

Preterm Thrombocytopenia and Delay of Ductus Arteriosus Closure

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abstract

OBJECTIVES: To evaluate whether preterm thrombocytopenia within 24 hours of birth is associated with delayed closure of patent ductus arteriosus (PDA) and higher proportion of hemodynamically significant PDA (Hs-PDA).

METHODS: Neonates (gestation 26^{0/7}–33^{6/7} weeks, age <24 hours) with known platelet count and PDA on echocardiogram were prospectively enrolled. Asphyxia, congenital infections, structural heart disease, major malformations and clinical sepsis were exclusions. Subjects were recruited in groups A (*n* = 35), B (*n* = 18), and C (*n* = 17) [platelet counts >150,000, 100,000–150,000 and <100,000 per μ L respectively] and underwent daily echocardiography until first closure of PDA, death, or day 10.

RESULTS: The primary outcome was time to first closure of PDA. Secondary outcomes included the proportion with PDA at 72 hours and 7 days, Hs-PDA, and PDA needing treatment. In groups A, B, and C, median (first–third quartile) platelet counts ($\times 100000/\mu$ L) were 2.28 (1.94–3.19), 1.25 (1.14–1.37), and 0.68 (0.54–0.83) and time to PDA closure was 2 (2–2), 2 (2–3), and 10 (6–10) days, respectively (log-rank test, *P* < .001). On Cox proportional hazard regression, platelet count (in multiples of 10 000 / μ L) independently predicted time to PDA closure (adjusted hazard ratio: 1.045; 95% confidence interval: 1.019–1.07). On day 7, 47.1% neonates in group C had PDA and none in groups A and B (*P* < .001).

CONCLUSIONS: Thrombocytopenia within 24 hours of birth independently predicts delayed PDA closure and PDA on day 7 in preterm neonates.

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Dr Kulkarni participated in the study design, recruited patients, performed echocardiography, collected data, and drafted the manuscript; Dr Dutta conceptualized and designed the study, supervised the collection of and analyzed the data, and critically revised and finalized the manuscript; Drs Sundaram and Saini participated in the study design, reviewed the echocardiography, and participated in the revision of manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT:

Thrombocytopenia at birth causes delayed ductus arteriosus closure in mice but the relationship in human preterm infants is unclear.

WHAT THIS STUDY ADDS: Platelet count <100 000 per μ L within 24 hours of birth is associated with delayed ductus arteriosus closure in human preterm neonates and is a risk factor for hemodynamically significant ductus arteriosus on day 7 of life.

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Patent ductus arteriosus (PDA) is a common problem in preterm neonates.¹ In recent years, a relationship between platelet count and closure of PDA has been proposed. Animal experiments have shown adherence of activated platelets to the lumen of the ductus arteriosus (DA) within minutes after birth, which may be crucial for DA closure by thrombosis and luminal remodeling.²

Human studies on the proposed relationship between platelet counts and PDA closure are retrospective, often poorly designed, and have arrived at conflicting conclusions. A recent systematic review reported a marginal association between thrombocytopenia in the first few days of life and PDA in very preterm infants. However, there were several shortcomings among the studies included in the meta-analysis.³ There are no prospective studies on this issue, and only a few that have evaluated thrombocytopenia within 24 hours of birth. Considering the gaps in the existing literature, we designed this prospective cohort study to evaluate whether thrombocytopenia on the first day of life in preterm neonates is associated with delayed PDA closure and with a higher proportion of hemodynamically significant PDA (Hs-PDA) at 72 hours and 7 days of life.

METHODS

We carried out a prospective cohort study in a level III NICU in northern India from July 2013 to December 2014. The Institute's ethics committee approved the study protocol.

Within 24 hours after birth, we screened all preterm infants (gestation of 26^{0/7} to 33^{6/7} weeks) who had a platelet count (by SF-3000 [Sysmex, Ramsey, MN] or LH-750 [Beckman Coulter, Brea, CA]) already performed for a clinical

indication and whose results were available. To maximize our chances of encountering relatively stable patients with thrombocytopenia, we also actively screened preterm infants born to mothers with pregnancy-induced hypertension (PIH). We enrolled consecutive subjects in the following groups within 24 hours of birth until the sample size in each group was met: group A, platelet count >150 000 per μL ; group B, platelet count of 100 000 to 149 000 per μL ; and group C, platelet count <100 000 per μL .

