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A STUDY ON RISK FACTORS, IMMEDIATE OUTCOME, AND A SHORT-TERM FOLLOW-UP STUDY OF NEONATES WITH NEONATAL THROMBOCYTOPENIA

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Abstract

Background: Neonatal thrombocytopenia (NT) (platelet count $< 150 \times 10^9$ /L) is a common finding in the neonatal intensive care unit (NICU). The main aim of this study was to assess risk factors, immediate outcome, and a short-term follow-up of neonates with NT. **Materials and Methods:** It was a Prospective Observational Study done with 550 neonates from October 2018 to August 2019 admitted to the NICU of a Tertiary Level Medical College Hospital in South Tamil Nadu, India. Neonates showing bleeding/having platelet count (<1.5 Lakhs/µL) were selected. An initial platelet count was done on admission, and counts were repeated 24 hours after therapeutic intervention. After that, treatment was given as per NICU protocols.**Result:** Severe thrombocytopenia (<50,000/µL) was present in 8.5%, moderate (<100,000/µL and ≥50,000/µL) in 17.01%. In group IIb (severe thrombocytopenia), a higher proportion of cases presented after 72 hours (55.31%). Maternal PIH, Intrauterine growth retardation (IUGR), septicaemia, assisted ventilation, disseminated intravascular coagulation (DIC), neonatal enterocolitis (NEC), intracranial (IC) bleeding variables were found to be statistically (p<0.001) associated with thrombocytopenia. The most common symptom was "not feeding well" in all three groups. Mortality was 37.12% in the Severe and 3.9% in the Moderate thrombocytopenia group. There was a 92.6 % increase in mean platelet count after 24 hours of blood transfusion. **Conclusion:** According to the current study, severe thrombocytopenia in sick neonates in NICU is a poor predictive factor.

INTRODUCTION

Thrombocytopenia (platelet count <150,000/µL) is the second most common haematological problem in Neonatal Intensive Care Units, with an 18%-35% prevalence rate and first being phlebotomy-induced anaemia.[1] It is more common among Extremely Low Birth Weight neonates (<or=1000 gms birth wt), Preterm babies (GA<or =34-36 weeks) or Sick neonates in NICUs. In contrast, only 2% of the neonates are thrombocytopenic at birth in term NB and Severe Thrombocytopenia (platelet count <50,000/µL) occurs in <3/1000 term infants [2-3]. There are two main underlying pathological mechanisms for NT: increased destruction/sequestration or decreased production of platelets. The underlying cause of NT can often be predicted by the timing of the onset of thrombocytopenia and its natural history.[4]However,

from a clinical point of view, many cases have a compound etiology for thrombocytopenia. In most cases, NT is mild to moderate and resolves without intervention. Life-threatening bleeding, intraventricular haemorrhage (IVH), or pulmonary haemorrhage with a high risk of neurodevelopmental impairment may occur in severe NT.[5-6] However, NT occurs less frequently in full-term (FT) infants than in preterm infants, as demonstrated in one cohort study where it was 2%.[7] Moreover, the main risk factors in FT infants were occult infection, placental insufficiency, and NAT, which differs from preterm risk factors, such as sepsis, TORCH infection, and necrotizing enterocolitis (NEC).[8]The influence of thrombocytopenia on the outcome of the neonate is a subject that has not been studied in detail in the past, and neither have articles assessed the value of neonatal thrombocytopenia as a prognostic indicator

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in sick neonates. After a detailed search of the indexed medical literature, it was found that there have been only a few articles on this topic from India.[9] One article studies the association between maternal pregnancy-induced hypertension (PIH) and neonatal thrombocytopenia, while the others are case reports and case series reports.[10] The lack of studies from India and the increasing prevalence of this condition in our NICU instigated us to do this study.

