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Incidence and Clinical Outcome of Neonatal Thrombocytopenia at a Tertiary Care Hospital - A Prospective Observational Study

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Abstract: ***Background: Neonatal thrombocytopenia (NT) is one amongst the most common hematological abnormality encountered in NICU. Aim of the present study was to find out the incidence and clinical outcome of NT and also studied the maternal and fetal risk factors, clinical course of NT during hospital stay. Method: A total of 100 neonates admitted to NICU were enrolled and studied in the Department of Pediatrics at Tertiary Care Centre in India during a period from 1st January 2020 to 31st December 2020. Results: The incidence of thrombocytopenia was 64%, of which severe thrombocytopenia was 32.81% in our NICU. Commonest etiologic factor associated with thrombocytopenia was septicaemia (48.43%). Neonatal factors associated with thrombocytopenia, especially severe thrombocytopenia was age at presentation, septicaemia, NEC and assisted ventilation. Maternal PIH was significantly associated with NT (p<0.001). Clinical signs and symptoms associated with severe thrombocytopenia were bleeding, purpura and delayed capillary refill. The course in the hospital for severe thrombocytopenia was relatively longer (17 days), involving longer period on supplemental oxygen (7 days) and IV fluids (12 days). Mortality (38.09%) and morbidity (4.76%) was significantly higher while discharged rate was less (61.90%) in babies with severe thrombocytopenia. Septicaemia was the commonest cause of death on whole (36.36%) followed by prematurity (27.27%), also in severely thrombocytopenic group. Conclusion: Thus, severe thrombocytopenia was found to be predictor of poor outcome in sick neonates of NICU. Also, low platelet count was an independent risk factor for poor outcome in current study. Hence it could be used as a prognostic indicator in NICU graduates.***

Keywords: Neonatal thrombocytopenia, Severe, Septicaemia, PIH, Purpura, Assisted ventilation, Mortality, Prematurity

1. Introduction

Neonatal thrombocytopenia is a common hematological issue in newborns, particularly premature babies and those admitted to neonatal intensive care units (NICUs). With an incidence of 18 - 35% in NICU patients, thrombocytopenia often indicates an underlying pathological process. Prematurity, sepsis, and maternal hypertension are significant risk factors. The condition's mechanisms include inadequate thrombopoietin production and fewer circulating megakaryocyte progenitors. This study aims to investigate the incidence, outcome, and maternal and fetal risk factors associated with neonatal thrombocytopenia in NICU admissions.

2. Methodology

After obtaining Institutional Ethical Committee approval and written informed consent from each participant's parents, a prospective observational study was conducted in the Department of Pediatrics at Tertiary Care Centre for one year from 1st January 2020 to 31st December 2020 with 100 newborns admitted to NICU. Neonates with congenital malformations, birth injuries, maternal medications like aspirin, warfarin etc were excluded from the study.

A detailed history inclusive of maternal, obstetric history, drug history and type of bleeding were taken. Gestational age was assessed according to New Ballard's score and at the time of birth APGAR score was observed at 1 min and 5 min and whether or not resuscitation was required, were observed. Growth assessment at birth or admission to detect intrauterine growth restriction was based on Colorado intra uterine growth charts. All neonates at admission had their weight, length, systemic examination (respiratory, cardiovascular, abdomen, central nervous system) and vitals (heart rate, respiratory rate, temperature, capillary filling time) recorded and examined for purpuric/petechial rashes, mucosal bleeding etc.

Blood was collected in sterile EDTA bulbs by venepuncture after taking all aseptic precautions. CBC was obtained from an automated hematology analyzer. Peripheral smear study, blood cultures were done using standard laboratory methodology. A Septic work up inclusive of absolute neutrophil count, total WBC count, Micro ESR, C reactive protein was done on all patients. If any two of the above mentioned were positive, then the neonate was labelled as having suspected septicaemia and based on their platelet counts at admission divided into no thrombocytopenia, mild, moderate and severe thrombocytopenia group.