We excluded infants with the following conditions: perinatal asphyxia (Apgar score <7 at 5 minutes or cord pH <7.1), clinical syndrome of early-onset sepsis (EOS) in the presence of risk factors for sepsis and/or chest radiograph suggesting pneumonia, suspected or proven intrauterine infection, echocardiographically proven congenital heart disease, major malformations, or syndromes known to be associated with PDA.

We enrolled infants after obtaining written informed parental consent, including a separate consent to perform a platelet count in case of infants born to mothers with PIH, because the latter was not a standard of care in our unit. We excluded subjects postenrollment if parents withdrew consent or if the quality of the echocardiograms was suboptimal and likely to affect measurement of the primary outcome.

The study period was up to 10 days. An investigator (V.V.K.), trained in neonatal echocardiography, performed serial echocardiograms once daily (at 24- \pm 4-hour intervals) from day 1 to day 7 and on day 10 or until PDA closure, death, or discharge, whichever was earlier. The author (V.V.K.) used a MicroMaxx Portable Ultrasound Machine (Sonosite, Inc, Washington, DC) with color Doppler mode and an 8–10 MHz curvilinear transducer. Within 18 hours of performing each

echocardiogram, the findings were confirmed by a blinded expert in neonatal echocardiography (either V.S. or S.S.S.) who viewed the video files of the echocardiogram. The experts' findings were considered the gold standard. For all subjects whose DA was declared closed, a repeat echocardiogram was performed after 24 hours to confirm that the PDA had not reopened.

We defined PDA as any detectable blood flow across the DA by color Doppler. Continuous and pulse-wave Doppler modes were used to confirm the presence, if any, and direction of blood flow across the DA. The investigator measured ductal diameter, maximum ductal velocity V_{max} (m/second), PDA to left pulmonary artery diameter, antegrade pulmonary artery diastolic flow, antegrade left pulmonary artery diastolic flow, left atrium to aorta and left ventricle to aorta ratios, left ventricular output, right ventricular output, left ventricular output to superior vena cava flow, E to A ratio (early diastolic filling to atrial contraction), isovolumetric-relaxation time, and diastolic flow pattern in the descending aorta according to standard views. He measured each parameter twice and averaged it to minimize intraobserver variability. When the difference between 2 readings was >20%, he repeated the entire measurement, which was immediately confirmed by an expert (V.S./S.S.S.). We scored the above parameters and used a composite score of ≥ 21 to define Hs-PDA, as per published validated criteria.⁴

In our unit, as part of routine clinical care, color Doppler echocardiograms are performed in extremely low birth weight infants within 24 hours of birth and in all other neonates whenever clinically indicated. All clinical and echocardiographic Hs-PDAs are treated pharmacologically.

