Acta Scientific PAEDIATRICS (ISSN: 2581-883X)

Volume 6 Issue 3 March 2023

Research Article

Frequency and Outcome of Thrombocytopenia in Neonates who are at Risk of Developing Thrombocytopenia - A Prospective-Observational Study

Arbari Saha*

Department of Neonatology, BSMMU, Dhaka, India

***Corresponding Author:** Arbari Saha, Department of Neonatology, BSMMU, Dhaka, India.

Received: June 13, 2022

Published: February 28, 2023

Abstract

Thrombocytopenia is the commonest hematological abnormality encountered in the neonatal intensive care unit (NICU). Thrombocytopenia is more common in certain risk group. This prospective– observational study was conducted among 78 consecutive at risk neonates admitted in NICU, Bangabandhu Sheikh Mujib Medical University (BSMMU). Platelet count was done in all at risk neonates at enrollment and less than 1,50,000/cu mm was taken as the cut off point for determining thrombocytopenia. If initial platelet count was low then platelet count was done every alternate day till discharge or normal. If initial platelet count revealed normal, then babies were followed up clinically whether 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. Among 78 pts, initial platelet count was low in 8 patients (10.2%) and in 29 (37.1%) pts subsequently developed risk factor and platelet count was done in those patients. Among them, 23 patients revealed thrombocytopenia. Overall 31 (39.7%) patients found thrombocytopenic among 78 at risk neonates. Pregnancy induced hypertension (PIH), neonatal sepsis, small for gestational age (SGA) and intra uterine growth restriction (IUGR), prematurity, Necrotizing Enterocolitis (NEC) were significantly associated with thrombocytopenia (p = <0.05). 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 (p = <0.037). Death rate was also higher in thrombocytopenic patients in comparison to non- thrombocytopenic patients (p value- 0. 007).

Keywords: Frequency; Thrombocytopenia; Neonates; Observational Study

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, sepsis are major causes of neonatal death. Thrombocytopenia is common findings in these sick neonates. If not detected early and intervention not taken, life threatening hemorrhage can occur. A healthy neonate, even a preterm, has the same mean platelet count as adults and a platelet count less than 150,000/cu mm 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 group 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, mother with ITP and in 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 or drug use [6]. The most common risk factor for late onset thrombocytopenia are sepsis and NEC [7]. Early-onset thrombocytopenia is defind as thrombocytopenia that occur 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 its therapeutic management can prevent bleeding manifestation and neurological sequelae in the thrombocytopenic neonate.

The objectives of this study are to find out the frequency, hospital outcome and associated factor of thrombocytopenia in at risk neonates.

Materials and Method

This is a prospective -observational study carried out in NICU, Department of Neonatology, BSMMU, Shahbagh, Dhaka from September 2016 to August 2017. Study protocol was approved by the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University. Admitted inborn neonates who were at risk for developing thrombocytopenia and outborn at risk neonates who admitted within 24hrs of birth in NICU, BSMMU were included in the study. Outborn at risk neonates those admitted after 24hrs of birth, baby with major congenital malformation, infants of parents who refused to give consent were excluded from the study. At risk newborn was defined as newborn having any of the following criteria during enrollment or during hospital stay**:** Positive maternal history 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, baby with Rh-incompatibility, neonates with a history of perinatal asphyxia, neonates presenting with sepsis and neonates who develop features of NEC.

Platelet count was done in all at risk neonates at enrollment and platelets count less than 1,50,000/cu mm was taken as the cut off point for determining thrombocytopenia. Two millilitres of venous EDTA sample were sent to Clinical pathology department of BSMMU. Platelet count was done by automated analyzer (Sysmex, xt-4000I). Low platelet counts were cross verified by peripheral smear study. If initial platelet count revealed normal, then babies were followed up closely clinically whether they develop any further risk condition for developing thrombocytopenia. If initial platelet count was low then platelet count was done every alternate day till normal. During the period from enrollment to discharge, if any baby develops thrombocytopenia at any time then baby was labelled as thrombocytopenic and those who never developed thrombocytopenia were labelled as non- thrombocytopenic groups. Enrolled neonates were observed clinically for any features of thrombocytopenia. Standard care was given to all enrolled neonates as per departmental protocol. Treatment of thrombocytopenia consisted of transfusion of random donor platelet as per unit protocol.