All the neonates were managed according to standard NICU protocol as per recent recommendations in the medical literature. 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 brain were performed whenever the need arises.

Statistical Analysis

Statistical analysis was performed using SPSS version 20 (SPSS Inc., Chicago). Descriptive data were presented as number or percentages. Quantitative variables were described as mean ± SD. Comparison of the groups for categorical

variables was done by Chi - square test. Continuous variables were analysed using unpaired two tailed student t - test Probability value of $p<0.05$ was considered significant while $p<0.01$ taken as highly significant.

3. Results

The overall incidence of thrombocytopenia in our NICU was 64%. The incidence of mild (25%) to moderate (42.18%) thrombocytopenia (<150, 000/µL & ≥50, 000/µL) accounted for 67.18% of all the neonatal thrombocytopenia. The incidence of severe thrombocytopenia (<50, 000/µL) on the whole was 32.81%. No thrombocytopenia (>150, 000/ cu mm) in 36% of neonates. The mean platelet count for all the groups was 1.733±0.82 lakhs/µL. Figure 1 show the mean platelet count in each group. The mean hemoglobin (g/dL) level of study population was 10.04±0.65 g/dL and mean total leukocyte count (TLC) was 9.14±0.70 thousand/mm^3.

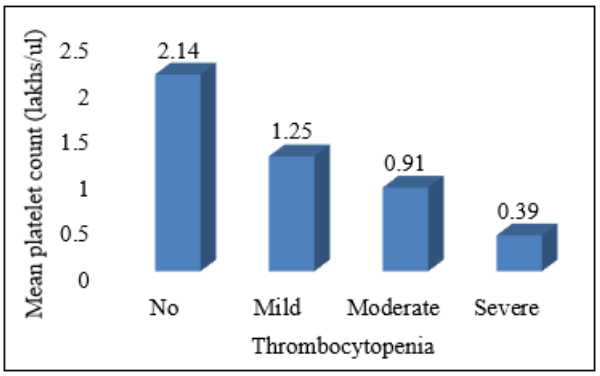

Figure 1: Showing the mean platelet count in each group

The most common etiologic association with thrombocytopenia was neonatal septicaemia. Maternal PIH was significantly associated with neonatal thrombocytopenia. Neonatal factors associated with neonatal thrombocytopenia, especially severe thrombocytopenia was age at presentation, septicaemia, NEC, and assisted ventilation, (Table 1). Gestational age as assessed by New Ballards' scoring system was not associated with neonatal thrombocytopenia with p value of 0.370.

Table 1: Etiologic profile: association between neonatal and maternal risk factors with thrombocytopenia

Neonatal factors		No thrombo. (N=36)	Mild (N=16)	Moderate (N=27)	Severe (N - 21)	P value
Gestational age	Preterm	02 (5.55%)	01 (6.25%)	02 (7.40%)	02 (9.52%)	0.135
	Term	34 (94.44%)	15 (93.75%)	25 (92.59%)	19 (90.47%)	
Age in hours	<72 hrs	28 (77.77%)	10 (62.5%)	20 (74.07%)	09 (42.28%)	0.015
	>72 hrs	08 (22.22%)	06 (37.5%)	07 (25.92%)	12 (57.14%)	
LBW		01 (2.77%)	01 (6.25%)	02 (7.40%)	02 (9.52%)	0.311
Septicaemia (SEP)		9 (25%)	09 (56.25%)	10 (37.03%)	12 (57.14%)	0.012
NEC		02 (5.55%)	03 (18.75%)	02 (7.40%)	04 (19.04%)	<0.001
Pneumonia (PNEU)		00 (0.0%)	01 (6.25%)	00 (0.0%)	01 (5.0%)	-
TTNB		00 (0.0%)	01 (6.25%)	01 (3.70%)	00 (0.0%)	-
Perinatal asphyxia (PA)		10 (27.77%)	06 (37.5%)	07 (25.92%)	05 (23.80%)	0.441
IUGR		07 (19.44%)	7 (43.75%)	8 (25.92%)	09 (42.85%)	0.134
Assisted Ventilation		01 (2.77%)	02 (12.5%)	03 (11.11%)	06 (28.57%)	0.023
Maternal factors		No Thrombo.	Mild	Moderate	Severe	P value
Maternal PIH		05 (13.88%)	04 (25.0%)	08 (29.62%)	15 (71.42%)	<0.001
GDM		11 (30.55%)	05 (31.25%)	09 (33.33%)	7 (33.33%)	0.234
Rh incompatibility		02 (5.55%)	01 (6.25%)	02 (7.40%)	02 (9.52%)	0.087
PROM		06 (16.66%)	03 (18.75%)	05 (18.51%)	4 (19.04%)	0.068
APH		01 (2.77%)	01 (6.25%)	02 (4.65%)	01 (4.76%)	0.127

