of production/regulation [9].
The aim of this study is to evaluate the effectiveness of platelet mass and indices in the first 24 h of life on the pharmacologic closure of hsPDA.

Material and methods

We conducted a retrospective cohort study between 1 May 2014 and 30 April 2015 at a tertiary NICU. Preterms with echocardiographic diagnosis of hsPDA and gestational age of <32 weeks or birth weight below <1500 g were included. The study was carried out at the NICU of Zeynep Kamil Maternity and Children’s Training and Research Hospital between 1 May 2014 and 30 April 2015. Local ethics committee approved the study. Written informed consent was obtained from the parents.

Prematurity with a gestational age of <32 weeks or birth weight below <1500 g and hsPDA were inclusion criteria. The exclusion criteria were incomplete data, severe asphyxia (Apgar score of ≤3 at 5 min), congenital heart disease (CHD), persistent pulmonary hypertension, congenital anomalies, hydrops fetalis and inherited errors of metabolism. Echocardiogram was used for the diagnosis of hsPDA.

Babies included in the study were randomized into two groups, according to the pharmacologic closure of PDA (Group 1: PDA closure; Group 2: PDA without closure). Gestational age, birth weight, gender, postnatal age and risk factors were recorded. Antenatal and postnatal risk factors in both groups were collected. Platelet counts and mean platelet volumes (MPVs) were determined using a Horiba Medical ABX pentra DF 120 Hematology Analyzer.

Hemodynamically significant PDA (hsPDA) was diagnosed with echocardiographic examination, which was routinely performed in very low birth weight (VLBW) infants at second day of life or afterward if it is needed. Hemodynamically significant PDA based on echocardiographic findings was defined as internal ductal diameter of ≥1.5 mm and/or with a left atrium (LA)/aortic root (AO) ratio ≥1.5. Two-dimensional (2D) color Doppler echocardiography of Philips En Visor C HD ultrasound (Royal Philips Electronics, Amsterdam, the Netherlands) and a multifre

 persistent pulmonary hypertension, congenital anomalies, hydrops fetalis and inherited errors of metabolism. Echocardiogram was used for the diagnosis of hsPDA.

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tal shunting flow 24–48 h after the end of pharmacotherapy; all other cases were defined as COX inhibitor treatment failure. Ligation was performed in patients after failure of pharmacotherapy.

Blood samples were drawn from patients after birth at first 24 h of life. Platelet measurements (and not later data) were collected to test the relationship with hsPDA occurrence and/or resistance to ibuprofen treatment. Samples for complete blood count were obtained either by venous umbilical catheter or venipuncture or by arterial puncture. Platelet count and MPV values were analyzed by the Coulter Counter Model LH (Coulter Electronics, Hialeah, FL). Platelet mass was obtained by multiplying of platelet count (×10³/mm³) and MPV (fl) values. Low platelet values were defined as platelet count below <150 × 10³/mm³. The study groups were compared in terms of demographics findings, morbidities and platelet indices like counts, mean platelet volume (MPV) and platelet mass (platelet count × mean platelet volume).

Statistical analysis was performed using the SPSS software [IBM SPSS v22 (IBM SPSS Inc., Armonk, NY)]. The variables were investigated using visual histograms, probability plots and Shapiro–Wilks’s test to determine whether they are normally or not normally distributed. Descriptive analyses were presented using means ± standard deviation for normally distributed variables, median (range) for the non-normally distributed variables and percentages for categorical variables. Normally distributed variables were compared by Student’s t-test, nonparametric variables by Mann–Whitney’s U-test and categorical variables by χ²-test. p values < 0.05 was considered as statistically significant.

Results

Among 303 neonates with a gestational week of <32 weeks admitted to the NICU during the study period and 107 (35%) of them were included in the study. One hundred ninety-six neonates had no hsPDA. Forty-three patients were excluded because of asphyxia (n = 6), congenital heart disease (n = 11), persistent pulmonary hypertension (n = 8), multiple congenital anomalies (n = 16), hydrops fetalis (n = 1) and inherited errors of metabolism (n = 1) (Figure 1). The study was performed with 77 preterm infants in Group 1 (PDA closure) and 30 preterm infants in Group 2 (PDA without closure). Patient characteristics are demonstrated in Table 1. Demographic characteristics, risk factors and platelet measurements were compared in both groups (Table 1). Groups were similar in terms of features, such as gestational weeks, birth weight, gender, preeclampsia, chorioamnionitis, RDS and early sepsis. Gestational weeks and birth weight of the patients were 28.3 ± 2.6 weeks, 1143 ± 389 g in Group 1 and 27.2 ± 2.9 weeks, 1015 ± 397 g in Group 2, respectively.