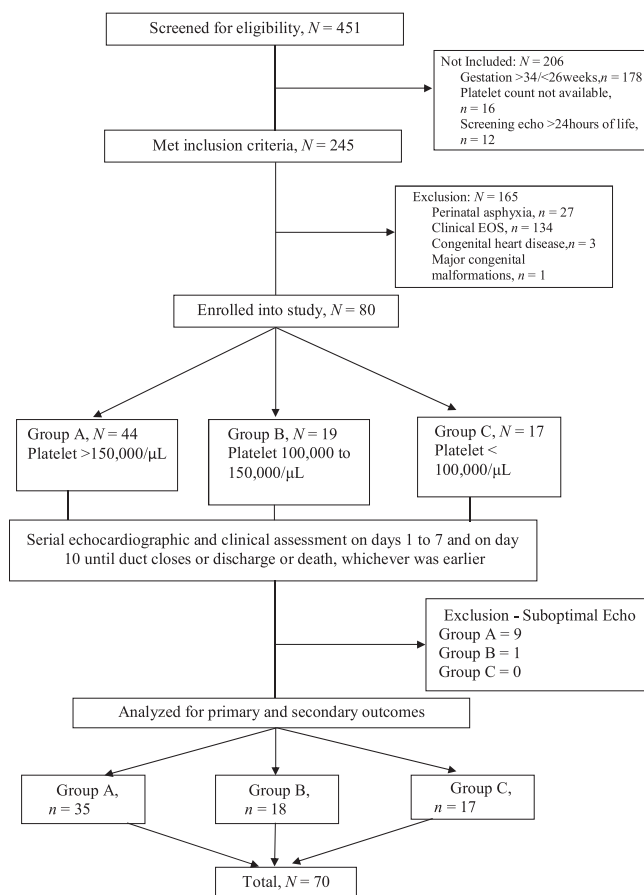


FIGURE 1
Flow of study participants.

In a previous study,² 35% of preterm infants with normal platelet counts had ductal closure versus 0% in the thrombocytopenic group. Assuming a 2 to 1 ratio between groups A and C, we required 36 and 18 subjects in these groups, respectively, to detect a 35% difference in PDA closure rate, with a 5% α error and 80% power. For convenience, 18 subjects were also recruited in group B.

We compared categorical variables across 3 groups by χ^2 test for trends. We tested normality of numerical variables by the Shapiro-Wilk test and Q-Q plot. If normally distributed, we compared them by analysis of variance for linear trends, and if skewed, by Jonckheere-Terpstra test. We compared the time to PDA closure by log-rank test for trends and the magnitude of the effect by hazard ratios (HRs) of closure of the

DA in groups C versus A (group A was the reference group).

We performed 2 time-to-event analyses with different sets of censoring variables. The first analysis was with a minimal set: death, discharge, or consent withdrawn before day 10; or nonclosure of PDA by day 10. The second was with an extended set of censoring variables: death, discharge, consent withdrawn; culture-positive sepsis; administration of platelets or nonsteroidal antiinflammatory drugs (NSAIDs) before day 10; or nonclosure of PDA by day 10. The rationale behind the extended set was that intercurrent sepsis, administration of platelets, and administration of an NSAID may alter the subsequent course of PDA closure, independent of the original platelet count.

For multivariable Cox proportional hazard regression on the full study population, we included baseline variables that were significant on univariate analysis and the actual platelet count (in multiples of 10 000 per μL) to determine the independent risk factors of time to DA closure. We used SPSS version 21 (IBM-SPSS, Armonk, NY) for data analysis.

RESULTS

Figure 1 shows the flow of study subjects. Thirty-five neonates in group A, 18 in group B, and 17 in group C completed the study and their data were analyzed. The baseline characteristics were similar across groups (Table 1).

Figure 2 shows Kaplan-Meier curves with the minimal and extended set of censoring variables. With the minimal set, the median (first-third quartile) time of PDA closure in group C was 10 days (6–10) versus 2 days (2–2) in group A and 2 days (2–3) in group B ($P < .001$). With reference to group A, the HR (95% confidence interval [CI]) of PDA closure in group C was 0.134 (0.06–0.32). This finding meant that among those whose DA was open until a certain day of follow-up, the immediate risk of PDA closure in group C was only 13.4% of that in group A.

The median time of PDA closure with the extended set was also significantly different ($P < .001$). With reference to group A, the HR (95% CI) of PDA closure in group C was 0.001 (0.04–0.43). Thus, with the extended set of censoring variables, among those whose DA was open until a certain day of follow-up, the immediate risk of PDA closure in group C was only 0.1% of that in group A.

We pooled data from the full study population and evaluated the following baseline variables on univariate analysis to determine

