A Study of Clinical Profile, Treatment and Outcome of Neonatal Thrombocytopenia

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Abstract: Neonatal thrombocytopenia is one of the most common hematological problems encountered in the NICU. We designed a study to determine the frequency, etiological profile, predisposing factors of thrombocytopenia in our NICU. The clinical impact of thrombocytopenia and its influence on the neonate's outcome were also studied. Methods: 179 consecutive NICU admissions in a 6 month period were included in our study. The subjects were grouped into 3 cohorts based on their platelet counts and their association with various variables was studied. The efficacy of the treatment protocol practiced for thrombocytopenia was evaluated. The neonates were followed up over a period of 6 months. To assess the prognostic value of severe thrombocytopenia; 12 variables that were significantly associated with poor outcome in the univariate analysis including low platelet count, along with other variables that are known to be associated with a poor outcome in NICU graduates, were subjected to multiple logistic regression using SPSS 13.0. Results: The prevalence of thrombocytopenia in our NICU was 39%. Septicemia was the common etiology. Maternal PIH, age at presentation, NEC, DIC, candiduria and assisted ventilation were identified as the predisposing factors. Severe thrombocytopenia was independently associated with a poor outcome based on multiple logistic regressions. Conclusion: Neonatal thrombocytopenia is far more common in our NICU as compared to that of the western studies. Septicemia is the most common cause. There are various predisposing factors for neonatal thrombocytopenia. Severe thrombocytopenic neonates are more likely to bleed and have a prolonged clinical course. Severe thrombocytopenia can be used as a prognostic indicator in sick NICU graduates. Fresh whole blood transfusion is a good alternative to platelet concentrates in the treatment of severe thrombocytopenia.
Keywords: Clinical Profile, Neonatal, Thrombocytopenia.

INTRODUCTION

A Total platelet count of < 1.5 lakh/cumm is defined as thrombocytopenia irrespective of the age of the individual [1]. With the exception of phlebotomy-induced anemia, thrombocytopenia is the commonest hematological abnormality encountered in the NICU (Neonatal intensive care unit) [2]. A quarter of all neonates admitted to NICU develop thrombocytopenia and in 20 % of them, it is severe, with the count falling below 50,000/μL. But only 1-2 % of healthy full-term neonates are thrombocytopenic [3]. In the past decade, there have been a lot of research articles pouring in regarding the etiopathogenesis, clinical presentation, and management of this entity, neonatal thrombocytopenia in the NICU. The influence of thrombocytopenia on the outcome of the neonate is a subject that has not been studied in detail in the past. Neither have articles assessed the value of neonatal thrombocytopenia as a prognostic indicator in sick neonates. The data is sparse regarding the neonatal thrombocytopenia in India [4]. The paucity of studies from India and the increasing prevalence of this condition in our NICU instigated us to take up a study that would assess the frequency, clinical spectrum and etiological profile and outcome of neonatal thrombocytopenia, in cases admitted to our NICU. NICU (level 3) at Prathima Institute of Medical Sciences, Karimnagar, is fully equipped with facilities to provide intensive care for preterm, small for gestational age babies. All neonates who were admitted in NICU were included in the study regardless of the cause of admission which helped us to assess the prevalence of thrombocytopenia in our NICU as a whole and also the etiological profile, clinical spectrum and outcome of neonates with thrombocytopenia.

MATERIALS AND METHODS

The present study was conducted in the Department of Pediatrics, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Institutional Ethical committee permission was obtained for the study. At admission, the parents and/ or the guardian were informed about the study and an oral 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. A previous History of PIH, Gestational Diabetes Mellitus, premature rupture of membrane, Rh Isoimmunization in the mother was recorded. 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 the Gestational age of all neonates was determined based on the New Ballard's scoring system [5]. 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. Other common sites of bleeding were also looked for. All the neonates underwent necessary blood investigations; Complete blood counts, Peripheral smear study, Blood culture. Peripheral smear study, blood cultures were done using standard laboratory methodology. CRP value of more than 6mg/dl was considered as abnormal. The next Step was to group the neonates, based on their platelet counts at admission. Group I / (Non thrombocytopenic) NTHR ≥150,000, Group II / (Thrombocytopenic) THR <150,000/μL, Group IIa / (Mild to moderate thrombocytopenia) <150,000/μL and ≥50,000/μL MTHR Group IIb / (severe thrombocytopenia) STHR < 50,000/μL, All cases in group IIb (STHR) investigations such as prothrombin time (PT), activated thromboplastin time (aPTT) was done as per standard protocol. The

following values were considered normal. Normal PT: 14-22 sec., Normal aPTT: 28-55 sec Platelet counts were repeated 24 hours after medical intervention in all cases in Group II (THR). Other investigations such as chest X-ray, neurosonogram, and CT brain were performed whenever the need arose. 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 as below. All neonates were followed up at least once in two weeks for a period of 6 months. In each visit, a detailed physical examination was done. Weight and Head circumference were measured and plotted on the Agarwal growth and development chart for affluent Indian children [6]. Growth parameter at a point of time lying below the 3rd percentile was considered to be abnormal. Neurodevelopment was assessed using the Denver II scale [7, 8]. Eight out of the 179 cases studied were lost for follow up and the details of their health status were not known hence they were excluded while assessing the outcome in the neonates.