Necrotizing enterocolitis (NEC); Transient tachypnea of the newborn (TTNB); Gestational diabetes mellitus (GDM); Pregnancy induced hypertension (PIH); Premature rupture of membrane (PROM); Ante partum hemorrhage (APH)

Severely thrombocytopenic neonates bled more frequently than other groups. The mean platelet count of neonates with bleeding was 1.19 (*10*/µL) which was statistically significant, (p=0.001). DIC, was significantly associated with severe thrombocytopenia. The causes of DIC were either perinatal asphyxia or septicaemia accounting for 28.33% and 43.51% of the cases (i. e., cases of DIC) respectively. However, instances of intra cranial hemorrhage (ICH) were higher in severely thrombocytopenic group (9.52%) than the other three groups and which was statistically significant (P<0.001). The clinical signs and symptoms associated with severe thrombocytopenia were bleeding, purpura and delayed capillary refill as shown in table 2.

Table 2: Clinical impact of thrombocytopenia

Signs and symptomatology		No. thromb	Mild	Moderate	Severe	P value
Bleeding	**Mucosal bleed**	06 (16.66%)	03 (18.75%)	06 (22.22%)	14 (66.66%)	0.003
	IC bleeding	01 (2.77%)	01 (6.25%)	01 (3.70%)	02 (9.52%)	<0.001
	Petechiae /purpura	02 (5.55%)	01 (6.25%)	02 (7.40%)	10 (47.61%)	<0.001
Other than bleeding	Apnea	02 (5.55%)	01 (6.25%)	03 (11.11%)	04 (19.04%)	>0.05
	Lethargy	13 (36.11%)	04 (25%)	07 (25.92%)	07 (33.33%)	
	Not feeding well	14 (38.88%)	05 (31.25%)	08 (29.62%)	08 (38.09%)	
	Seizures	04 (11.11%)	03 (18.75%)	06 (22.22%)	07 (33.33%)	

	Neuro depression	06 (16.66%)	04 (25%)	08 (29.62%)	09 (42.85%)	
	Respiratory distress	03 (8.33%)	04 (25%)	06 (22.22%)	07 (33.33%)	
	Delayed capillary refill	05 (13.88%)	03 (18.75%)	08 (29.62%)	11 (52.38%)	0.021
	Abdominal distension	01 (2.77%)	04 (25%)	05 (18.51%)	06 (28.57%)	>0.05

The proportion of mortality (38.09%) was high in the severely thrombocytopenic group, also morbidity (4.76%) was more in the form of ICH or convulsion in severe group whereas less number of severe neonates discharged (61.90%) from the hospital as compared to other three groups. The septicaemia was the most common cause of death (36.36%) followed by prematurity (27.27%), (Figure 2), also in the severely thrombocytopenic group septicaemia and prematurity was the most common cause of death.

