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Research Article

To Study the Clinical Profile, Causes and Outcome of Thrompocytopenia in Neonates Admitted in Tertiary Care Hospital

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ABSTRACT

Background: Thrombocytopenia is one of the most common hematological abnormalities in newborns. It occurs mainly in preterm or sick neonates and is caused by decreased platelet production or increased platelet consumption. **Aim:** To study the clinical profile, causes and outcome of thrombocytopenia in neonates admitted in Tertiary Care Hospital. **Methods:** A profile of 150 consecutive neonates admitted to the NICU's in Postgraduate department of Pediatrics, G.B pant General Hospital over a period of 2 years (October 2018 to November 2020) irrespective of their underlying morbidity were taken up for the study. All the neonates, except who were lost for follow up and those who expired, were followed up after their discharge once in a period of 6 months. **Results:** The most common maternal risk factor was anaemia which was present in 72 (48%) babies and association of anaemia with severe neonatal thrombocytopenia was statistically significant (P value <0.05). Early onset neonatal thrombocytopenia was more common, and it was associated with mild to moderate neonatal thrombocytopenia. Sepsis was the commonest cause of neonatal thrombocytopenia and was found in 79 (52.7 %) babies. PT INR, appt was done in 54 and it was abnormal in 26 (48.14 %) babies. This was statically significant. The mortality was significantly high in severe thrombocytopenia group (46.7%) as compared to other 2 groups and it was not statistically significant. **Conclusion:** Our study concludes that, severe thrombocytopenia can be used as a prognostic indicator in sick neonates. But to generalize this statement, and apply to all neonatal admissions, more studies are required in this regard with similar results.

Keywords*: Thrombocytopenia, Neonates, anaemia, NICU's, Prevalence, Mortality.*

INTRODUCTION

Thrombocytopenia, defined as a platelet count of less than 150 x 10^9 /l, is one of the most common hematological abnormalities in newborns. It occurs mainly in preterm or sick neonates and is caused by decreased platelet production or increased platelet consumption. In most cases, the thrombocytopenia is mild and does not warrant intervention. When severe thrombocytopenia (platelet count <50 x 10^9 /l) occurs, the

majority of neonates will receive prophylactic platelet transfusions, with the aim to prevent bleeding. The etiology of thrombocytopenia in neonates varies according to the underlying disease, but is either based on increased platelet consumption, decreased platelet production or a combination of these [1-4] .

In preterm neonates, early-onset thrombocytopenia is often related to chronic fetal hypoxia as observed in IUGR, pregnancy-induced hypertension, preeclampsia, Hemolysis-elevated Liver enzymes and Low Platelets syndrome and maternal diabetes [4-8] . It is thought that chronic fetal hypoxia induces increased erythropoiesis, which in turn suppresses platelet production in the bone marrow. In these cases, thrombocytopenia is usually mild to moderate and recovers spontaneously within 10 days [1,3,4,5,8]. Thrombocytopenia in neonates with IUGR is often associated with other hematological abnormalities such as neutropenia or erythroblastosis [6,8].

The most frequent cause of late-onset thrombocytopenia is acquired bacterial infections, such as in neonatal sepsis, and necrotizing enterocolitis (NEC) [1,6,8,9]. In case of infection, thrombocytopenia develops rapidly, is often severe and may take several weeks to recover [8] . One of the major mechanisms leading to low platelet counts in neonatal sepsis is disseminated intravascular coagulation with increased platelet consumption.

Several clinical factors must be taken into account when assessing the cause of neonatal thrombocytopenia. These factors include time of onset of the thrombocytopenia, maternal and perinatal history (including gestational age at birth, birthweight, etc.), the clinical status of a neonate and physical examination findings. Also, 5–10% of low platelet counts are based on measurement errors. Therefore, a low thrombocyte count should always be repeated. Diagnostic tests to rule out FNAITP should be considered in any neonate with moderate-to-severe early-onset thrombocytopenia without additional etiological explanations such as IUGR or infection [10,11].