RESULTS

A total of 179 consecutive neonatal admissions were included in our study as per the inclusion and exclusion criteria laid down. The subjects were divided into three groups based on their platelet counts, as has already been mentioned.

Table-1: divisions of the neonatal thrombocytopenia

Groups of Percentage of subjects the total	Description	Number of patients	Percentage
Group I	No Thrombocytopenia (≥150,000/μL)	108	61%
Group II	Thrombocytopenia (<150,000/μL)	51	28%
Group IIa	Mild to moderate thrombocytopenia < 150,000/μL and > 50000/μL	20	11%
Group IIb	Severe thrombocytopenia >50,000/μL	20	11%

The prevalence of thrombocytopenia was 39%. The prevalence of severe thrombocytopenia (<50,000/μL) was 11%. Severe thrombocytopenia accounted for 28.17% of all neonatal thrombocytopenias. The mean platelet count for all the groups was 1.603± 0.71 lakhs/cumm. It was significantly associated with thrombocytopenia. In both groups, IIa and IIb the prevalence of maternal PIH were high (27.45% & 95%) respectively. The P value obtained by the Chi-square method was <0.001 and it was highly significant. The odds ratio of thrombocytopenia and Maternal PIH was also calculated and it was 4.8 with a confidence interval of 2.4-9.3. Other maternal factors such as gestational

diabetes mellitus, Rh incompatibility, and premature rupture of membrane, antepartum hemorrhage, place, and mode of delivery were not significantly associated with thrombocytopenia. In both groups, IIa and IIb the prevalence of maternal PIH was high (27.45% & 95%) respectively. The P value obtained by the Chi-square method was <0.001 and it was highly significant. The odds ratio of thrombocytopenia and Maternal PIH was also calculated and it was 4.8 with a confidence interval of 2.4-9.3. Other maternal factors such as gestational diabetes mellitus, Rh incompatibility, premature rupture of membrane, antepartum hemorrhage, place, and mode of delivery were not significantly associated with thrombocytopenia.

Table-2: Maternal PIH and thrombocytopenia

	Group I	Percentage within group	Group IIa	Percentage within group	Group IIb	Percentage within group
H/O Maternal PIH present	21	19.44	14	27.45	19	95
No history of maternal PIH	87	80.55	36	70.85	1	5

It was observed that in group IIb (severe thrombocytopenia) that a higher proportion of cases had presented after 72 hours (55%) compared to the other two groups (25 & 21.57%). This association was statistically significant and shows that in our study severely thrombocytopenic neonates tend to present later than 72 hours compared with cases with mild to moderate thrombocytopenia and no thrombocytopenia. Septicemia, as proven by blood culture, was significantly associated with thrombocytopenia. While the prevalence of septicemia was 60% in the severely thrombocytopenic group, it was 33 and 25% in the mild to moderate and no thrombocytopenia group respectively. NEC was significantly associated with thrombocytopenia with 10% and 11% of babies from Group IIa and Group IIb, respectively, being diagnosed with NEC. While there were no cases of NEC in the Group I.

Table-3: showing the association of NEC with thrombocytopenia in different groups

	Group I	Percentage within group	Group IIa	Percentage within group	Group IIb	Percentage within group	P value
NEC	0	0	6	11.76	2	10	<0.001

The prevalence of bleeding was 50% in the severely thrombocytopenic group while it was 15.7% and 19.6% respectively in the mild to moderate and no thrombocytopenia group respectively. The mortality was significantly high in the severely thrombocytopenic group (60%) compared to the other two groups 3.7 & 3.92% respectively. The proportion of babies with a not satisfactory immediate outcome was higher in the mild to the moderate thrombocytopenic group and no thrombocytopenia group Out of the 179 cases there were 18 mortalities, 8 of them were lost for follow up. Those 8 cases that were lost for follow up were excluded while assessing the outcome in the different groups.