TABLE 1 Comparison of Baseline Characteristics Between Groups

Characteristic	Group A (n = 35)	Group B (n = 18)	Group C (n = 17)	P
Gestational age, median (first–third quartile), completed weeks	32 (29–32)	32 (29.75–33)	31 (29.5–32.5)	.8
Birth weight, mean ± SD, g	1271.11 ± 258.5	1163.83 ± 234.8	1078.06 ± 241.2	.009
Male sex, n (%)	18 (51.4)	11 (61.1)	7 (41.1)	.5
Delivery by LSCS, n (%)	9 (25.7)	10 (55.5)	14 (82.3)	.001
One-minute Apgar score <5	10 (28.5)	3 (16.67)	3 (17.6)	.5
Cord pH, median (first–third quartile)	7.25 (7.21–7.3)	7.29 (7.21–7.37)	7.23 (7.20–7.24)	.4
Platelet count, median (first–third quartile), ×10 ⁵ cells per μL	2.28 (1.94–3.19)	1.25 (1.14–1.25)	0.68 (0.54–0.83)	<.001
Maternal hypertension, n (%)	18 (51.4)	18 (51.4)	16 (94.1)	.010
pPROM, n (%)	4 (11.4)	0	1 (5.8)	.03

LSCS, lower segment cesarean section (delivery); pPROM, preterm premature rupture of membranes.

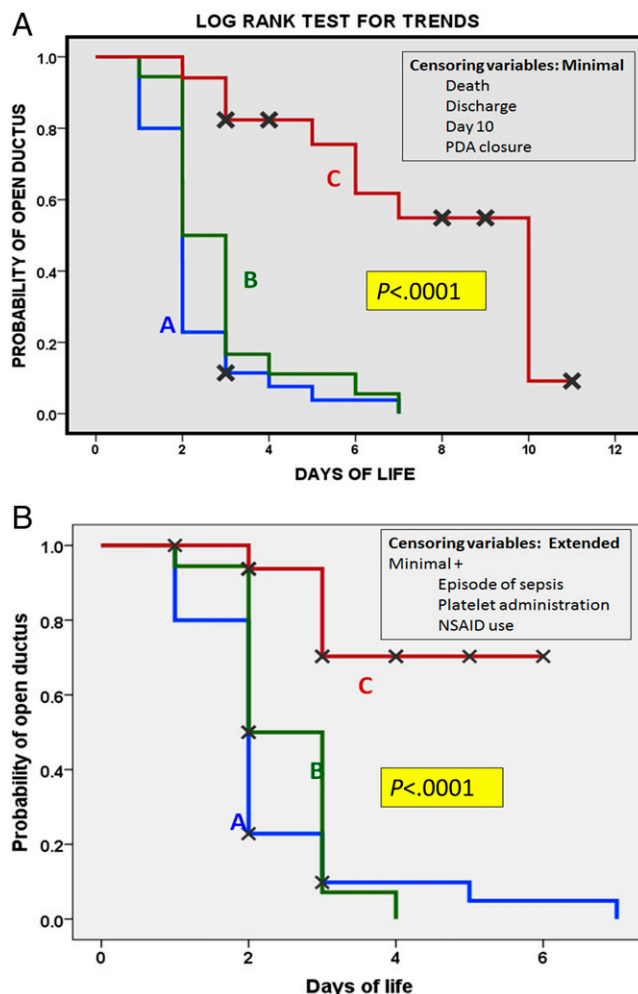


FIGURE 2 Kaplan-Meier survival curves comparing groups A, B, and C for time to PDA closure with minimal (A) and extended (B) sets of censoring variables.

significant associations with time to PDA closure: absolute platelet count (as multiples of 10 000 per μL), gestational age, indication for platelet count, Apgar at

1 minute, cord blood pH, preterm premature rupture of membranes, gestational hypertension, sex, birth weight, and mode of delivery (Table 2). Among these, platelet

count, birth weight, indication for platelet count, and gestational hypertension were significantly associated with time to PDA closure.

When we included these variables as predictor variables in a Cox proportional hazards regression model, only the absolute platelet count (as multiples of 10 000 per μL) emerged as an independent predictor of time to closure of PDA (Table 2). The adjusted HR (95% CI) was 1.045 (1.019–1.07; $P < .001$), indicating that for each increment in platelet count by 10 000 cells per μL, the immediate risk of closure of PDA increases by 4.5% compared with the baseline risk.

