



## A Study On Etiology Of Clinical Profile And Outcome Of Neonatal Thrombocytopenia

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### Abstract

#### Background

Thrombocytopenia is defined as a platelet count of less than 1.5 lakhs / cu. mm, regardless of gestational age. Early-onset (less than 72 hrs) has a benign and predictable outcome, whereas late-onset (more than 72 hrs) is more severe. In the past decade, there has been a lot of research regarding the etiology, clinical profile, and management of neonatal thrombocytopenia.

**Aim And Objectives:** Our study is aimed at finding out the etiological profile, studying the clinical spectrum and immediate outcome of neonates admitted with thrombocytopenia in our NICU. Predisposing factors of neonatal thrombocytopenia.

**Methods:** This study also helped us to assess the various factors predisposing to neonatal thrombocytopenia and the efficacy of the treatment protocol to manage neonatal thrombocytopenia practiced in our NICU at the Department Of Paediatrics, Government Medical College, Karur in the year 2021. The neonates admitted to our NICU for various reasons first underwent a screening test of complete blood count. Those neonates who were found to have low platelet counts ( $\leq 1,50,000 \mu\text{L}$ ) were included in the study. As per the proforma, a detailed history which included maternal history like age of the mother, parity, details of the previous pregnancy, blood group of the mother, history of intake of drugs that would lead to thrombocytopenia, complications of the present pregnancy like PIH, gestational diabetes mellitus and antenatal ultrasound findings. Regarding labour, the time of onset of rupture of membranes, any antepartum bleed, mode and place of delivery, APGAR scores, and in cases of birth asphyxia the detailed resuscitative measures done were enquired and recorded. The asphyxiated babies were further classified based on the sarnat staging. Gestational age assessment was done based on New Ballard „s scoring system. Every neonate underwent a detailed physical examination to find a cause for thrombocytopenia or the effect of thrombocytopenia such as mucosal bleeding in the form of GI bleeding, petechiae, purpura, etc. Gastric lavage was done in all the neonates to check for any altered blood in the gastric aspirate. Other signs of bleeding were also looked for. The babies were closely monitored for shock.

**Results:** The study group consists of 42% of term babies and 58% of preterm babies. Among the severely thrombocytopenic infants in the study group, 45% were term babies and 55% were preterm babies. Around half of the preterm babies included in the study group were late preterm. 28% of preterm babies had severe thrombocytopenia. Maternal PIH was significantly associated with thrombocytopenia. The p-value obtained by the Chi-square method was 0.00 which is significantly high. Other maternal factors such as GDM, Rh incompatibility, APH, PROM, and mode of delivery were not significantly associated with thrombocytopenia. Septicemia as proven by blood culture was found to be significantly associated with thrombocytopenia. The prevalence of septicemia was significantly high in both groups. The incidence of severe thrombocytopenia was

significantly high in gram-negative sepsis when compared to gram-positive sepsis. DVC was found to be strongly associated with severe thrombocytopenia. In the study group, 35 cases had DIVC (7%) of which 4% were due to sepsis and 3% were due to birth asphyxia. Cases with DIVC had a significant mortality of around 91%. While one-third of the cases of intramural asphyxiated babies had superadded sepsis, among extramural babies almost half of the asphyxiated babies had sepsis. The prevalence of bleed was significantly high 179 cases had some form of mucosal bleeding. This shows that severely thrombocytopenic infants bleed more frequently

**Conclusion:** Low birth weight followed by septicemia was the major etiology associated with both mild and severe thrombocytopenia. The predisposing factors associated with neonatal thrombocytopenia were maternal PIH, prematurity, septicemia, NEC, DIC, and assisted ventilation. Glaringly perinatal asphyxia was not associated with neonatal thrombocytopenia in the present study. The mortality rate (21.05%) was far more common in the severe thrombocytopenic group. Moreover, low platelet count was found to be an independent risk factor for a poor outcome in our cohort.

