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Frequency and outcome of thrombocytopenia in neonates who are at risk of developing thrombocytopenia - a prospective observational study

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Abstract

Thrombocytopenia is the commonest hematological abnormality encountered in the neonatal intensive care unit (NICU). This prospective, observational study was conducted among 78 consecutive at-risk neonates admitted in NICU, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from September 2016 to August 2017. Platelet count was measured in all at risk neonates at enrollment and less than 1,50,000/cmm was consiered as the cut off point for determining thrombocytopenia. Platelet count was measured every alternate day till discharge or normalisation of platelet count if the initial platelet count was low. If initial platelet count revealed normal, then the babies were followed up clinically if they develop any further risk condition for developing thrombocytopenia. During the period from enrollment to discharge, if any baby develops thrombocytopenia at any time then baby was defined as thrombocytopenic. Overall 39.7%patients found to be thrombocytopenic among 78 at-risk neonates. Pregnancy induced hypertension (PIH), neonatal sepsis and small for gestational age (SGA), intra uterine growth restriction(IUGR), prematurity, necrotizing enterocolitis (NEC) were significantly associated with thrombocytopenia. Sepsis and NEC were found to be independent risk factor for thrombocytopenia. Regarding outcome, length of hospital stay was significantly more in thrombocytopenic patients than non-thrombocytopenic patients. Death rate was also higher in thrombocytopenic patients in comparison to non-thrombocytopenic patients.

Introduction:

Thrombocytopenia is the commonest hematological abnormality encountered in the neonatal intensive care unit (NICU) after phlebotomy-induced anemia.[1] Perinatal asphyxia, prematurity/low birth weight, and sepsis are major causes of neonatal death. Thrombocytopenia is a common finding in these sick neonates. If not detected early & intervention not taken, life-threatening hemorrhage can occur. A healthy neonate, even preterm, has the same mean platelet count as adults, and a platelet count less than 150,000/cmm is defined as thrombocytopenia.[2] Thrombocytopenia develops in 22–35% of sick newborn babies admitted to neonatal intensive care units (NICUs) and in 50% of sick preterm.[3] Its incidence reaches 70% in newborn infants with birth weight <1000gm.[4] Thrombocytopenia is more common in certain risk groups such as low birth weight, preterm, small for gestational age, hypoxia at birth, umbilical line placement, respiratory assistance, hyperbilirubinemia, phototherapy, respiratory distress syndrome, sepsis especially by candida infection, meconium aspiration, NEC, the mother with ITP and in a preterm infant with hypertensive mother.

Thrombocytopenia is classified as mild (100,000-<150,000/cmm of blood), moderate (50,000-<100,000/cmm) and severe (<50,000/cmm of blood).[5] The risk factors for early-onset thrombocytopenia

are pre-eclampsia, pregnancy-induced hypertension, intrauterine growth restriction, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), maternal diabetes & drug use.[6] The most common risk factor for late-onset thrombocytopenia are sepsis and NEC.[7] Early-onset thrombocytopenia is defined as thrombocytopenia that occurs before 72 hours of age and late-onset thrombocytopenia that occur after 72 hours of age.[8] Though thrombocytopenia is so prevalent it is often ignored in the surmise that it will resolve spontaneously. In most cases, neonatal thrombocytopenia is mild to moderate and can be resolved without intervention. However, life-threatening bleeding or intracranial hemorrhage (ICH) with a high risk of neurodevelopment impairment may occur in severe thrombocytopenia (platelets <50 ×109/L).[9] Early detection and management can prevent bleeding and neurological sequelae in the thrombocytopenic neonate. The objectives of this study were to find out the frequency, hospital outcome & associated factors of thrombocytopenia in at-risk neonates.

Methods

This observational study was carried out in NICU, Department of Neonatology, BSMMU, Dhaka from September 2016 to August 2017. Admitted inborn neonates who were at-risk for developing thrombocytopenia and out born at-risk neonates who were admitted within 24 hrs of birth in NICU, BSMMU were included in the study. A total of 78 neonates were included in the study. Out born at-risk neonates who were admitted after 24 hours of birth, babies with major congenital malformation, and infants of parents who refused to give consent were excluded from the study. The at-risk newborn was defined as a newborn having any of the following criteria during enrollment or during the hospital stay i.e. positive maternal history of pregnancy-induced hypertension (PIH), gestational diabetes mellitus (GDM), maternal infection, positive drug history (Heparin, Hydralazine, Thiazide), & history of autoimmune disease (SLE, ITP). Prematurity, low birth weight, intrauterine growth restriction (IUGR) / small for gestational age (SGA) babies, babies with Rh-incompatibility, neonates with a history of perinatal asphyxia, neonates presenting with sepsis, and neonates who had developed features of NEC.