The proportions of neonates with a PDA at 72 hours of age were 8.6%, 16.7%, and 82.4% in groups A, B, and C, respectively ($P < .001$) (Table 3). Only group C had subjects (47.1%) with a PDA at 7 days of age. Of these, 64.3% had Hs-PDA. The PDA had closed in all subjects in groups A and B by day 7. The proportion whose PDA required pharmacologic treatment was significantly higher in group C compared with groups A and B (15 of 17 [88.2%], 1 of 35 [2.9%], 2 of 18 [11.1%], respectively; $P < .001$). Mortality during the study period in groups A, B, and C was 5 (14.3%), 1 (5.6%), and 5 (29.4%) deaths, respectively ($P = .035$). None in the entire cohort had blood culture-proven sepsis during the duration of the study.

TABLE 2 Univariate and Multivariate Analysis of Baseline Characteristics for Time to PDA Closure

Predictor Variable	Univariate Analysis		Multivariate Cox Proportional Hazards Regression	
	Unadjusted HR (95% CI)	Unadjusted HR, <i>P</i>	Adjusted HR (95% CI)	Adjusted HR, <i>P</i>
Platelet count (expressed as multiples of 10000 per μ L)	1.051 (1.027–1.076)	<.001	1.045 (1.019–1.07)	<.001
Indication for platelet count ^a	0.561 (0.34–0.94)	.03	0.61 (0.21–1.8)	.4
Maternal PIH	0.48 (0.28–0.81)	.006	0.457 (0.16–1.34)	.2
Birth weight	1.00 (1.00–1.0)	.03	1.001 (1.0–1.002)	.09
Apgar score at 1 minute	1.17 (0.63–2.18)	.6	—	—
Cord pH	0.92 (0.01–153.47)	.9	—	—
pPROM	2.28 (0.9–5.76)	.08	—	—
Gestational age	1.03 (0.91–1.17)	.6	—	—
Maternal chronic hypertension	0.640 (0.2–2.05)	.4	—	—
Male sex ^b	1.18 (0.72–1.95)	.5	—	—
Mode of delivery ^c				
Elective LSCS	0.55 (0.07–4.1)	.6	—	—
Emergency LSCS	0.62 (0.37–1.04)	.07	—	—

N = 70. El, ; Em, ; LSCS, lower segment cesarean section (delivery); pPROM, preterm premature rupture of membranes.

^a Maternal PIH was compared with “others” as the reference group.

^b Female was the reference group.

^c Vaginal delivery was the reference group.

TABLE 3 Comparison of Secondary Outcomes Between Groups

Outcome	Group A (<i>n</i> = 35)	Group B (<i>n</i> = 18)	Group C (<i>n</i> = 17)	<i>P</i>
Any PDA at 72 hours, <i>n</i> (%)	3 (8.6)	3 (16.7)	14 (82.4)	<.001
Any PDA at 7 days, <i>n</i> (%)	0	0	8 (47.1)	<.001
Hs-PDA at 72 hours (among those with a PDA), <i>n/N</i> (%)	2/3 (66.7)	1/3 (33.3)	9/14 (64.3)	.6
Hs-PDA at 7 days (among those with a PDA), <i>n</i> (%)	0	0	6/8 (75)	<.001
Medical treatment received for PDA, <i>n</i> (%)	1 (2.9)	2 (11.1)	15 (88.2)	<.001

DISCUSSION

The results of our study showed that neonates with an initial platelet count <100 000 per μ L took a significantly longer time to achieve PDA closure. This phenomenon held true even when the follow-up time of subjects was censored for intercurrent events that had the potential of altering the subsequent course of PDA closure, such as sepsis, platelet transfusion, and NSAID administration. Subjects with a platelet count <100 000 per μ L had a significantly higher proportion with a PDA at 72 hours and 7 days. The absolute platelet count was an independent predictor of hazard of PDA closure after adjusting for potential confounders.

We limited our study to neonates whose platelet counts were available within 24 hours of birth on the basis of previous observations that the formation of a platelet plug and partial to complete occlusion of the DA lumen in preterm mice was

shown by the first 24 hours of life.² We hypothesized that the role of platelets, if any, would primarily be within the first 24 hours. However, we recognize that this time frame of 24 hours may not necessarily be true. Thrombocytopenia secondary to PIH has its nadir at ~4 days of postnatal life.⁵ In our study, ~94% of neonates with a platelet count <100 000 per μ L had thrombocytopenia attributable to PIH. Ductal constriction is also delayed by a few days⁶ in preterm infants compared with full-term infants and approximately coincides with the nadir of thrombocytopenia secondary to PIH. Thus, the lack of platelet counts beyond the first day of life in our study precluded the investigation of the effect of late-onset thrombocytopenia.