**Keywords:** Neonates, Thrombocytopenia, Coagulation Profile, Low Birth Weight, Septicemia

### Introduction

Thrombocytopenia is defined as a platelet count of less than 1,50,000/ $\mu$ L irrespective of the individual's age. In NICU it is the commonest hematological abnormality encountered except for phlebotomy-induced anemia.<sup>1</sup> Around 22-35% of neonates admitted to NICU will develop thrombocytopenia and 20% of them will develop severe thrombocytopenia. Neonatal thrombocytopenia is a significant cause of morbidity and mortality, particularly in sick newborns, premature babies and neonates admitted to neonatal intensive care units, and usually indicates an underlying pathologic process.<sup>2</sup> The important causes of thrombocytopenia in neonates are sepsis, birth asphyxia, prematurity, intra-uterine growth retardation, hyperbilirubinemia, respiratory distress syndrome, meconium aspiration syndrome, and low birth weight. Apart from platelet count, bleeding manifestations depend on underlying ailments.<sup>3</sup> Multiple disease processes can cause thrombocytopenia in neonates and these can Among healthy-term infants, the incidence of thrombocytopenia ranges from 0.7 to 0.9%.<sup>4</sup> The paucity of studies from Indian literature and the increasing prevalence of this condition in our NICU, instigated us to take up this study which would assess the frequency, clinical spectrum, etiological profile, and short-term outcome of neonatal thrombocytopenia cases admitted in our NICU.<sup>5</sup>

**Methods:** This study also helped us to assess the various factors predisposing to neonatal

thrombocytopenia and the efficacy of the treatment protocol to manage neonatal thrombocytopenia practiced in our NICU at the Department Of Paediatrics, Government Medical College, Karur in the year 2021. The neonates admitted to our NICU for various reasons first underwent a screening test of complete blood count. Those neonates who were found to have low platelet counts( $\leq$ 1,50,000 $\mu$ L) were included in the study. As per the proforma, a detailed history which included maternal history like age of the mother, parity, details of the previous pregnancy, blood group of the mother, history of intake of drugs that would lead to thrombocytopenia, complications of the present pregnancy like PIH, gestational diabetes mellitus and antenatal ultrasound findings. Regarding labour, the time of onset of rupture of membranes, any antepartum bleed, mode and place of delivery, APGAR scores, and in cases of birth asphyxia the detailed resuscitative measures done were enquired and recorded. The asphyxiated babies were further classified based on the sarnat staging. Gestational age assessment was done based on the New Ballards scoring system. Every neonate underwent a detailed physical examination to find a cause for thrombocytopenia or the effect of thrombocytopenia such as mucosal bleeding in the form of GI bleeding, petechiae, purpura, etc. Gastric lavage was done in all the neonates to check for any altered blood in the gastric aspirate. Other signs of bleeding were also looked for. The babies were closely monitored for shock. Inclusion criteria: Neonates admitted to our NICU who were found to

be thrombocytopenic were included in the study group. Exclusion criteria: Neonates whose parents or guardians did not give consent for the study were excluded from the study. Under strict aseptic precautions, venepuncture is done and blood was collected in sterile EDTA tubes and shifted immediately to the hospital laboratory within 10-15 minutes. Complete blood count was done using an automated hematology analyzer. Using the standard methodology, peripheral smears were done. The septic work which included C reactive protein, and blood cultures was done in all the neonates included in the study group. After this, the neonates were grouped into two groups based on their platelet

counts. Group, I included those neonates with a platelet count between 50,000/cu.mm –1, 50,000/cu.mm. Group II included neonates with a platelet count of <50,000/cu.mm. The neonates in whom DIVC was suspected underwent screening for DIVC by measuring prothrombin time(PT), activated thromboplastin time( aPTT), and fibrinogen levels. After the appropriate treatment, a repeat platelet count was done to know the prognosis of the baby. Whenever needed other investigations like an X-ray chest, Ultrasound cranium, and CT Brain were done. The diagnosis was made based on standard diagnostic criteria as per the medical literature.