The paucity of studies from India and the increasing prevalence of this condition in our NICU, instigated us to determine the clinical profile, causes and outcome of thrombocytopenia in neonates admitted to NICU in our hospital.

MATERIAL AND METHODS:

The present study was done to know the clinical profile, causes and outcome of neonates admitted to the NICU with thrombocytopenia. Further assessment of the factors predisposing to thrombocytopenia and efficacy of the treatment protocol in managing neonatal thrombocytopenia was also assessed.

Source of Data:

150 consecutive neonates admitted to the NICU's in Postgraduate department of Pediatrics, G.B pant General Hospital over a period of 2 years (October 2018 to November 2020) irrespective of their underlying morbidity were taken up for the study. All the neonates, except who were lost for follow up and those who expired, were followed up after their discharge once in a period of 6 months.

Study Design: It was a 2 year prospective observational study of neonates admitted to NICU.

Inclusion Criteria:

- Neonates consecutively admitted to NICU from October 2018 to November 2020 were included in the study.

Exclusion criteria:

- Those neonates, whose complete blood counts and other necessary investigations were not done.
- Neonates, whose parents or guardian did not agree to be a part of the study.

At admission the parents and / or the guardian were informed about the study and an informed consent was obtained. A detailed history inclusive of maternal history and obstetric history with a focus on history suggestive of a bleeding and its type in the newborn or the mother was obtained as per the proforma. Information regarding a number of conditions that have been implicated by past studies to be associated with neonatal thrombocytopenia was prospectively recorded.

A history of PIH, gestational diabetes mellitus, premature rupture of membrane, Rh isoimmunization in the mother was asked for. These diagnoses were made as per standard diagnostic criteria laid down. History of consumption of drugs by the mother that can predispose to neonatal thrombocytopenia was also documented. Gestational age of all neonates was determined based on the New Ballard's scoring system.

Growth assessment at birth or admission to detect intrauterine growth restriction was based on Colorado intra uterine growth charts. Every neonate had a detailed physical examination as in the proforma with a focus on purpuric/petechial rashes, mucosal bleeding etc. All neonates at admission underwent a gastric lavage to look for any altered blood in the aspirate. Maternal blood was differentiated from neonatalblood using the Apt - Downey test. Other common sites of bleeding were also looked for.

All the neonates underwent necessary blood investigations, viz.

1. Complete blood count (inclusive of hemoglobin estimation and hematocrit).
2. Peripheral smear study, if required.
3. Blood culture.
4. Septic work up (Absolute neutrophil count, Total WBC count, DLC and mean platelet value).
5. Routine urine examination, urine for fungal balls.

A Septic work up inclusive of absolute neutrophil count, Total WBC count, C reactive protein was done on all patients. If any two of the above mentioned were positive then the neonate was labeled as having suspected septicemia. Quantitative determination of CRP was done by latex turbidimetry. A value of more than 6mg/dl was considered as abnormal.

Investigations such as prothrombin time (PT), activated thromboplastin time (aPTT) and assay for fibrin degradation products (FDP) were also done.

A qualitative and semi-quantitative latex slide test was done wherever feasible to detect cross linked fibrin degradation products. Positive results occurred in the form of agglutination indicating D-dimer (sent outside under JSSK) above 200ng/ml. No agglutination indicated a negative result.

Platelet counts were repeated 24 hours after medical interventions in all cases. Other investigations such as urine sediment for fungal hyphae, chest X-ray, neurosonogram and CT (Computed tomography) brain were performed whenever the need arose.

Due to lack of laboratory facility, tests for platelet alloimmunization were not conducted on all suspected cases as per recommendations. All diagnoses were based on standard diagnostic criteria laid down in indexed medical literature. All the neonates were managed according to standard NICU protocol as per recent recommendations in the medical literature.

On the day of discharge all the neonates underwent a detailed clinical examination. The neonates were classified at discharge based on their immediate outcome.