We did not enroll subjects with a clinical syndrome of EOS, because sepsis is potentially a confounder that affects platelet count and function, and through incompletely understood mechanisms,

independently predisposes to PDA. We did not define EOS on the basis of blood culture because subjects had to be recruited within 24 hours of birth, by which time all blood culture reports were not available. Previous authors have also attempted to adjust for sepsis in multivariate regression models.^{2,7,8} We also excluded perinatal asphyxia, a potential confounder that is associated with thrombocytopenia and platelet dysfunction and that is independently associated with PDA.^{9–11}

Unlike our study, authors of several previous studies^{7,8,12–14} administered prophylactic NSAIDs as a part of unit policy and this could have altered the day of PDA closure in their studies. None of the aforementioned retrospective studies reported a uniform policy of timing of echocardiographic evaluation and definition of Hs-PDA. Because ours was a prospective study, we could perform serial echocardiograms

strictly at 24-hour intervals and were better able to time the actual PDA closure. We were also able to accurately define and prospectively record baseline covariates that were adjusted for in multivariate analysis.

There was significant statistical heterogeneity reported in the recent meta-analysis.³ Echtler et al,² Alyamac Dizdar et al,¹⁴ and Dani et al⁷ found an association between platelet count and PDA, whereas Fujioka et al,¹⁵ Shah et al,¹² and Sallmon et al⁸ did not. Boo et al¹³ conducted a prospective study to determine the predictors of failed PDA closure after the administration of a single course of indomethacin. They observed low platelet count as an independent risk factor for failure and hypothesized that possibly impaired thrombus formation within the ductal lumen could be the culprit. Thrombocytopenia is a well-known contraindication¹⁶ for the use of NSAIDs, such as indomethacin and ibuprofen, because they cause platelet dysfunction. This situation of NSAID use is likely to pose a problem in the treatment of PDA secondary to thrombocytopenia and may require the use of medications that are known to cause less platelet dysfunction.

The results of our study suggest that moderate thrombocytopenia (platelet counts of 100 000–150 000 per μL) is not a risk factor for delayed PDA closure. Previous retrospective studies did not divide the thrombocytopenia group any further and hence were not able to distinguish between cutoff values of 150 000 and 100 000 per μL .^{2,15} Moreover, previously published normative data suggest that the fifth centile of normal platelet count in preterms born at ≤ 32 weeks' gestation is 104 200 per μL and for ≤ 37 weeks is 123 000 per μL .¹⁷ Because the lower limit of normal platelet count in preterm infants is between 100 000 and 150 000 per μL it may explain why patients in group B did not have delayed PDA closure. We quantified the effect of progressive increase in platelet counts in increments of 10 000 per μL on risk of PDA closure, a finding that, in the future, may guide therapeutic attempts to achieve PDA closure.

The strengths of our study were a prospective design with a diligent echocardiography protocol, adjustment for potential confounders, and the use of a recently validated score for determining Hs-PDA. The study was limited by our failure

to assess platelet functions due to logistic and financial reasons. The number of subjects recruited in our study was low and a larger study may be required to achieve conclusive results.

CONCLUSIONS

Thrombocytopenia within 24 hours of birth is associated with delayed PDA closure in preterm neonates between 26^{0/7} and 33^{6/7} weeks' gestation after adjustment for confounders. Thrombocytopenic preterm infants also had a significantly higher proportion of PDA on days 3 and 7 and of Hs-PDA on day 7 of life.

ABBREVIATIONS

CI:	confidence interval
DA:	ductus arteriosus
EOS:	early-onset sepsis
HR:	hazard ratio
Hs-PDA:	hemodynamically significant patent ductus arteriosus
NSAID:	nonsteroidal antiinflammatory drug
PDA:	patent ductus arteriosus
PIH:	pregnancy-induced hypertension

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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