**Results**

**Table :1 Distribution Of The Study Group Based On The Platelet Count:**

<b>THROMBOCYTOPENIA</b>	<b>Number</b>	<b>Percentage</b>
GROUP-I Mild–Moderate Thrombocytopenia	355	71
GROUP-II -Severe thrombocytopenia	145	29
<b>TOTAL</b>	500	100
Range (Min-Max)	25,000 – 1,40,000	

**Figure 1: Distribution Of Etiology Among The 145 Cases Of Severe Thrombocytopenia**

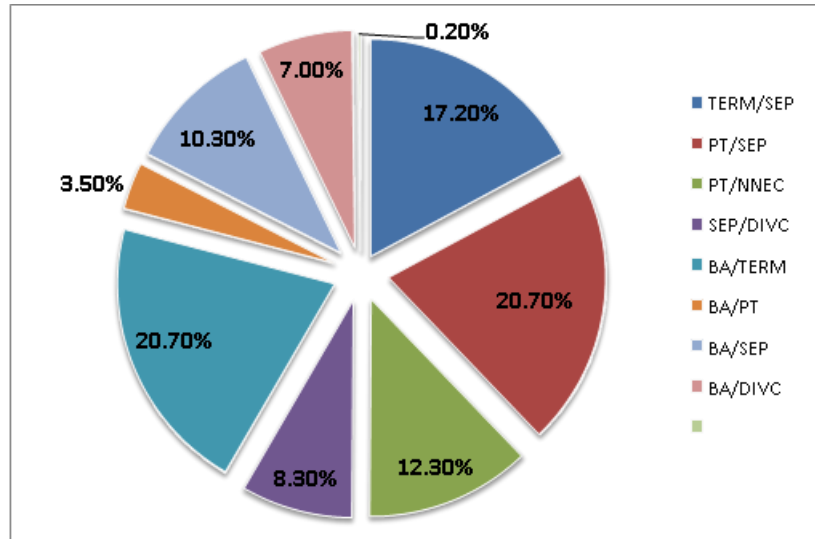


Figure :1 As depicted in the pie charts, the most common cause in both the groups is Septicemia which is followed by birth asphyxia

**Table 2 Based On The Gestational Age**

	NO OF CASES	TERM- 210	PRETERM- 290
GROUP I	355	145(41%)	210(59%)
GROUP II	145	65(45%)	80(55%)

Table:2 The study group consists of 42% of term babies and 58% of preterm babies. Among the severely thrombocytopenic infants in the study group, 45% were term babies and 55% were preterm babies.

**Table 3 Distribution Based On Weight:**

Weight	GROUP I	GROUP II
<= 1 KG	9(3%)	10(6.6%)
1-2 KG	145(42%)	76(50%)
>2 KG	196(55%)	64(43.4%)

The above table shows that majority of the cases in group II were LBW infants with a birth weight of 1-2 kg.

**Table 4: Platelet Count And Pih Status**

	GROUP-I		GROUP-II	
	No of Patients ( N )	Percentage ( % )	No of Patients ( N )	Percentage ( % )
WITH PIH	55	15.50	85	58.60
WITHOUT PIH	300	78.90	60	41.40
TOTAL	355	100	145	100
Chi-square	19.57			
p-value	0.001 (SIGNIFICANT)			

