Original Article

Risk Factors and Outcome of Neonatal Thrombocytopenia

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Abstract

Introduction: About 30% of neonates develop thrombocytopenia during hospital admission. Inevitable and irreversible complications can be prevented by determining the risk factors of neonatal thrombocytopenia. The present study was undertaken to determine the risk factors and outcome of neonatal thrombocytopenia in neonates admitted to Neonatal Intensive Care Unit Benazir Bhutto Hospital Rawalpindi.

Materials and Methods: A prospective study was conducted to evaluate the risk factors for neonatal thrombocytopenia (NT) in 160 neonates. Neonatal and maternal risk factors were recorded and neonates were categorized into three groups based on the severity of thrombocytopenia.

Results: A higher percentage of the neonates 89 (55.6%) were male. The majority (61.9%) had moderate neonatal thrombocytopenia while 21.9% had severe neonatal thrombocytopenia. A highly significant difference was observed for the distribution of gestational age, platelet count, birth weight, and age at admission (for all p-value ≥0.0001) among different groups. Multivariate logistic regression revealed a significant independent association of prematurity, birth asphyxia, and low birth weight with neonatal thrombocytopenia.

Conclusion: Prematurity, low birth weight, and birth asphyxia were the significant causes of Neonatal thrombocytopenia. The mortality rate increased significantly with the severity of thrombocytopenia.

Key Words: Neonatal thrombocytopenia, prematurity, birth asphyxia, gestational hypertension.

Introduction

Platelets are non-nucleated tiny cellular fragments produced in the bone marrow as a result of cytoplasmic fragmentation of megakaryocytes.[1] Platelet production in the fetus starts around 5th week of gestational age. By the end of the second trimester, the fetus has platelet count in the normal range of 150 to 450 × 10^9/L.[2] Platelet count below 150 × 10^9/L in neonates is defined as Neonatal Thrombocytopenia(NT).[3] Thrombocytopenia might develop during fetal life and neonates are presented with decreased platelet count at birth. A higher prevalence rate (18–35%) of NT is observed in premature neonates as compared to 2% of full-term neonates.[4] Depending on the population being studied, there could be variation in the incidence of thrombocytopenia. Several fatal conditions like low birth weight, prematurity, sepsis, birth asphyxia, hypotension, exchange transfusion, and some maternal conditions like hypertension can cause thrombocytopenia in newborns.

The chances of developing thrombocytopenia rise with a degree of prematurity.[5] Similarly, a negative association between birth weight and thrombocytopenia is reported. Low-birth weight neonates had a 2.52-fold higher risk for developing thrombocytopenia.[6,7] Gestational hypertension is another important risk factor contributing to NT. The rate and severity of thrombocytopenia in neonates of mothers suffering from gestational hypertension vary. Among the neonates born to mothers with gestational hypertension, the prevalence of NT differs extensively from 9.2 to 36%.[8,9]

This study aims at finding thrombocytopenia and its associated risk factors in the NICU and outcome of NT in terms of mortality, improvement, and intraventricular hemorrhage.

Materials and Methods

A prospective study was conducted at the Department of NICU, Benazir Bhutto Hospital, and Rawalpindi from July 2018 to January 2019. The sample size of 160 was calculated according to WHO criteria.

Inclusion Criteria: Neonates with thrombocytopenia admitted to NICU. Both genders were included.

Exclusion Criteria: Neonates with congenital anomalies, twin babies, and those whose parents did not give the consent were excluded from the study

After informed written consent from parents, the neonates meeting inclusion criteria, born between July 2018 and January 2019 at the Department of Pediatrics Benazir Bhutto Hospital were enrolled in the study. The study was approved by the ethics committee of Rawalpindi Medical University. The severity of thrombocytopenia was categorized as follows: mild, a platelet count of 100,000 to 150,000/µL; moderate, a platelet count of 50,000 to < 100,000/µL; severe, a platelet count of 30,000 to <50,000/µL[10]. Based on the time of onset NT has been grouped into two classes early-onset (EOT), which is within 72 h of life, and late-onset (LOT), after 72 h of life.[11,12] Asphyxia was defined according to the Statement of the American College of Obstetricians and Gynecologists.[13]

Two ml of blood was collected aseptically in EDTA containing tubes. Giving due credence to neonates' condition and difficulty in sample collection appropriate volume adjustments were incorporated as automated Hematology analyzers can measure for less volume. The tubes were kept on a roller mixer for 10 minutes to ensure proper mixing. As a quality control measure, a thin smear of each sample was made and stained with field stain. Light microscopy of the stained film was done to rule out platelet clumps and to ensure even dispersion of platelets. This practice eliminated the possibility of false low platelet count. Enrolled neonates were observed prospectively and platelet count was done at presentation and subsequently as and when required with sysmex. All reports were verified by the Consultant Hematologist and risk factors associated with thrombocytopenia were assessed. Study participants were followed for a one-month duration to see the outcome of improvement, intraventricular hemorrhage, and mortality.