Platelet count was measured in all at-risk neonates at enrollment and count less than 1,50,000/cmm was considered as the cut-off point for determining thrombocytopenia. Low platelet counts were cross-verified by a peripheral smear study. If the initial platelet count revealed normal, then the babies were followed-up clinically if they develop any further risk conditions. If any risk condition developed i.e. sepsis, NEC then platelet count was repeated. If the initial platelet count was low, then the platelet count was repeated every alternate day till discharge. During the period from enrollment to discharge, if any baby developed thrombocytopenia at any time then the baby was labeled as thrombocytopenic group. Those who never developed thrombocytopenia were labeled as non-thrombocytopenic group. Standard care was given to all enrolled neonates as per departmental protocol. Treatment of thrombocytopenia consisted of transfusion of random donor platelet as per protocol. The pattern of onset of thrombocytopenia was classified as early if it developed <72 hours of birth and late if it presented after 72 hours. The severity of thrombocytopenia was graded as mild, moderate, and severe. The outcome of the enrolled neonates was assessed in terms of length of hospital stay, death, or survival.

Results

Initial platelet count was found low in 8 patients (10.2%). A total of 29 patients subsequently developed risk conditions and platelet count was measured. Among them, 23 revealed thrombocytopenia, and 6 patients had normal platelet count. During the period from enrollment to discharge, total 31 patients were found thrombocytopenic.

Baseline demographic characteristics & maternal characteristics of thrombocytopenic and non-thrombocytopenic neonates were compared. Statistically significant difference was found in mean birth weight and gestational weight ($p = 0.001$ & 0.001 respectively). Regarding gender and mode of delivery, there was no significant difference between the two groups. Regarding maternal characteristics, PIH was found significantly associated with the thrombocytopenic group ($p = 0.02$). While considering GDM and maternal infection, there was no significant difference between the two groups. (Table-I)

Table-I

Comparison of baseline characteristics of thrombocytopenic and non-thrombocytopenic neonates (N=78)

Characteristics	Thrombocytopenic group(n=31)	Non-Thrombocytopenic group (n=47)	P-value
Gestational age (weeks)	32.74 ± 2.1	34.76 ± 2.3	0.001
Birth weight (g)	1587 ± 514	2206± 698	<0.0001
Mode of delivery			
LUCS, n (%)	27 (84.3)	33(71.7)	0.08
NVD, n(%)	4(15.6)	14 (28.2)	
Sex			
Male, n (%)	15(48.4)	24(51.1)	0.817
Female, n (%)	16(51.6)	23(48.9)	
PIH, n (%)			
Yes	16(51.6)	12(25.5)	0.02
No	15(48.3)	35(74.5)	
GDM, n (%)			
Yes	5(16.2)	12(25.5)	0.325
No	26(83.8)	35(74.5)	
Maternal infection, n (%)			
Yes	8(25.8)	8(17)	0.347
No	23(74.2)	39(83)	

Among the total of 78 patients, 31 patients were found thrombocytopenic in this study. The frequency of thrombocytopenia in the at-risk neonate in NICU, BSMMU was found approximately 39.7% (Table-II).

Table-II

Frequency of thrombocytopenia in at risk neonate

At risk baby	78
Thrombocytopenia	31
Frequency	39.7%

According to the age of onset, thrombocytopenic babies were classified as early and late-onset groups. Early & late-onset thrombocytopenia was 25.8% and 74.2% respectively (Table-III).