MATERIALS AND METHODS

This prospective observational study was performed on 140 of 550 consecutive neonates admitted to the NICU of Tirunelveli medical college hospital from October 2018 to August 2019. All the neonates, except those who were lost for follow-up and those who expired, were followed up after their discharge for 3 months. All neonates born in our hospital and admitted to NICU in TVMCH with thrombocytopenia were included in the study. Early neonatal deaths and morbidity were also included in the study. Neonates with major congenital malformations, babies born outside our hospital and admitted to our NICU (extramural), cases involving maternal medications like aspirin and warfarin, congenital cardiac malformations and surgical conditions in neonates were excluded from the study. At admission, the parents and the guardian were informed about the study and oral informed consent was obtained. A detailed history, including maternal and obstetric history with a focus on history suggestive of bleeding and its type in the newborn or the mother, was obtained per the proforma. In addition, information regarding several conditions implicated by past studies to be associated with neonatal thrombocytopenia was prospectively recorded. A history of PIH, gestational diabetes mellitus, premature rupture of membrane, and Rh isoimmunization in the mother was asked for. These diagnoses were made as per the standard diagnostic criteria laid down. History of consumption of drugs by the mother that can predispose to neonatal thrombocytopenia was also documented (see annexure). The gestational age of all neonates was determined based on New Ballard's scoring system. Growth assessment at birth or admission to detect intrauterine growth restriction was based on Fenton's intrauterine growth charts. Every neonate had a detailed physical examination, as in the proforma, focusing on purpuric/petechial rashes, mucosal bleeding, etc. Other common sites of bleeding were also looked at. All the neonates underwent necessary blood investigations, i.e., Complete blood count (including haemoglobin estimation and hematocrit), Peripheral smear study. A Septic workup, including Blood culture, Absolute neutrophil count, Total WBC count, Micro ESR, and C reactive protein, was done on all patients. If any of those mentioned above were positive, the

neonate was labelled as having suspected septicemia. Quantitative determination of CRP was done by latex turbidimetry using SPINREACT CRP TURBILATEX. A value of more than 0.6mg/L was considered abnormal. Most of the cases in group IIb (Severe thrombocytopenia) investigations, such as prothrombin time (PT), activated thromboplastin time (APTT), and INR, were also done. The next step was to group the neonates based on their platelet counts at admission. Platelet counts were repeated 24 hours after medical interventions in all cases. Other investigations, such as chest X-ray, neuro sonogram and CT (Computed tomography) brain, were performed whenever the need arise. Due to a lack of laboratory facilities, tests for platelet alloimmunization were not conducted on all suspected cases as per recommendations. All diagnoses were based on standard diagnostic criteria in the indexed medical literature. All the neonates were managed according to standard NICU protocol as per recent recommendations in the medical literature. All the neonates underwent a detailed clinical examination on the day of discharge. The neonates were classified at discharge based on their immediate outcome as below:

Satisfactory
The outcome was considered satisfactory if the patient fulfilled all the following criteria. All acute problems should have become passive, baby should be accepting breastfeeding or Paladai feeds, adequate weight gain for 3 consecutive days.

- The baby's weight should be more than or equal to 1.5kg at discharge.
- There is no associated morbidity such as hypoxic-ischemic encephalopathy, persistent seizures, intracranial bleeding etc.

Not satisfactory If the patient does not fulfil even one of the criteria mentioned above.

Expired Self-explanatory
All neonates were followed up at least once for 3 months. During each visit, a detailed physical examination was done. In addition, weight and head circumference were measured and plotted on the growth and development charts. The growth parameter at a point of time lying below the 3rd percentile was considered abnormal. Neurodevelopment was assessed using the Denver II scale. Denver II consists of 125 tasks items, which are arranged on the test forms in 4 areas (a) Personal- social, (b) Fine motor- adaptive, (c) Language (d) Gross motor.

The Denver II is interpreted as follows
- Normal: No delays and a maximum of one caution in the various test items
- Suspect: 2 or more cautions and more delays.

Based on their physical growth and neurodevelopment in the 3rd month, the neonates were classified as having a good (g), fair (f), poor (p), and expired (e) outcome. Infants were classified as having a poor outcome if their neurodevelopment outcome was suspect, as per the Denver II

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development scale, on two different occasions, irrespective of their physical growth (Table 2). Any mortality was recorded both at discharge and at follow-up.

Table 2: Definition of the various groups according to an outcome.

Outcome	Denver II	Weight and head circumference
Good (g)	Normal(N)	= or ≥ 3rd centile
Fair(f)	Normal	<3rd centile
Poor(p)	Suspect(S)/expired	or = 3rd centile (irrespective of their growth)

Descriptive data are presented as numbers or percentages. Comparison of the groups for categorical variables was done by Chi-square test. Continuous variables were analyzed using unpaired two-tailed student t-tests or by one-way analysis of variance (ANOVA). A 'P' value below 0.05 was considered significant.