After collection, data was entered into a personal computer and was edited, analyzed, and plotted in tables. Frequency of thrombocytopenia was calculated by percentage. Comparison was performed by chi-square test for categorical variables, independent t-test for quantitative variables. P value less than 0.05 has considered statistically significant. Association of risk factor with thrombocytopenia was identified by chi-square test. Significant risk factors were then assessed with multivariate logistic regression test. Data was analyzed using the statistical package for social sciences (SPSS) version 20.0.

Pattern of onset of thrombocytopenia were classified as early if it developed <72 hours of birth and late if it presented after 72 hours. Severity of thrombocytopenia was graded as mild, moderate and severe. Outcome of the enrolled neonates were assessed in terms of length of hospital stay, death or survival.

Results

Among the 83 enrolled neonates, 5 patients were dropped out due to denial of parents to give consent, left against medical advice and denial to give blood for subsequent sampling. Initial platelet count was low in 8 patients (10.2%). 29 pts subsequently developed risk factor and platelet count was done. Among them 23 revealed thrombocytopenia and 9 pts had normal platelet count.

During the study period, total no of eligible pt 83

- 2 Parents denied giving consent.
- 1 left against medical advice.
- 2 withdrawn consent during subsequent sampling.
- Total 78 infant were analyzed.

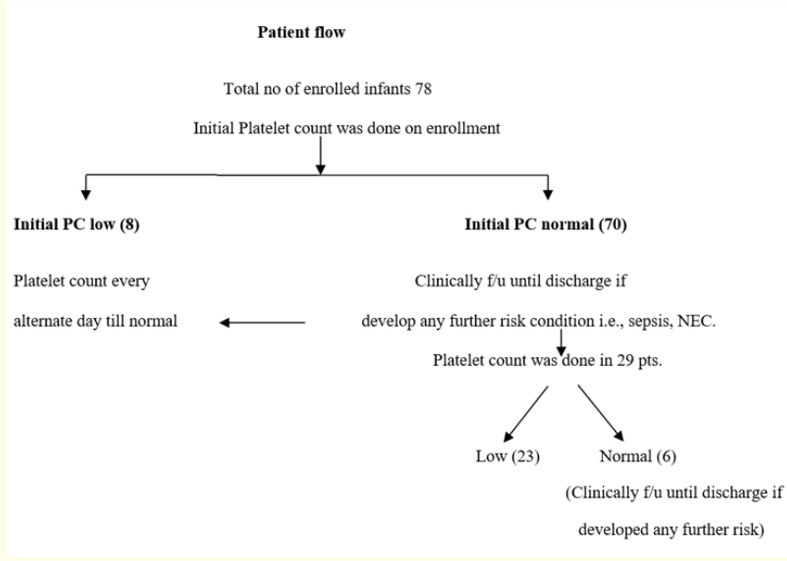

Figure 1: Diagram of flow of participants in the study.

Baseline demographic characteristics and maternal characteristics, of thrombocytopenic and non-thrombocytopenic neonates were compared. Statistically significant difference was found in mean birth weight and gestational weight (p value were 0.001 and 0.001 respectively). Regarding gender and mode of delivery there were no significant difference between two groups. Regarding maternal characteristics, PIH was found significantly associated with thrombocytopenic group (p value = 0.02) (Table 1). There was no significant difference in GDM and maternal infection among two groups.

Frequency of thrombocytopenia in at risk neonate in NICU, BSMMU was found approximately 39.7% (Table 2). Early and late onset thrombocytopenia was 25.8% and 74.2% respectively (Table 3). Regarding severity, mild, moderate and severe thrombocytopenia was observed in 22.6%, 29% and 48.4% neonates respectively (Table 4). Among the 31 neonates with thrombocytopenia 16 (51.6%) pts 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 and GI bleeding were 18.7%. (Table 5).