DISCUSSION

A considerable number of studies has shown that the average fetal platelet count is above 150,000 / μL by II trimester of pregnancy and that it remains fairly constant thereafter [6]. So by implication, platelet counts in neonates, irrespective of their gestation ages, below 150,000/μL represents thrombocytopenia just as in older children and adults. Some authors classify NT into mild (<150,000/μL and ≥ 100,000/μL), moderate (<100,000/μL and ≥ 50,000/μL), severe (<50,000/μL) [1, 2]. Thrombocytopenia is present in 0.7-2 % of all newborn births in the generation population while severe thrombocytopenia occurs in 0.1-0.25 % [7, 8]. A population-based surveillance study done on cord blood samples from 4489 term infants showed that 2% of the generation population was thrombocytopenic at birth and only 0.24 % had a platelet count < 50,000/μL (severe thrombocytopenia) [9]. Another large-scale study conducted by Uhryonowska et al; showed an incidence of 0.9 % among the generation population [8]. In both the studies the common cause for severe thrombocytopenia in healthy term infants was alloimmune thrombocytopenia. DIC occurs in 10% of sick infants admitted to NICU [7]. In neonates, it usually complicates severe illness, such as bacterial/viral sepsis, HMD, MAS or asphyxia. Thrombocytopenia along with prolonged PT, APTT, increased FDP, increased D-dimers with decreased fibrinogen levels are the lab abnormalities in DIC [10]. In 40- 50% of cases of DIC the platelet count falls below 50,000/μl. 80-90% of patients with NEC develop Thrombocytopenia and many have platelets in the range of 30,000 to 60,000/μl [11]. In the study conducted by Castle et al; birth asphyxia was significantly associated with Thrombocytopenia [12]. So did Oren et al; who also reported that birth asphyxia was more common in Thrombocytopenia than non-thrombocytopenics [13]. The underlying cause might be either hypoxia impairing the megakaryopoiesis or the prevalence of thrombocytopenia was 39% and severe thrombocytopenia was 11% in our NICU The most common etiologic association with thrombocytopenia was septicemia; Maternal PIH was significantly associated with neonatal thrombocytopenia. Neonatal factors associated with neonatal thrombocytopenia, especially severe thrombocytopenia, were an age at presentation, septicemia, DIC, NEC and assisted ventilation. Mucosal bleeding was significantly associated with thrombocytopenia (P=0.002). While 50% of the severely thrombocytopenic neonates had mucosal bleeding only 15.7% and 19.6% of the other two groups had the bleeding tendency. The types of bleeding included G.I bleed and bleed from the E.T. tube (pulmonary hemorrhage) and bleeding from the oral cavity. This association reflects that severely thrombocytopenic neonates are more prone to bleed. Investigations to rule out IC bleed i.e. neurosonogram

and CT brain were done only in 37 cases of the 179. Among these cases, the majority (56.8%) were severely thrombocytopenic. Among severely thrombocytopenic cases 13 underwent neurodiagnostic workup, 8 turned out to have IC bleed. Hence there was as a strong correlation between IC bleed and severe thrombocytopenia (P<0.01).

The incidence of petechiae and purpura was significantly associated with severe thrombocytopenia (P<0.001) with 45% of these neonates having them. This association has been well reported and documented in the past [14]. The most common symptom other than bleeding was "not feeding well". But this symptom is a nonspecific one that can be associated with any sick neonate. Hence this finding is of not much clinical significance. The most common sign other than bleeding in the severely thrombocytopenic group was delayed capillary refill (>3sec). This association might either be due to shock in sick, especially septicemic neonates, who are known to have severe thrombocytopenia or might be due to excessive blood loss [15]. But we couldn't document hypotension due to the unavailability of continuous intra-arterial BP monitoring. 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 the higher degree of severity of the underlying illness or due to the effect of sample size, in the severely thrombocytopenic group. Short-term outcome at 6 months Proportion of poor neurodevelopmental outcome was significantly higher (31.57%) among the severely thrombocytopenic neonates compared to the other two groups. If severe thrombocytopenia itself was responsible for the poor outcome, then all the neonates with severe thrombocytopenia and poor outcome should have had IC bleed. But 33.3% of neonates with both severe thrombocytopenia and the poor outcome did not have radiological evidence of IC bleed. So probably the underlying pathology, that produced a low platelet count, might have also affected the developing brain detrimentally. Hence severe thrombocytopenia might just be a marker of the severity of the underlying illness that led to the poor outcome, rather than being its direct cause. Severe thrombocytopenia is an independent risk factor for poor outcome.

CONCLUSION
It can be concluded that thrombocytopenia is very much common among our NICU admissions. Septicemia was 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 is very much associated with severe thrombocytopenia at presentation.

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