**Table 5: The Distribution Of Early Onset Thrombocytopenia:**

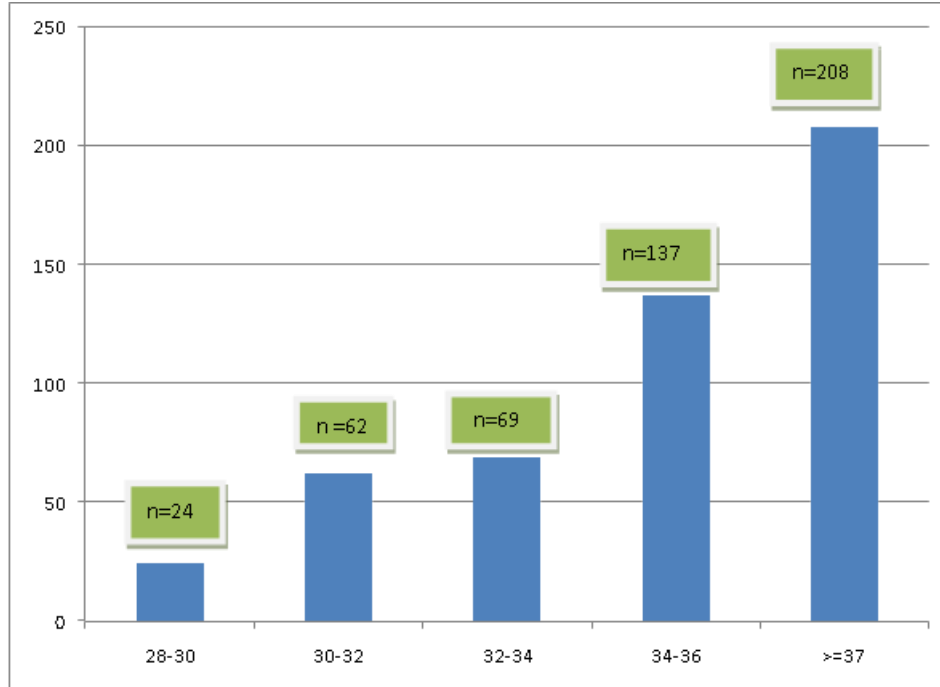
	NO OF CASES-205
DAY 1	10(5%)
DAY 2	118(59%)
DAY 3	77(37%)

**Table 6: The Distribution Of Late-Onset Thrombocytopenia:**

	NO OF CASES-295
DAY 4-10	216(73%)
DAY 11-20	65(22%)
DAY 21-29	14(5%)

The cases in the two groups were further divided into six subgroups each based on their age at presentation. It was observed that a significantly higher proportion of cases presented only after 72 hours.

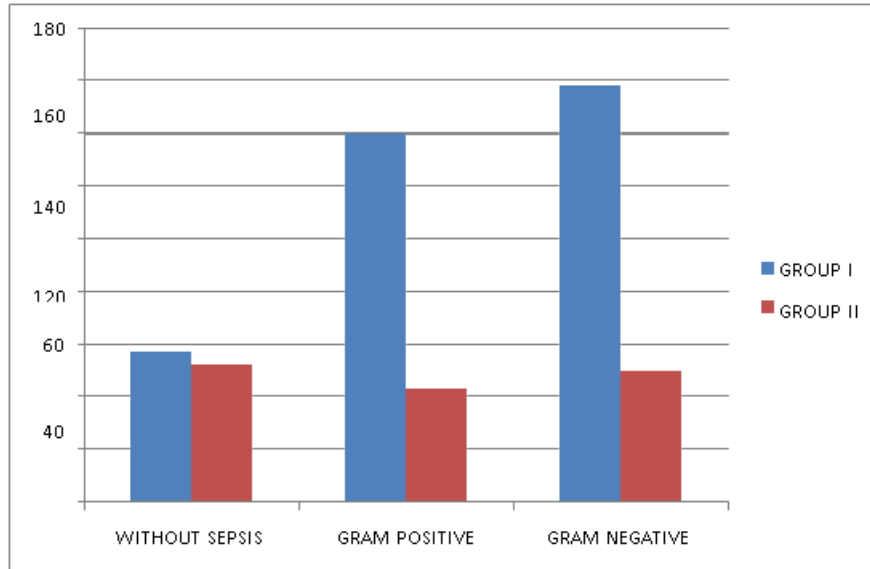
**Graph 2: Showing The Distribution Based On The Gestational Age And Platelet Count**



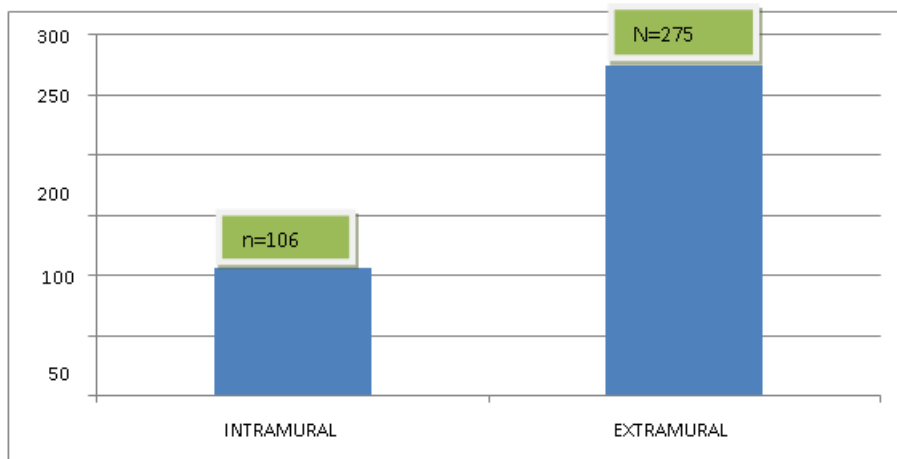
**Table 7:Platelet Count And Sepsis Workup**