Statistical Analysis

The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 21.0 (SPSS Inc., Chicago, Illinois, USA). Statistical software SPSS and Microsoft Excel were used to carry out the statistical analysis of data. Descriptive statistics of data including percentages and means were reported. Comparison of the groups for categorical variables was done by Chi-square test. Continuous variables were analyzed using unpaired two tailed student t test or by oneway analysis of variance (ANOVA). Graphically, the data was presented by bar and pie diagrams. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Out of 150 patients with neonatal thrombocytopenia, 95 (63.3 %) were males and 55 (36.7 %) were females, with male: female ratio of 1.73: 1. The subjects were divided into 3 groups based on their platelet counts. 69 (46%) patients had mild thrombocytopenia, 53 (35.3 %) babies had moderate and 28 (18.7%) babies had severe thrombocytopenia. [Table 1].

Table 1: Gender distribution and severity among the study population

Variables	Percentage (%)
Male / Female	**63.3/36.7**
Mild thrombocytopenia	**46**
Moderate thrombocytopenia	**35.3**
Severe thrombocytopenia	**18.7**

According to gestation, 40 (26.7 %) preterm were appropriate for gestational age and 54 (36%) preterm were small for gestational age. 52 (34.7%) full term were appropriate for gestational age and 4 (2.6 %) full term were small for gestational age. Thrombocytopenia in pre term was statistically significant (P value <0.05). Low birth weight (<2.5 kg) constituted 99 (66%) of total babies with neonatal thrombocytopenia [Table 2].

Table 2: Characteristics of Neonates with Thrombocytopenia

Characteristics	Mean±SD (%)
GA at birth (wk)	**34.5 ± 3.4**
Birth weight (g)	**1957 ± 948**
Preterm	**62.7**
Term	**37.3**
SGA	**38**
Low birth weight (<2.5 kg)	**66**

GA, gestational age; SGA, small for gestational age; wk, week

The most common maternal risk factor was anaemia which was present in 72 (48%) babies followed by PROM 45 (30%), PIH 28 (18.7%), oligohydramnios 4 (2.7 %) babies and eclampsia in 3 (2%) babies. Out of these risk factors, association of anaemia with severe neonatal thrombocytopenia was statistically significant (P value <0.05) [Table 3].

Table 3: Distribution of patients according to their maternal risk factors

Maternal factors	present	Groups			Total	X^2value	Pvalue
		GroupI	GroupII	GroupIII			
PIH	Yes	13	13	2	28	3.29	0.186
	No	56	39	27	122		
Eclampsia	Yes	0	3	0	3	-	-
	No	69	50	28	147		
PROM	Yes	16	15	14	45	3.66	0.159
	No	53	37	15	105		
Anemia	Yes	39	16	17	72	6.01	<0.05
	No	30	36	12	78		
Oligohydroamnios	Yes	2	2	0	4	-	-
	No	67	51	28	146		

PIH, Pregnancy Induced Hypertension; PROM, Premature rupture of membrane

Sepsis was the commonest cause of neonatal thrombocytopenia and was found in 79 (52.7 %) babies. RDS in 22 (14.7 %), Birth asphyxia was present in 16 (10.7 %) babies, MAS in 15 (10%) babies, neonatal hyperbilirubinemia in 9 (6%) babies and NEC in 7 (4.7%). Sepsis was associated with severe neonatal thrombocytopenia and it was statistically significant (P value 0.0001). Out of 79 babies with sepsis, 54 (68.35%) babies had late onset thrombocytopenia and it was statically significant (P value 0.00003) [Fig 1].