Statistical Analysis: Data was analyzed using SPSS version 25.0. Mean ± SD were calculated for gestational age, birth weight, and platelet count. Kruskal Wallis test, a nonparametric alternative to one-way ANOVA was used to compare the continuous variable. Categorical variables were compared by the χ^2 test. The frequency of associated risk factors and outcomes of neonatal thrombocytopenia were calculated. Effect modifiers like gender and severity of thrombocytopenia were controlled by stratification. The P-value of ≤ 0.05 was significant.

Results

The majority of neonates had moderate NT with early-onset (83.1%). Prematurity, low birth weight, neonatal jaundice, gestational hypertension, and birth asphyxia were the commonest risk factors (Table 1). A highly significant difference was observed for the distribution of gestational age, platelet count, birth weight, and age at admission (for all p-value ≥ 0.0001) among different NT groups (Table 2). No significant difference was observed for the prevalence of birth asphyxia (χ^2=1.65; p-value=0.438) among different NT groups.

In multivariate regression analysis, prematurity, birth Asphyxia, and low birth weight showed a significant independent association with NT. (Table 4)

Mortality rates of thrombocytopenic groups gradually increased with the severity of the disease.

The highest percentage of 20 (57.1%) of neonates with severe thrombocytopenia encounter death compared to moderate 32 (32.3%) and mild 4(15.4%) groups. The mortality rate among different thrombocytopenic groups was significantly different χ^2-12.45; p-value 0.002. Overall, 56 (35 %) neonates died, 53 (94.6%) had early-onset, and 3 (5.4 %) had late-onset.

Table 1: Baseline demographic and clinical information of the study participant

Risk Factors	Frequency	Percentage(%)
Gender		
Male	89	55.6
Female	71	44.4
Gestational Age		
Premature	23	14.4
Mature	137	85.6
Birth weight		
Low	29	18.1
Normal	131	81.9
Birth Asphyxia		
Yes	46	28.8
No	114	71.2
Gestational Hypertension		
yes	43	14.4
No	117	85.6
Neonatal Jaundice		
Yes	23	29.6
No	137	73.1
Time of onset		
Early-onset	133	83.1
Late-onset	27	16.9
Thrombocytopenia Groups		
Mild	26	16.3
Moderate	99	61.9
Severe	35	21.9
Survival		
Improvement	104	65
Intraventricular hemorrhage	0	0
Death	56	35

Table 2: Means, gestational age, birth weight, platelet counts, and age at admission in Thrombocytopenia groups compared with Kruskal Wallis test

Group	No.	Gestational Age (week) Mean±SD	Birth Weight(kg) Mean±SD	Platelet count Mean±SD	Age at Admission (hrs) Mean±SD	p-value
Mild	26	39.4 ± 1.17	3.05 ± 0.14	105.2 ± 3.98	75.6 ± 28.5	<0.001
Moderate	99	38.6 ± 1.20	2.77 ± 0.30	81.3 ± 12.34	53.3 ± 31.7	<0.001
Severe	35	37.2 ± 1.57	2.52 ± 0.24	42.5 ± 4.26	27.4 ± 10.31	<0.001

Table 3: Comparison of Categorical Risk Factors among different types of thrombocytopenia using Chi-square Test

Risk Factors		Groups				χ^2-value	p-value
		Group 1	Group 2	Group 3	Total		
Low Birthweight	**Yes**	**0**	**17 (58.6%)**	**12 (41.3%)**	**29 (18.1%)**	**15.64**	**<0.001**
	No	**26 (19.8%)**	**82 (62.5%)**	**23 (17.5%)**	**131 (81.9%)**		
Prematurity	**Yes**	**1 (4.3%)**	**9 (39.1%)**	**13 (56.2%)**	**23 (14.3%)**	**16.77**	**<0.001**
	No	**25 (18.2%)**	**90 (65.6%)**	**22 (16.05)**	**137 (85.6%)**		
Birth asphyxia	**Yes**	**6 (13.0%)**	**32 (69.5%)**	**8 (17.3%)**	**46 (28.7%)**	**1.65**	**0.438 NS**
	No	**20 (17.5%)**	**67 (58.7%)**	**27 (23.6%)**	**114 (71.2%)**		
Gestational Hypertension	**Yes**	**8 (18.6%)**	**33 (76.4%)**	**2 (4.6%)**	**43(26.9%)**	**12.78**	**0.002**
	No	**18 (15.3%)**	**66 (56.4%)**	**33 (28.2%)**	**117 (73.1%)**		
Neonatal jaundice	**Yes**	**11 (47.8%)**	**11 (47.8%)**	**1 (4.3%)**	**23 (14.3%)**	**18.17**	**<0.001**
	No	**15 (10.9%)**	**88 (64.2%)**	**34 (24.8%)**	**137 (85.6%)**		