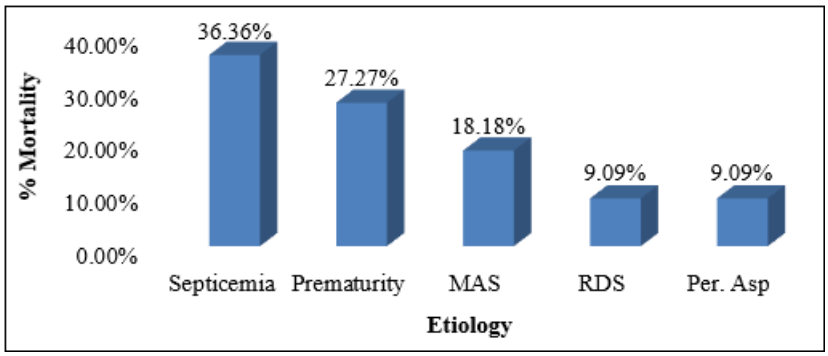

Figure 2: Distribution of mortality based on the etiology

From the table 3, it was observed that the blood culture positivity was found in 43 out of the 100 cases, C - reactive protein was positive in 44 cases. Klebsiella was the commonest organism found in blood culture (41.86%). The other gram - positive organisms encountered were Escherichia Coli (30.23%), Pseudomonas (6.97%), Staphylococcus (6.97%) and Acinetobacter (2.32%). The Gram - positive organisms grown were Coagulase negative Staphylococci (4.65%), Group B Beta Hemolytic Streptococcus (4.65%) and Enterococcus (2.32%).

Table 3: Evaluation of CRP as a distinguishing parameter for Gram positive and Gram - Negative cases

CRP	Culture Positive	Culture Negative	Total
CRP Positive	41	03	44
CRP Negative	02	54	56
Total	43	57	100

4. Discussion

Thrombocytopenia is a significant cause of morbidity and mortality in the sick preterm and full - term infant [8, 9]. The prevalence varies from less than 1% up to 90% depending on the population studied [10, 11]. In the present study the overall incidence of thrombocytopenia in NICU was 64% which is comparable with the study done by Nadyal et al where the incidence of neonatal thrombocytopenia was 63.8% [12]. The higher overall incidence of thrombocytopenia in current study was probably because of high neonatal septicaemia as confirmed in other studies [13, 14] which also explains the severity of thrombocytopenia (32.81%). However, the mild and moderate thrombocytopenia together constituted 67.18% of total thrombocytopenic babies which was similar to the earlier studies [3, 15]. In severe thrombocytopenia group the mean platelet count was lower as compared to mild and moderate thrombocytopenia groups. This might just be a reflection of the higher prevalence of severe thrombocytopenia in our NICU.

In the present study, the etiological profile on the whole was similar to other NICU studies from India [16], with septicaemia, perinatal asphyxia and very low birth weight accounting for the majority of the admissions. Septicaemia accounted for most of the cases in severe, mild, and moderate thrombocytopenia group as shown by Patil et al and Zaccheaus et al, [17, 18]. In western studies only 10% of septicaemia with severe thrombocytopenia had evidence of DIC [3] whereas in current study it was 28.57%. Neonatal alloimmune thrombocytopenia is a significant contributor to neonatal thrombocytopenia. However, due to limited facilities, investigations to confirm feto - maternal platelet alloimmunization were not conducted, making it impossible to determine the frequency of this condition in our NICU. . NEC, as diagnosed by Bell's criteria, was significantly associated with thrombocytopenia ($P<0.001$). All the neonates in present study with radiological evidence of NEC had neonatal thrombocytopenia. This finding agrees with the well - known fact that thrombocytopenia is one of the major lab markers of NEC [3]. The majority of severely thrombocytopenic neonates (57.14%) present after 72 hours and the common etiology, in these neonates, were septicaemia and NEC [3]. Unlike previous studies [19, 20], gestational age was not found to be associated with low platelet counts in this study. This may be due to the fact that many term neonates were sick and septicemic, whereas some preterm neonates were admitted for routine preterm care and had normal platelet counts. There was significant association between mechanical ventilation ($P<0.023$).28.57% of the neonates in the severe thrombocytopenia group were mechanically ventilated one time or the other similar to other studies [21]. The use of fresh whole blood for exchange transfusions in this study may have prevented an association between exchange transfusion and thrombocytopenia, unlike previous findings [22] linked to non - fresh blood.