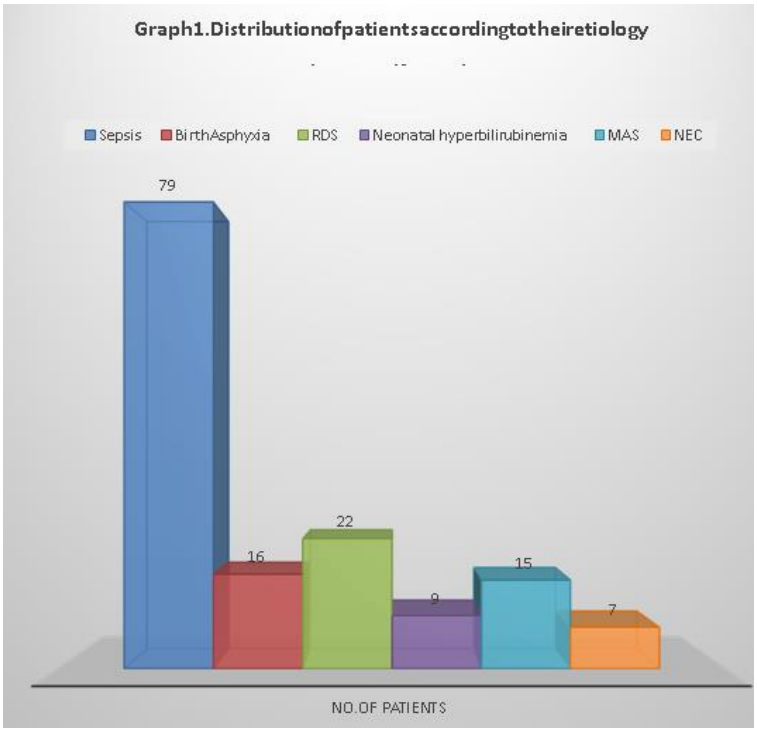

Fig 1.

The most common symptom of thrombocytopenia was apnea in 42 (28%) followed by lethargy in 36 (24%), feeding difficulty in 35 (23.3%) and convulsions in 30 (20%) babies. All the above symptoms were predominantly present in moderate and severe neonatal thrombocytopenia. Also, majority of apnea cases were seen in pre-term babies. In our study, 33 (22%) presented with petechiae/purpura, 16.7% with GI bleeding and 2% babies with pulmonary bleeding. Petechiae/purpura was statistically significant (P value 0.000735) [Fig 2]. PT INR, appt was done in 54 and it was abnormal in 26 (48.14%) babies. This was statically significant (P value 0.05). Blood transfusion was given in 38 (25.3%), platelet transfusion in 4 (2.7%) and FFP in 40 (26.7%) babies.

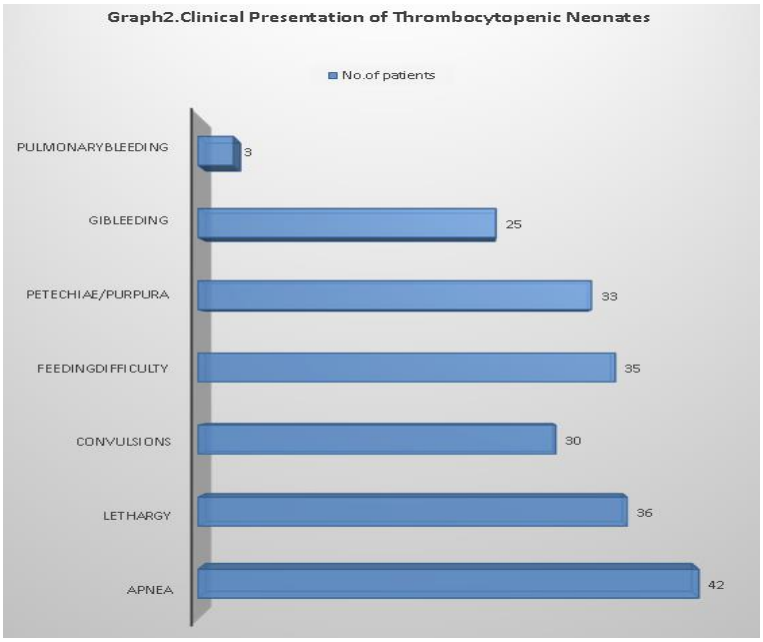

Fig 2.