SEPSIS WORK UP	GROUP-I		GROUP-II	
	No of Patients ( N )	Percentage ( % )	No of Patients ( N )	Percentage ( % )
CULTURE POSITIVE	298	84	93	64
CULTURE NEGATIVE	57	16	52	36
TOTAL	355	100	145	100
Chi-square	7.79			
p-value	0.01(significant)			

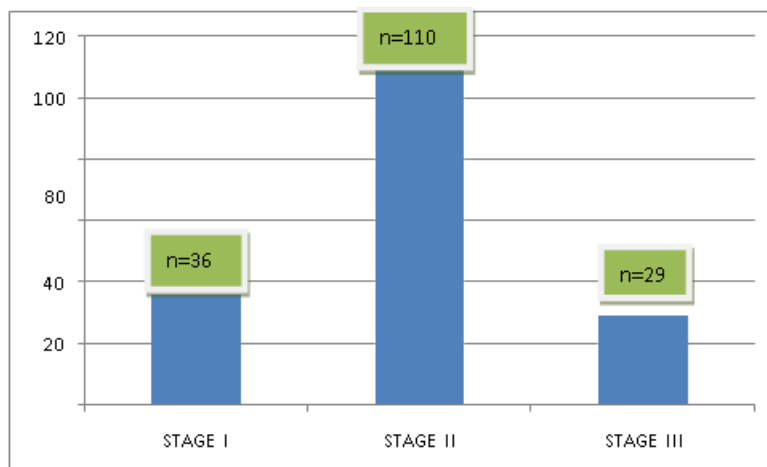
**Graph : 3 Platelet Count And Sepsis Workup**



**Graph 4: Showing The Distribution Of Septicemia Cases Among Extramural And Intramural Cases**



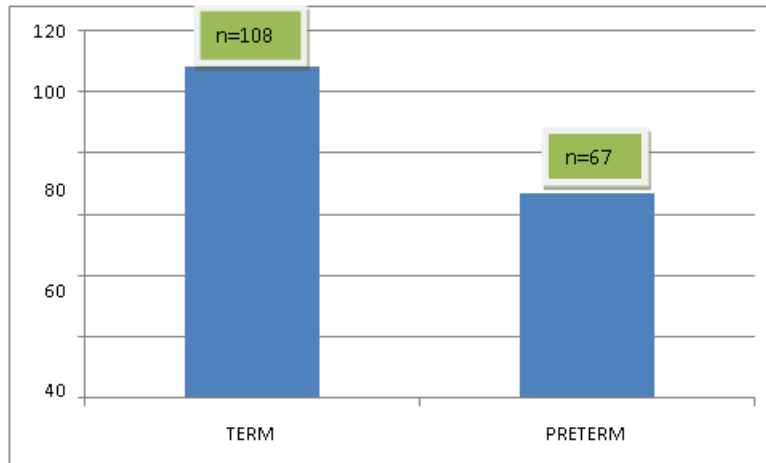
**Graph:5 Distribution Of Birth Asphyxia Cases**



The birth asphyxia cases in the study group (175) were classified based on the sarnat staging into three categories. The majority of the cases were in stage 2.

Term babies were more commonly asphyxiated than preterm babies in the study group. This is clearly shown in the following table:

**Figure 6: Showing The Distribution Of Birth Asphyxia Cases Among Term And Preterm Babies**



In our study male babies were seen as more commonly asphyxiated than female babies.