RESULTS

A total of 550 consecutive neonatal admissions were included in our study per the inclusion and exclusion criteria. The subjects were divided into three groups based on their platelet counts, as in [Table 3]. The prevalence of thrombocytopenia, on the whole, was 25.45%. The prevalence of severe thrombocytopenia (<50,000/µL) on the whole was 8.5%. Mild to moderate thrombocytopenia (<150,000/µL and 50,000/µL) accounted for 17.01% of all neonatal thrombocytopenia. The mean platelet count for all the groups was 1.603±0.71 lakhs/µL.

Table 3: Subject distribution in the various group

Groups	Platelets count at admission	No. of subjects N (%)	Mean platelet count (mean ±SD)
I (Non-thrombocytopenic)	>150,000/µL	410 (74.54%)	2.04 ±0.47 lakhs/µL
II (Thrombocytopenic)	<150,000/ µL	140 (25.45%)	-
IIa (Mild to moderate thrombocytopenia)	Between >150,000/µL to <50,000/ µL	93 (17.01%)	1.15 ± 0.27 lakhs/µL
IIb (Severe thrombocytopenia)	<50,000/ µL	47 (8.5%)	0.37 ± 0.097 lakhs/µL

The cases in the 3 groups were divided into two subgroups, each based on the age of presentation, either before or after 72 hours. In group IIb (severe thrombocytopenia), a higher proportion of cases had presented after 72 hours (55.31%) compared to the other two groups (26.88% and 21.70% for Group II and I, respectively. In our study, severely thrombocytopenic neonates tend to present later than 72 hours compared with cases with mild to moderate thrombocytopenia and no thrombocytopenia [Table 4].Maternal PIH, Intrauterine growth retardation (IUGR), septicaemia, assisted ventilation, disseminated intravascular coagulation (DIC), neonatal enterocolitis (NEC), intracranial (IC) bleeding, variables were found to statistically (p<0.001) associated with thrombocytopenia thereby reported significantly higher in moderate (Group IIa) and severe (Group IIb) thrombocytopenia groups [Table 4]. In addition, bleeding was also reported to be significant (p<0.001) associated with platelet count in our study. Neonate with bleeding was reported with 1.16 lakh/µL platelet count, whereas 1.7 lakh/µL platelets were reported with neonates without bleeding.

Table 4: Observation of maternal PIH and Thrombocytopenia

		Groups I	Groups IIa	Group IIb
Maternal PIH	History of Maternal PIH	79 (19.44%)	26 (27.95%)	34 (72.34%)
	NO history of maternal PIH	331 (80.55%)	67 (72.04%)	13 (27.65%)
Age at presentation	<72 hours	321 (78.529%)	68 (73.11%)	21 (44.68%)
	>72 hours	89 (21.70%)	25 (26.88%)	26 (55.31%)
IUGR assessment	NO IUGR	323 (78.78%)	52 (55.91%)	27 (57.44%)
	IUGR	87 (21.21%)	41 (44.08%)	20 (42.55%)
Septicaemia	No	307 (74.87%)	61 (65.59%)	19 (40.42%)
	Yes	103 (25.12%)	32 (34.40%)	28 (59.57%)
	NEC	21 (5.2%)	11 (11.8%)	8 (17%)
IC Bleeding	IC haemorrhage	2 (0.48%)	1 (1.075%)	4 (8.51%)
	No IC haemorrhage	408 (99.51%)	92 (98.92%)	43 (91.48%)
Immediate outcome	Expired	13 (3.15%)	3 (3.92%)	17 (37.12%)
	No satisfactory	216 (52.77 %)	75 (80.64%)	23 (48.93%)
	Satisfactory	181 (44.14 %)	15 (16.12%)	7 (14.89%)

The most common symptom was "not feeding well" in all three groups. The delayed capillary refill symptom was significantly associated (p<0.001) with severe thrombocytopenia. The prevalence of a capillary refill of more than 3 seconds was 50 % in the severely thrombocytopenic group. The most common sign in the mild to moderate thrombocytopenic and no thrombocytopenia groups were signs of neurological depression. Evidence of GI bleed was also more prevalent in Group IIb, but its association with the severe thrombocytopenia group was not statistically significant.The hospital course was evaluated regarding the number of days on intravenous fluids, supplemental oxygen support