Table 4: Multivariate Binary Forward Logistic Regression Analysis

Risk factors	Odds ratio	95%CI	p-value
Prematurity	13.556	3.722, 49,36	<0.001
Birth Asphyxia	39.229	11.867, 129.67	<0.001
Low birth weight	6.909	1.935, 24.67	0.003

Table 5: Comparison of mortality rates between Male and Female

Groups	Outcome			
	Survived	Died	χ^2-value	p-value
Female	48 (67.6)	23 (32.4%)	0.382	0.618
Male	56 (62.9)	33 (37.1 %)		
Total	104 (65%)	56 (35%)		

Discussion

Thrombocytopenia is the common hematological abnormality seen in NICU, often culminating in severe complications if not detected and managed properly. We observed that 61.9 % of the neonates had moderate NT and 21.9% had severe NT. Our results are similar to Tirupathi et al[14] who found 81% of the neonates suffering from moderate to severe thrombocytopenia but different from Rech et al, Von Lindern et al, khalessi et al and Gupta et al where the majority of the neonates had mild to moderate thrombocytopenia.[4,15,16,17]

We had 83.1%of neonates with early onset of thrombocytopenia while only 16.5% were having a late onset of NT. Our results are similar to Bagale and Bhandari who reported 91.8% of neonates with early-onset thrombocytopenia, and 8.2% with late-onset thrombocytopenia.[18] Similarly, Jeremiah et al reported 84.4% of the neonates with early-onset thrombocytopenia and 15.6% with late-onset thrombocytopenia.[19]

Among the neonatal risk factors, our birth asphyxia rates of 28.8% were similar to Rech et al Bagale et al and Eslami et al[4,18,20] who found neonatal asphyxia rate of 25%, 31.9%, and 35.1% respectively but different from Ulusoy et al and von Lindern et al who found asphyxia rate of 3-11%.[11,15]

Prematurity is a well-known risk factor for developing NT.[15,21] In the present study, 13 (56.2%) of premature neonates develop severe thrombocytopenia. Our findings are in line with those of Tirupathi et al Nandyal et al and Hanoudi.[14,21,22] We had 29 (18.1%) low birth weight neonates in our study. Prematurity and low birth weight are highly correlated. We like many other groups found a significant association of prematurity and low birth weight with NT.[6,14,16,20,23] Premature low birth weight neonates have limited capacity to undo the damage caused by enhanced destruction of platelets. Ig Gtransfer from Placental to fetal circulation rises with maturity. This process is hindered in premature, low birth weight neonates which make them vulnerable to NT.[17]

Regarding the maternal risk factors contributing to NT, we observed that 14.4% of neonates had gestational hypertension. Our findings are in line with other groups[14,16,23] but contrary to 46.4% reported by Eslami et al.[20]

We like others found no difference in the incidence of thrombocytopenia in both genders.[20,25,26,27]

We observed a mortality rate of 35% contrary to the 7–10% rate reported by other groups.[15,27] It can be ascribed to improper prenatal evaluation and enrollment in Gynea and Obs Department that further leads to problems with fetal evaluation and childbirth. Association of high mortality with severe thrombocytopenia can be taken as a prognostic marker to assess neonatal wellbeing.

Impaired megakaryopoiesis, inadequate platelet production, and increased platelet destruction are the commonly incriminated pathophysiologic mechanism in NT. The underlying cause of NT can be delineated, to a greater extent, from the timing of the onset of thrombocytopenia. NT within 72 hrs of childbirth is usually due to fetal hypoxia as in infants born to mothers with gestational hypertension. NT due to sepsis and necrotizing enterocolitis presents after a few days of life and is usually severe. An explained etiology of NT usually predicts an immune etiology. Bleeding risk is minimal in fetal hypoxia as compared to sepsis. The need for platelet transfusion varies in accordance with etiology and bleeding risk.[28]

Conclusion

1- Neonatal thrombocytopenia is a reversible and treatable condition. Identification of associated risk factors and management to prevent severe bleeding and morbidity is important.
2- Premature, low birth weight neonates having birth asphyxia were more prone to develop thrombocytopenia.
3- Mortality is significantly associated with severe thrombocytopenia. Hence the degree of thrombocytopenia can be used as a prognostic marker to assess neonatal wellbeing.

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