On comparison of neonatal characteristics between thrombocytopenic group and non-thrombocytopenic group statistically significant difference was found in prematurity, LBW, SGA, Sepsis and NEC. No statistically significant difference was found in case of Asphyxia and Rh incompatibility (Table 5). Multivariate regression analysis was done for predicting association with thrombocytopenia. Only sepsis was found to be independent risk factor for developing thrombocytopenia (Table 6). Regarding outcome, number of

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 (%) NVD, n (%)	 27 (84.3) 4 (15.6)	 33 (71.7) 14 (28.2)	0.08
Sex Male, n (%) Female, n (%)	 15 (48.4) 16 (51.6)	 24 (51.1) 23 (48.9)	0.817
PIH, n (%) Yes No	 16 (51.6) 15 (48.3)	 12 (25.5) 35 (74.5)	0.02
GDM,n (%) Yes No	 5 (16.2) 26 (83.8)	 12 (25.5) 35 (74.5)	0.325
Maternal infection, n (%) Yes No	 8 (25.8) 23 (74.2)	 8 (17) 39 (83)	0.347

Table 1: Comparison of baseline characteristics of thrombocytopenic and non-thrombocytopenic neonates (N = 78). P-value is significant < 0.05.

At risk baby	78
Thrombocytopenia	31
Frequency	39.7%

Table 2: Frequency 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%

Table 3: Type of thrombocytopenia in at risk neonate.

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)

Table 4: Various grades of thrombocytopenia &pattern of bleeding manifestation in thrombocytopenic babies.

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)	
No	30 (96.7)	43 (91.5)	0.351

Table 5: Comparison of Neonatal characteristics among thrombocytopenic and non-thrombocytopenic neonates.

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

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

Table 6: Results of multivariate regression analysis for predicting occurrence of thrombocytopenia.

Variable		Thrombocytopenic group (n = 31)	Non-thrombocytopenic group (n = 47)	P value
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%)	

Table 7: Outcome of enrolled infants.

patient who stayed >14 days in hospital was significantly higher in thrombocytopenia group in comparison to non-thrombocytopenia group. Mortality rate was also higher in thrombocytopenia group than non-thrombocytopenia (35.4% vs 8.6%, P value-0.007) (Table 7).

Discussion

In this prospective observational study, the frequency of thrombocytopenia in at risk neonates is found 39.7%. In previous studies conducted in Srilanka 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 lower in thrombocytopenia group in comparison to non- thrombocytopenia group. Difference is statistically significant. Study conducted in Tehran by Khalessi N and colleagues, also shows 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 to other study which shows 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 also no significant difference was observed between two groups in this study.

Regarding maternal characteristics Pregnancy Induced Hypertension was found significantly associated with thrombocytopenia. (51.6% case in thrombocytopenic group and 25.5% cases in non-thrombocytopenic group. P-value was. 02). 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% has thrombocytopenia. No full-term babies had thrombocytopenia. This may be because small no of sample. Other studies showed variable results. 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 contributed to severe thrombocytopenia. LBW was significantly associated with thrombocytopenia in this study (p = .047). Similarly Charoo BA and colleagues 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). 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 which was similar to the results in our 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*. 2008) 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. Contradictory to this study, Sharma., *et al*. (2015) 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 [20] and in other study done by Sola MC., *et al*, incidence of mortality 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.

Recommendation

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 and improve outcome. A large sample, multicenter study should be conducted to support the current study.

Acknowledgement

Authors like to pay their sincere thanks and gratitude to Bangabandhu Sheikh Mujib Medical University for funding this research.

Bibliography

1. Roberts I and Murray NA. "Neonatal thrombocytopenia: causes and management". *Archives of Disease in Childhood-Fetal and Neonatal Edition* 88.5 (2003): F359-364.