Table-III

Type of thrombocytopenia in at risk neonate

Total no of thrombocytopenic neonates	No. of patients (n=31)	Percentage (%)
Early onset	8	25.8%
Late onset	23	74.2%

According to severity, thrombocytopenic babies were classified as mild, moderate, and severe. Mild, moderate, and severe thrombocytopenia was observed in 22.6%, 29%, and 48.4% of neonates respectively. Among the 31 neonates with thrombocytopenia, 16 (51.6%) patients had frank bleeding in various forms. GI bleeding was most common (56.2%). Other types of bleeding were skin bleeding (18 .7%) & bleeding through ET tube (6.25%). Combined Skin bleeding & GI bleeding was 18.7%.(Table-IV)

Table-IV

Changes of visual acuity of all 3(three) patient after injection methyl prednisolone

Grades of thrombocytopenia	Total no. (n=31)	Percentage (%)	Bleeding menifestation present	Pattern of bleeding
Mild	7	22.6%	no	No
Moderate	9	29%	3	GI Bleeding
Severe	15	48.4%	13	Skin bleeding(3) GI Bleeding(6) Combined GI and Skin Bleeding(3) Bleeding through ET tube(1)

While comparing the neonatal characteristics between the thrombocytopenic group and the non-thrombocytopenic group, a statistically difference was found in respect to prematurity, LBW, SGA, Sepsis, and NEC. No statistically significant difference was found in asphyxia & Rh-incompatibility. (Table - V)

Table-V

Comparison of Neonatal characteristics among thrombocytopenic and non-thrombocytopenic neonates

Characteristics	Thrombocytopenic group(N=31)	Non-Thrombocytopenic group(N= 47)	P-Value
Prematurity, n (%)			
Yes	31(100%)	34(72.3%)	0.001
No	0(0.0)	13(27.7%)	
LBW, n (%)			
Yes	27(87.1)	32(68.1)	0.047
No	4(12.9)	15(31.9)	
SGA/IUGR, n (%)			
Yes	11(35.5)	7(14.9)	0.035
No	20(64.5)	40(85.1)	
Asphyxia, no (%)			
Yes	7(22.5)	4(8.5)	0.08
no	24(77.4)	43(91.5)	
Sepsis, n (%)			
Yes	25(80.6)	18(38.3)	<0.001
No	6(19.4)	29(61.7)	
NEC, n (%)			
Yes	6(19.4)	0(0.0)	0.002
No	25(80.6)	47(100.0)	
Rh-incompatibility, (%)			
Yes	1(3.2)	4(8.5)	0.351
No	30(96.7)	43(91.5)	

Statistical test: Chi square test, P-value is significant <0.05

Multivariate regression analysis was done for predicting the association with thrombocytopenia. Only sepsis was found to be an independent risk factor for developing thrombocytopenia. (Table - VI)

Table-VI

Results of multivariate regression analysis for predicting occurrence of thrombocytopenia

Characteristics	Odds Ratio	95%CI	P value
PIH	2.1	0.642-6.919	0.219
LBW	1.4	0.272-8.174	0.645
SGA	0.451	0.111-1.83	0.266
Sepsis	4.3	1.3-14.05	0.02

Regarding outcome, the number of patients who stayed more than 14 days in hospital was significantly higher in the thrombo- cytopenia group in comparison to the non-thrombocytopenia group. The mortality rate was also higher in the thrombocytopenia group than non- thrombocytopenia (35.4% vs 8.6%, P value-0.007). (Table - VII)

Table-VII

Outcome of enrolled infants

Variable		Thrombocytopenic group (N=31)	Non-Thrombocytopenic group (N= 47)	P-Value
Prematurity, n (%)				
Length of hospital stay(days)	<14 days	11(35.5%)	29(61.7)	<0.037
	>14days	20(64.5)	18(38.3)	
Survival (no, %)		20(64.6)	43(91.4%)	0.007
Death (no, %)		11(35.4%)	4(8.6%)	

Discussion

In this observational study, the frequency of thrombocytopenia in at risk neonates was found to be 39.7%. In previous studies conducted in Sri Lanka and India, prevalence rate documented were 55% and 63% respectively[10,11] which is much higher than this study. Variable prevalence rates were documented in different studies most probably because of wide variations in case inclusion, sample size and geographic variation.

Regarding demographic characteristics, mean birth weight was significantly lower in thrombocytopenia group in comparison to non-thrombocytopenia group. Study conducted in Tehran by Khalessi N and colleagues also showed similar result.[12] Mean gestational age in this study was also lower in thrombocytopenia group in comparison to non-thrombocytopenia group. The result is consistent with another study which show the mean gestational age at birth among thrombocytopenic neonates was 32.2±2.5 weeks which was less than the average gestational age at birth among all neonates (P=0.0001).[12] No statistically significant difference in gender was observed between neonates with and without thrombocytopenia in this study. Regarding mode of delivery, no significant difference was observed also between two groups in this study.