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and duration of stay. It was found that all three variables were significantly associated with thrombocytopenia, and 87.5 % of Group IIb (severe) babies and 82% of Group IIa (moderate) had to stay longer than a week while only 50% of the neonate in the Group I (non-thrombocytopenic) had to do s.
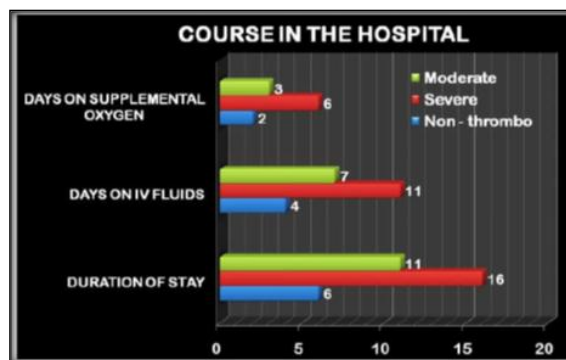

Figure: 1 Graph showing the course in the hospital of various groups of babies

Table 5: Mortality analysis in a different group

Mortality	Septicaemia	MAS	RDS	Per. Asp	Con. An	Prematurity	Total
Group I	4	3	1	0	0	5	13
Group IIa	1	1	0	0	0	1	3
Group IIb	8	2	2	2	1	2	17
Mortality	39.3	18.1	9.09	6.06	3.03	21.21	33

The observation of immediate outcome was carried out in the present study, and it was found that the mortality was significantly high in the severely thrombocytopenic group (Group IIb: 37.12%) compared to the other two groups Group I with 3.15% and Group IIa with 3.92% respectively. The proportion of babies with unsatisfactory immediate outcomes was higher in the mild to a moderate thrombocytopenic group and no thrombocytopenia group. Septicaemia was the most common cause of death in the severely thrombocytopenic group, accounting for 39.93% of the mortality [Table 4, 5]. Observation of outcome after 3 months of discharge showed that of 140 cases, there were 20 mortalities, and 18 were lost for follow-up. Those 18 cases lost for follow-up were excluded while assessing the outcome in the different groups. Higher mortality was reported in the severe thrombocytopenia group (Group IIb) [Figure 2].
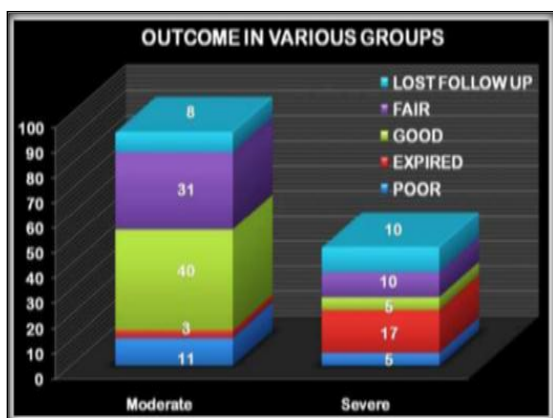

Figure 2: Outcome analysis in the study groups

Among the cases followed up, the proportion of cases with the poor neurodevelopmental outcome (i.e., suspect outcome in Denver II) was higher in group IIb, i.e., severely thrombocytopenic group (43.70%) to the other group (21.50 %). The efficacy of the treatment protocol practised in our NICU was assessed based on the percentage increase in platelet count 24 hours after blood or platelet transfusion. There was a 92.6 % increase in mean platelet count after 24 hours of blood transfusion, whereas after whole blood transfusion, there was a 78.69% increase in mean platelet counts.

DISCUSSION

The prevalence of thrombocytopenia in our study was 25.45%. However, Castle et al. reported a 22% prevalence, and Oren et al. found a 5.41 % prevalence of thrombocytopenia.11,12 This higher prevalence in our study is probably due to a higher proportion of septicaemia neonates in our NICU admissions. The proportion of severe thrombocytopenia (8.5%) among the neonatal in our study was also found on the higher side. This is probably a reflection of a higher contribution of septicaemia to neonatal thrombocytopenia in our NICU than other etiologists. The mean platelet count among our NICU admissions was 1.603 lakh /μl. This is once again on the lower side compared to other studies.[13] This might reflect the higher prevalence of severe thrombocytopenia in our NICU. It was observed that 55.31% of the severely thrombocytopenic neonates presented after 72 hours of life, while only 25% and 21.7 % did so in the other two groups. These findings in the present study are in agreement with earlier reported studies.[14]Maternal PIH was significantly associated with neonatal thrombocytopenia (P<0.001), and this finding agrees with studies conducted by Burrows et al.15 The maternal PIH is associated with mild to moderate thrombocytopenia rather than severe thrombocytopenia in other studies. In contrast, in our study, it was associated with severe thrombocytopenia. This could again be explained by the frequent exposure of these neonates to infection