![Figure 1. Flow diagram of the study groups in hsPDA. *CHD: Congenital heart disease, PDA: Patent ductus arteriosus; PPH: Persistent pulmonary hypertension.](image-url)
The mean platelet count in the first postnatal 24 h was $211.3 \pm 89.2 \times 10^3$/mm$^3$ in Group 1 and $216.5 \pm 26 \times 10^3$/mm$^3$ in Group 2. The mean platelet count did not differ significantly between groups ($p = 0.783$). The number of patients with low platelet count ($<150 \times 10^3$/mm$^3$) was 15 (19.5%) in Group 1 and 5 (16.7%) in Group 2. There was no statistical significant difference between the study groups in terms of low platelet count ($p = 0.672$). The mean ± SD values of MPV were similar, 8.5 ± 1.1 fl in Group 1 and 8.7 ± 0.6 fl in Group 2 ($p = 0.535$) (Figure 2). The platelet mass values that were obtained by multiplying of platelet count and platelet volume and platelet mass after pharmacologic closure of hsPDA.

Results are mean ± standard deviation, rate (percent), or median (range).

<table>
<thead>
<tr>
<th>Table 1. Demographic and perinatal characteristics of the study groups.</th>
<th>Group 1 $(n = 77)$</th>
<th>Group 2 $(n = 30)$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational week, wk</td>
<td>28.3 ± 2.6</td>
<td>27.2 ± 2.9</td>
<td>0.060</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>1143 ± 389</td>
<td>1015 ± 397</td>
<td>0.134</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>40 (52%)</td>
<td>13 (43%)</td>
<td>0.423</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>58 (75%)</td>
<td>21 (70%)</td>
<td>0.245</td>
</tr>
<tr>
<td>Multiple birth, n (%)</td>
<td>10 (13%)</td>
<td>3 (10%)</td>
<td>0.517</td>
</tr>
<tr>
<td>Premature rupture of membranes, n (%)</td>
<td>20 (26%)</td>
<td>9 (30%)</td>
<td>0.385</td>
</tr>
<tr>
<td>Preeclampsia, n (%)</td>
<td>27 (35%)</td>
<td>8 (27%)</td>
<td>0.406</td>
</tr>
<tr>
<td>Histologic chorioamnionitis, n (%)</td>
<td>5 (6%)</td>
<td>0 (0%)</td>
<td>0.153</td>
</tr>
<tr>
<td>Antenatal steroid, n (%)</td>
<td>31 (40%)</td>
<td>14 (47%)</td>
<td>0.273</td>
</tr>
<tr>
<td>APGAR scores at 5th min, median (min-max)</td>
<td>7 (6-9)</td>
<td>8 (6-9)</td>
<td>0.164</td>
</tr>
<tr>
<td>Respiratory distress syndrome, n (%)</td>
<td>68 (88%)</td>
<td>29 (97%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Early sepsis, n (%)</td>
<td>22 (28%)</td>
<td>11 (37%)</td>
<td>0.469</td>
</tr>
</tbody>
</table>