Regarding maternal characteristics, pregnancy induced hypertension was found significantly associated with thrombocytopenia. (51.6% in thrombocytopenic group and 25.5% in non-thrombocytopenic group). The other two factors GDM and maternal infection were not found statistically significant.

Regarding neonatal characteristics, prematurity was significantly associated with thrombocytopenia. Among 84% of preterm baby, 47.6% had

thrombocytopenia. No full term babies had thrombocytopenia. This may be due to the small sample size in this study. Prematurity is a risk factor for thrombocytopenia due to decreased platelet production and when this was associated with sepsis, the increased consumption of platelets further contributes to severe thrombocytopenia.

LBW was significantly associated with thrombocytopenia in this study (p=.047). Charoo BA and colleagues also stated that neonatal thrombocytopenia was more common among low birth weight babies.[13] However, Sharma et al showed low birth weight was not significantly associated with thrombocytopenia (P=0.47).[10] Gupta and colleagues stated that LBW babies showed statistically significant thrombocytopenia due to their limited ability to compensate for accelerated destruction of platelets. Placental transport of IgG from maternal to fetal circulation increases with maturity and this transport is hampered in low birth weight babies which make them more prone for sepsis.[14]

In this study, sepsis was significantly associated with thrombocytopenia (P=<0.001).[14] Gupta et al observed that 81.5% of septic neonates developed low platelet counts. In studies conducted by Patil et al & Zaccheaus et al, sepsis was associated with severe thrombocytopenia with results similar to the current study.[15,16] Among the septic neonates, 25% had positive blood culture. Organisms isolated from the blood of septic babies in order of frequency were: Klebsiella, Acinetobacter & Pseudomonas. Klebsiella was the most commonly isolated organism observed in study by Arif SH et al.[17] Septicemia leads to thrombocytopenia due to both decreased production and increased consumption of platelets and hence results usually in severe thrombocytopenia. Sepsis also causes DIC, immune-mediated destruction and decreased production of platelets from infected marrow. In this study, SGA was significantly associated with thrombocytopenia (P=0.035).

Maruyama H et al found growth restriction to be a significantly independent risk factor for thrombocytopenia which is consistent with our study.[18] In our study, total 5 patient had NEC and all of them had thrombocytopenia. In contrast to the current study, Sharma et al showed NEC was not significantly associated with thrombocytopenia (P=0.058).[10] In this study, perinatal asphyxia was not significantly associated with thrombocytopenia (P=0.08). However, Relationship between the severity of thrombocytopenia and the severity and staging of hypoxic ischemic encephalopathy was demonstrated in study conducted by Nursen et al.[19] Thrombocytopenia in HIE may be due to increased platelet destruction as mean platelet value was raised. In multivariate regression analysis, only sepsis and NEC were found to be independent risk factor for developing thrombocytopenia. Bonifacio L and colleagues observed that mucocutaneous bleeding complicated 18.4% of cases with severe and late-onset thrombocytopenia.[20] In this study 16 (51.6%) of at risk neonates with thrombocytopenia developed bleeding. Von Lindern et al showed that out of all included neonates with thrombocytopenia, 29% received a platelet transfusion.[21] In this study 18 (58%) high risk neonates with thrombocytopenia received platelet transfusions.

Regarding outcome, among 31 thrombocytopenic neonates, 11 died. Mortality rate was 35.4% compared to 8.6% in non-thrombocytopenic neonates. Previous study done by Bonifacio L et al also demonstrated that mortality rate among the non-thrombocytopenic neonates was 1.4% as compared to 16.7%, 32.4%, and 45.8% in preterm neonates with mild, moderate and severe thrombocytopenia respectively.[20] In another study done by Sola MC et al, incidence of mortality was found to be 34% in preterm neonates.[22]

Conclusion

Frequency of thrombocytopenia in at risk neonate in NICU, BSMMU was approximately 39.7%. Prematurity, LBW, PIH, sepsis and SGA/IUGR, NEC were significantly associated with thrombocytopenia. Duration of hospital stay and mortality rate were higher in thrombocytopenic neonates than non- thrombocytopenic neonates and survival rate was higher in non-thrombocytopenic neonates than thrombocytopenic neonates among at risk neonates.

As the prevalence of neonatal thrombocytopenia is high, it is important to look for platelet count, severity, degree and pattern of onset of thrombocytopenia in each and every case of at risk neonates admitted to NICU, which will help the clinician in diagnosis, planning investigations and aid in appropriate management & improve outcome. A large sample, multicenter study should be conducted to support the current study

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