Overall incidence of maternal PIH was 42.18% which was similar to the study conducted by Dahmane Ayadi I et al [23]. In other studies [13, 17, 23, 24] also maternal PIH is

associated with mild to moderate thrombocytopenia rather than severe thrombocytopenia while in current study, PIH was associated with severe thrombocytopenia. This could be explained by the frequent exposure of these neonates to infection, due to the relatively high prevalence of septicaemia in present study that leads to a precipitous fall in platelet count.

It is very difficult to critically assess the clinical impact of neonatal thrombocytopenia. In the present study, severely thrombocytopenic neonates bled more frequently. The mucosal bleeding was significantly associated with thrombocytopenia which is comparable with the study conducted by Patil et al [17]. The average platelet count of the bleeding neonate was, 1.19±102 *10*/µL. It was more than 50, 000/µl probably because neonates bleeding due to causes other than quantitative platelet deficiencies such as VKDB were also included. But still the association between the platelet count and mucosal bleeding was significant (P<0.001). DIC, as diagnosed by both an increase in PT, APTT, and fibrin degradation products, was significantly associated with severe thrombocytopenia. While 27.3% of the severely thrombocytopenic cases had evidence of DIC only 2.2% had such laboratory finding in the mild to moderate thrombocytopenia group. The causes of DIC were either perinatal asphyxia or septicaemia accounting for 28.33% and 43.51% of the cases (i. e., cases of DIC) respectively. Instances of intra cranial hemorrhage (ICH) were higher in severely thrombocytopenic group (9.52%) than the other three groups and which was statistically significant (P<0.001). The clinical finding of purpura and petechiae were diagnosed when the skin lesions were red circumscribed, non - blanchable, with less than 1cm ones called as petechiae and more than 1 cm ones referred to as Purpura. The incidence of purpura and petechiae was significantly associated with thrombocytopenia (p<0.001). similar to Homans A et al study [25]. The most common symptom aside from bleeding was "not feeding well", but this is a non - specific symptom common in sick neonates. A more significant finding was delayed capillary refill (>3 sec) in 52.38% of severely thrombocytopenic neonates, which may be associated with shock or excessive blood loss in these critically ill patients [26]. Due to the unavailability of continuous intra - arterial or oscillometric BP monitoring hypotension was not documented.

90.47% of the severely thrombocytopenic neonates and 86.04% of moderately thrombocytopenic neonates had to stay longer than a week, they also spent more time on IV fluids and supplemental oxygen. This might be related to the severity of the underlying sickness in these neonates and/or due to the increased incidence of complications during their stay. The overall mortality in present study was 11% which is less than other studies [20, 23]. It was observed that the proportion of mortality was high in the severely thrombocytopenic group (38.09%) as compared to mild to moderate (4.65%) and non - thrombocytopenic group (2.77%). These findings are correlated with the previous studies [17, 24]. The septicaemia was the most common cause of death on the whole (36.36%) followed by prematurity (27.27%), also in the severely thrombocytopenic group septicaemia and prematurity was the most common cause of death. These findings are in accordance with the study done by Rathi P [27].

The efficacy of the treatment protocol practiced was assessed based on percentage increment in platelet count after 24 hours of intervention. It was found that though platelet transfusion produced a higher increment in platelet count (93.16%) compared to fresh whole blood transfusion (79.81%), the discrepancy was not statistically significant.

5. Conclusion

The low platelet count was an independent risk factor for poor outcome in current study and could be used as a prognostic indicator in NICU graduates. Also, sepsis along with thrombocytopenia was noted with poor outcome. Severe thrombocytopenia is associated with adverse outcomes, including prolonged hospitalization, increased oxygen and IV fluid requirements, and higher mortality and morbidity. But to generalize this statement and apply to all neonatal admissions, more studies are required in this regard with similar results. Though fresh whole blood transfusion might not be a good option, as platelet transfusion in severe thrombocytopenia is a good alternative to platelet concentrates in times of its unavailability.

Conflict of Interest Statement:
None declared.

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