The underlying mechanisms are in some cases impaired platelet production, while in others increased consumption is effectively. Low platelet counts may be also a common marker of bacterial infections that could contribute to the development of pneumonia (by the secretion of endogenous prostaglandins) [11]. Experimental studies suggested that platelet-triggered ductal occlusion is critical in the closure of hsPDA, but whether platelet count contributes to hsPDA in humans is controversial. Echtler et al. hypothesized that platelets might have a role in the closure of DA. They have identified in newborn mice platelet-initiated thrombotic occlusion constricted DA and speculated that platelet aggregation, adhesion and synthesis could lead to failure in the closure of hsPDA [6]. Sallmon et al. reported in a retrospective large study with 1350 very low birth weight (VLBW; <1500 g) infants, including 592 extremely low birth weight (ELBW; <1000 g) infants, that thrombocytopenia in the first 24 h after birth is not associated with hsPDA. However, they reported impaired platelet function, due to immaturity and critical illness, rather than platelet number and could play a role in hsPDA [12]. Fujio K et al. did not find an association between thrombocytopenia and incidence of hsPDA [13]. Conversely. Echtler et al. reported in 123 preterm infants born at 24–30 weeks’ gestation that mild thrombocytopenia (platelet counts 101 000–140 000/ml) at the first day of life is a risk factor for failure of DA closure and demonstrated induced dysfunction of platelet adhesion which led to persistent DA [6].

Recently, Ahamed et al. investigated in a retrospective cohort study in infants with gestational age (GA) of <32 weeks’ and birth weight <1500 g whether platelet count could predict the likelihood of successful closure of PDA with indomethacin. They found older gestational age, male gender and higher platelet count at time for the treatment of hsPDA are predictors of successful ductal closure with indomethacin [14]. Treatment with indomethacin is associated with adverse reactions, such as reduced renal, mesenteric and cerebral perfusion. Unlike to indomethacin, ibuprofen does not affect the basal cerebral blood flow and has fewer side effects on renal hemodynamics [15]. Therefore, we used ibuprofen in the treatment of hsPDA and investigated the relationship between platelet count and response to hsPDA with ibuprofen. We found that platelet count does not influence the pharmacologic treatment of hsPDA. Similar to our results, Dani et al. investigated in a cohort study at 163 ELBW infants the effect of platelet count on failure to closure of hsPDA. They found that low platelet counts increased the risk of developing hsPDA, but did not affect the pharmacologic closure rate [16]. Alyamac et al. evaluated 154 premature infants with hsPDA ($n = 154$) and a control group without PDA ($n = 207$), retrospectively. They found that platelet counts were significantly lower in the study group than in the control group ($p < 0.001$) and shows in a multivariate analysis an association between hsPDA and low platelet count <150 000 but not with other platelet indices. Baseline platelet counts of the infants in whom ductus closed or persisted after pharmacologic treatment were similar in this
study. They found not an association between platelet count and persistence or closure after pharmacologic treatment. An association between pharmacologic closure of hsPDA and other platelet values was not detected [17]. Karpakkin S, reported large platelets have a greater potential risk of prothrombotic reactions [18]. Therefore, we investigated MPV values to identify the risk of treatment failure in patients with hsPDA, but found no significant difference between the study groups. Reported data show platelet mass as a better predictor of production/regulation coagulation [9]. Requirement of platelet transfusions based on platelet mass index and platelet counts are compared in different trials [19–21]. We investigated in our study also the relationship between platelet mass (mean platelet count multiplied by MPV) and medical closure of hsPDA, but found not a significant association and speculate that other factors may be more effective in closure of DA. Recently, Demir et al. reported in a retrospective study, which were 115 preterm newborns included, platelet mass may be a more significant indicator than platelet count in closure of hsPDA [22]. In our study, we found not a statistically significant difference between platelet mass indices in both groups. However, our study has still limitations. The first limitation is the retrospective design. The relatively small sample size of the population is the second limitation. Our study includes a single-center experience, which was the third limitation. The inability to evaluate changes of platelet indices like platelet mass, MPV in relationship to platelet count and the possible effect on hsPDA of factors, such as medications and genetics, are other limitations. Prospective randomized controlled trials with larger sample size are needed to estimate the effect of platelet indices on pharmacologic closure of hsPDA.

Conclusion
Our data suggest that platelet count, MPV, and platelet mass did not influence the effectiveness of ibuprofen in closure of hsPDA. Further studies are needed to determine the factors which affecting the closure of hsPDA.

Acknowledgments
Akar S performed the research. Karadag N and Yildirim TG, Karatekin G, Yavuz T, Ovali F designed the research study. Toptan HH, Dincer E, Tuten A collected data. Topcuoglu S, Karatepe HO contributed essential reagents and tools. Akar S, Ozalkaya E analyzed the data. Karadag N, S Akar wrote the article.

Declaration of interest
The authors report no conflicts of interest.

References

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