The mortality was significantly high in severe thrombocytopenia group (46.7 %) as compared to other 2 groups and it was not statistically significant (p value 0.2286). The mortality was high in late onset neonatal thrombocytopenia group (40.7%) as compared to early onset neonatal thrombocytopenia group (28 %) but it was statistically not significant. Out of 43 deaths, 27 (18 %) due to sepsis followed by NEC 4 (2.6%), RDS 4 (2.6 %), MAS 3 (2 %), birth asphyxia 3 (2 %) and neonatal hyperbilirubinemia 2 (1.3 %). Death due to sepsis was significantly high [Fig 3].

While the proportion of mortality was high in the severely thrombocytopenic group. The proportion of babies with a satisfactory immediate outcome was higher in the mild to moderate thrombocytopenic group.

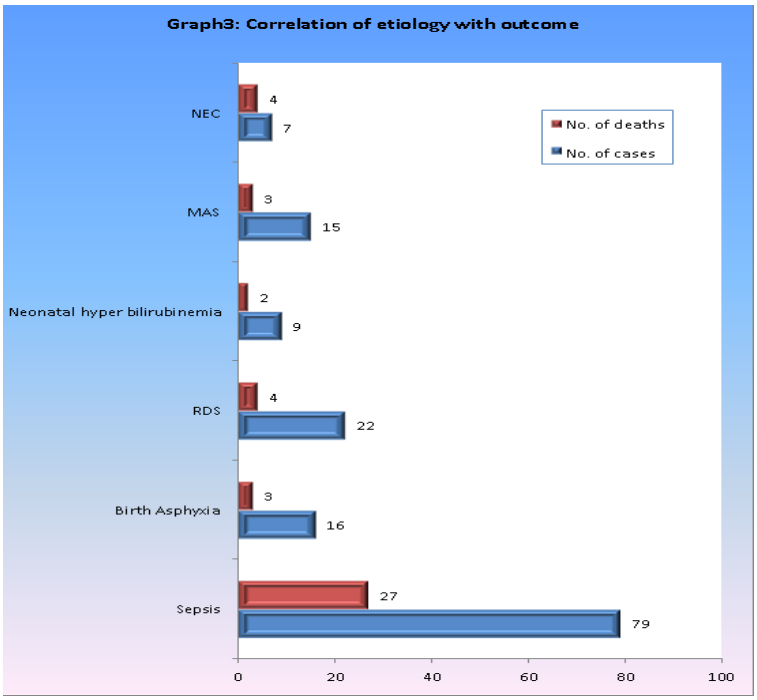

Fig 3.

DISCUSSION

Neonatal thrombocytopenia is one of the commonest hematological abnormality encountered in NICU and if it is not detected and managed properly can result in devastating complications [12]. The etiology and predisposing factors are many and they interact in a complex manner to produce neonatal thrombocytopenia. As in any other neonatal illness the manifestations are protean and severe neonatal thrombocytopenia is known to be associated with a poor outcome [13 - 16].

In our study, 95 (63.3 %) were males and 55 (36.7 %) were females, with male: female ratio of 1.73: 1. The high proportion of male babies with thrombocytopenia in this study is probably due to high incidence of sepsis among male babies. Khalessi N et al [17] , Sheikh MA et al [18] , Chandra A et al [19] , noted that the incidence of neonatal sepsis was higher in males than female neonates. This is probably due to the fact that the factors regulating the synthesis of gamma globulin are situated on the X- chromosone and male has only one X- chromosome [20, 21].

In a study with 2,549 neonates, Kent et al. [22] reported that risk of intracranial hemorrhage and septicemia are higher in male neonates. Also, Bhat et al. [23] showed that in neonates born to mothers with maternal pregnancy -induced hypertension neonatal thrombocytopenia was more frequent in male gender.

The severity of neonatal thrombocytopenia in our study was mild in 69 (46%), moderate in 53 (35.3%) and severe in 28 (18.7%). Moderate and severe thrombocytopenia together constituted 54% of total thrombocytopenic babies. In studies conducted by Khalessi et al [17] , Ghamdi et al [24] and Gupta et al [25], mild thrombocytopenia was more common. In a study conducted by Nandyal et al [26] on 99 neonates, severe thrombocytopenia was present in 65.6% of babies and in Bonifacio et al [27] study, severe thrombocytopenia was present in 51% of babies. Our results were similar to studies conducted by Khalessi N et al [17], and Ghamdi AM et al. [24]. The high prevalence of moderate and sever thrombocytopenia in this study was probably because of higher proportion of septicemic babies in our NICU which is a tertiary care centre.