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due to our study's relatively high prevalence of septicaemia, resulting in a steep fall in platelet count. IUGR was also found to be significantly associated with thrombocytopenia, which is in agreement with other studies showing a strong association between both IUGR and thrombocytopenia.[16]The 25% of severely thrombocytopenic cases had evidence of DIC, whereas only 1.9% of DIC was found in the mild to moderate thrombocytopenia group. DIC is known to be initiated by bacterial toxins, such as exotoxins and lipopolysaccharide, producing endothelial dysfunction. Quantitative and qualitative differences exist between the toxins secreted by various bacteria. There was no association between gram-negative septicaemia and thrombocytopenia in our study. In comparison, such an association has been shown to occur in certain studies. It might be because of interspecies variation in the pathological mechanism of septicaemia among various gram-negative bacteria.[17]NEC and IC bleeding incidence were statistically significantly associated with thrombocytopenia (p<0.001). All the neonates in our study with NEC and IC bleeding had neonatal thrombocytopenia. This finding is in agreement with the well-known fact that thrombocytopenia is one of the major markers of NEC.[18]The most common symptom other than bleeding was "not feeding well". But this symptom is non-specific and can be associated with any sick neonate. Hence this finding is not of much clinical significance. The most common sign other than bleeding in the severely thrombocytopenic group was delayed capillary refill (>3 sec.). This association might either be due to shock in sick, especially septicaemia neonates, who are known to have severe thrombocytopenia, or it might be due to excessive blood loss. Neurological depression was the most common sign in the no thrombocytopenia and the mild to moderate thrombocytopenia group. This association might be due to increased prevalence of perinatal asphyxia in these groups.[19]While 87.5% of the severely thrombocytopenic neonates had to stay longer than a week, they also spent more time on IV fluids and supplemental oxygen. These findings in the present study are in agreement with earlier reported studies.[20] This might be related to the severity of the underlying sickness in these neonates or the increased incidence of complications during their stay. The mortality rate was very high, 37%, among the severely thrombocytopenic neonates, while only 3.72% and 3.92%, respectively, in the mild to moderate and no thrombocytopenia groups. The proportion of a "non-satisfactory" outcome was more (80.39%) in the mild to moderate thrombocytopenia group, while it was 30 and 52.77% in the severe thrombocytopenia and no thrombocytopenia group. Hence a poor immediate outcome was associated with thrombocytopenia. This association might be due to an increased susceptibility of neonates to complications in the severely thrombocytopenic group.[21]Observation of outcome after 3 months of discharge showed that of 140 cases, there were 20 mortalities, and 18 were lost for follow-up. Those 18 cases lost for follow-up were excluded while assessing the outcome in the different groups. Higher mortality of 17 (37%) was reported in the severe thrombocytopenia group (Group IIb) as compared to moderate thrombocytopenia group 3(3.92%) mortality. Gupta et al. also reported similar findings in their investigations.[22]The efficacy of the treatment protocol practised in our NICU was assessed based on the percentage increase in platelet count 24 hours after blood or platelet transfusion. It was found that though platelet transfusion produced a higher increment in platelet count compared to fresh whole blood transfusion, the discrepancy was not statistically significant (p<0.001). It can be concluded that fresh whole-blood transfusion might not be as good an option as platelet transfusion in severe thrombocytopenia. Still, it could be a good alternative to platelet concentrates in times of its unavailability. These findings in our study are in agreement with earlier reported studies.[23]

CONCLUSION

Thrombocytopenia is a highly prevalent condition among our NICU admission. The most significant and frequent cause of it is septicaemia. Several maternal and neonatal causes can bring on thrombocytopenia. Severe thrombocytopenia upon presentation is strongly linked to immediate and short-term poor outcomes. The most important finding of our research was the possibility of using severe thrombocytopenia in sick neonates as a prognostic marker. However, further research with comparable findings is needed before we can generalise this statement and apply it to other newborn hospitalizations. Fresh whole blood transfusion is a good alternative to platelet concentrates in treating severe thrombocytopenia.

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