2. Veneri D., *et al*. "Thrombocytopenias: a clinical point of view". *Blood Transfusion* 7.2 (2009): 75.

3. Roberts IA and Murray NA. "Neonatal thrombocytopenia: new insights into pathogenesis and implications for clinical management". *Current Opinion in Pediatrics* 13.1 (2001): 16-21.

4. Gomella TL., *et al*. "Neonatology management, procedure, on-call problems, disease and drugs". Seventhedn. McGraw Hill education, Lange (2013).

5. Gupta A., *et al*. "Incidence of thrombocytopenia in the neonatal intensive care unit". *Medical Journal Armed Forces India* 67.3 (2011): 234-236.

6. Eslami Z., *et al*. "Thrombocytopenia and associated factors in neonates admitted to NICU during years 2010-2011". *Iranian Journal of Pediatric Hematology and Oncology* 3.1 (2013): 205.

7. Murray NA., *et al*. "Platelet transfusion in the management of severe in intensive care unit patients". *Transfusion Medicine* 12.1 (2002): 35-41.

8. Rennie MJ. "Rennie and Roberton's Textbook of Neonatology". 5th Edition. Churchill Livingstone, Elsevier (2012): 777.

9. Holzhauer S and Zieger B. "Diagnosis and management of neonatal thrombocytopenia". *Seminars in Fetal and Neonatal Medicine* 16.6 (2011): 305-310.

10. Sharma A and Thapar K. "A prospective observational study of thrombocytopenia in high-risk neonates in a tertiary care teaching hospital". *Sri Lanka Journal of Child Health* 44.4 (2015).

11. Sonam S., *et al*. "Study of thrombocytopenia in neonatal intensive care unit". *Indian Journal of Pathology and Oncology* 3.1 (2013): 55-59.

12. Sanii S., *et al*. "The prevalence and risk factors for neonatal thrombocytopenia among newborns admitted to intensive care unit of Aliasghar children's hospital". *Iranian Journal Blood Cancer* 5.2 (2013): 41-45.

13. Charoo BA., *et al*. "Nosocomial sepsis-induced late onset thrombocytopenia in a neonatal tertiary care unit: a prospective study". *Hematology/Oncology and Stem Cell Therapy* 2.2 (2009): 349-353.

14. Gupta AK., *et al*. "Neonatal thrombocytopenia and platelet transfusion". *Asian Journal of Transfusion Science* 6.2 (2012): 161-164.

15. Patil S., *et al*. "Outcome of neonates with thrombocytopenia". *Journal of Evolution of Medical and Dental Sciences* 3.17 (2014): 4533-4539.

16. Jeremiah ZA and Oburu JE. "Pattern and prevalence of neonatal thrombocytopenia in Port Harcourt, Nigeria". *Pathology and Laboratory Medicine International* 2 (2010): 27-31.

17. Arif SH., *et al*. "Thrombocytopenia and bacterial sepsis in neonates". *Indian Journal of Hematology and Blood Transfusion* 28.3 (2012): 147-150.

18. Maruyama H., *et al*. "Thrombocytopenia in preterm infants with intrauterine growth restriction". *Actamedica Okayama* 62.5 (2008): 313-317.

19. Nursen B., *et al*. "Perinatal asphyxia and thrombocytopenia". *Ondokuzmayıs Tıp Dergisi* 16.2 (1999): 100-105.

20. Bonifacio L., *et al*. "Thrombocytopenia related neonatal outcome in preterms". *The Indian Journal of Pediatrics* 74.3 (2007): 269-274.

21. Von Lindern JS., *et al*. "Thrombocytopenia in neonates and the risk of intraventricular hemorrhage: a retrospective cohort study". *BMC Pediatrics* 11.1 (2011): 1-7.

22. Sola MC., *et al*. "Evaluation and treatment of thrombocytopenia in the neonatal intensive care unit". *Clinics in Perinatology* 27.3 (2000): 655-679.