In our study, out of 150 babies, 99 (66 %) were low birth weight babies and 51 (34 %) were babies with birth weight ≥2.5kg. Low birth weight babies significantly had severe thrombocytopenia and babies with birth weight ≥2.5kg had moderate thrombocytopenia. Our results were similar to studies conducted by Khalessi et al [17] in which 59.1% babies with thrombocytopenia were low birth weight babies. Studies conducted by Robert and Murray [28] also state that neonatal thrombocytopenia was more common among low birth weight babies.

Beiner ME et al [16] showed that 31% of preterm babies developed thrombocytopenia. In our study, 40 (26.7 %) preterm were appropriate for gestational age and 54 (36%) preterm were small for gestational age. 52 (34.7%) full term were appropriate for gestational age and 4 (2.6 %) fullterm were small for gestational age. Full term babies had moderate thrombocytopenia and preterm babies had severe neonatal thrombocytopenia which was statistically significant (P value <0.05).

In our study, anemia was the commonest maternal risk factor. 48% mother had anemia and it was associated with all type thrombocytopenia. Other maternal risk factors were PROM in 30%, PIH 18.7%, oligohydramnios in 2.7 % and eclampsia in 2% babies. All these risk factors were associated with severe thrombocytopenia. Among all these factors, association of anemia with severe neonatal thrombocytopenia was statistically significant (P value <0.05). Our results were similar to Meena SL et al. [29], who showed anemia as the most common maternal risk factor followed by PROM. In a study by Tirupath K et al [30], an association has been documented between anemia and thrombocytopenia. Anemia increases perinatal risks for mothers and neonates; and increasesoverall infant mortality. Although the mechanism of thrombocytopenia is not well understood in this subset of population, it could be due to number of reasons.

Among neonatal risk factors sepsis was the most common cause of neonatal thrombocytopenia which was found in 79 (52.7%) babies and was associated with severe neonatal thrombocytopenia. In preterm babies, sepsis was most commonly due to fungal infection, whereas in term babies, sepsis was mosltly due to bacterial infection. The percentage of sepsis among thrombocytopenic babies in Nandyal et al [26] study was22.2%, Gupta et al [25] study was 42% and Khalessi et al [17] study was 24.1%.

Mortality rate of neonates admitted to the NICU with thrombocytopenia in our study was 8%, which was similar to Feng et al. [31] (9.2%), Manktelow et al. [32] (8.1%) and Parappil et al. [33] (6.5%). The overall mortality in thrombocytopenic babies in this study was28.6%. Mortality was high (40.7%) in late onset neonatal thrombocytopenia group, however it was statistically not significant.
Out of 43 deaths, 27 (18%) due to sepsis followed by NEC 4 (2.6%), RDS 4 (2.6 %), MAS 3 (2%), birth asphyxia 3 (2%) and neonatal hyperbilirubinemia 2 (1.3%). Death due to sepsis was significantly high.

CONCLUSION

Neonatal thrombocytopenia is a treatable and reversible condition. Hence, it is important to identify neonates at risk and initiate transfusion therapy to prevent severe bleeding and potentially significant morbidity. Septicemia is its most important and most common cause. Various maternal and neonatal factors can be associated with thrombocytopenia. Severe thrombocytopenic neonates bleed more frequently and can have unstable vital signs such as poor perfusion at presentation. Poor outcome both immediate and short term are very much associated with severe thrombocytopenia at presentation. The most significant conclusion of our study was that severe thrombocytopenia can be used as a prognostic indicator in sick neonates. But to generalize this statement, and apply to all neonatal admissions, more studies are required in this regard with similar results.

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