**Table:8 Platelet Count And Bleeding**

TYPE OF BLEEDING	GROUP-I		GROUP-II	
	No of Patients (N)	Percentage ( % )	No of Patients (N)	Percentage ( % )
WITH BLEED	47	13.20	132	91
NO BLEED	308	86.80	13	9
TOTAL	355	100	145	100
Chi-square	57.81			
p-value	0.000(SIGNIFICANT)			

The prevalence of bleed was significantly high. 179 cases had some form of mucosal bleeding. In group, I the prevalence was 13% whereas in group II it was higher at 91%. This shows that severely thrombocytopenic infants bleed more frequently. The p-value was calculated by chi-square test and found to be 0.00 which was significantly high. Petechiae are less than 1 cm in size, red circumscribed and nonblanchable lesions and purpura are the same lesions when more than 1 cm in size. 40% of the cases in group II had this type of skin bleed



**Table:9 The Type Of Bleed**

BLEED TYPE	TOTAL	GROUP I	GROUP II
GI BLEED	140(80%)	42	98
SKIN (PETECHIAE/PURPURA)	25(14.2%)	8	17
GI/PULMONARY	15(8.5%)	4	11
GI/SKIN	15(8.5%)	-	15

**Table 10: The Mortality Pattern**

GROUP I- 30 CASES		GROUP II-82 CASES			
SEPSIS	BIRTH ASPHYXIA + SEPSIS	SEPSIS	BIRTH ASPHYXIA + SEPSIS	BIRTH ASPHYXIA	IU INF
12	18	26	25	30	1
GRAM POSITIVE-10 GRAM NEGATIVE-20		GRAM POSITIVE-21 GRAM NEGATIVE-30			

Sepsis was the most common cause of death among both groups. Among sepsis, gram-negative septicemia caused higher mortality when compared to gram-positive sepsis.

**Table 11: The Pattern Of Mortality In Group I:**

NO OF CASES	TERM	PRETERM	MCH	FCH	EXTRAMURAL	INTRAMURAL

	14	16	19	21	25	5
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Among group I babies, the extramural babies had higher mortality when compared to their counterparts. The mortality pattern was almost the same among term and preterm infants.

**Table 12: The Pattern Of Mortality In Group Ii:**

	TERM	PRETERM	MCH	FCH	EXTRAMURAL	INTRAMURAL
NO OF CASES	42	40	63	19	60	22

Among group II babies, a higher proportion of mortality was seen among extramural babies and male babies when compared to their counterparts due to the relatively higher incidence of sepsis and birth asphyxia among these babies in the study group.

**Discussion**

A common hematological abnormality encountered in NICU is neonatal thrombocytopenia. There are many predisposing factors for thrombocytopenias and they interact in a complex manner to cause thrombocytopenia. Like other illnesses, the manifestations are variable and the severe form of neonatal thrombocytopenia is very well documented to be associated with poor outcomes.<sup>6</sup> The total number of admissions in the study period was calculated which was around 2437 and the incidence of thrombocytopenia was found to be 21% which is almost similar to the other studies in which it ranges from 20%-40%. Similar to the other Indian studies, the etiological profile in our study showed septicemia and perinatal asphyxia as the common causes for neonatal thrombocytopenias. In both groups, septicemia accounted for most of the cases. Perinatal asphyxia was the next most common cause.<sup>7</sup> According to Western medical literature, prematurity, IUGR, and birth asphyxia were the common causes of neonatal thrombocytopenias whereas in our study septicemia was the common cause. The mechanism by which septicemia leads to thrombocytopenia is by

both decreased platelet production as well as increased platelet consumption and sequestration in the enlarged spleen usually resulting in severe thrombocytopenia. This difference may be due to the higher incidence of septicemia in our extramural admissions thus clearly showing the need for strict aseptic precautions while conducting deliveries as well as in handling newborn babies.<sup>8</sup> Intrauterine infection, CMV infection causing thrombocytopenia was found in a case. The baby had hepatosplenomegaly, and severe thrombocytopenia causing purpuric spots and mucosal bleeding. CT Brain showed diffuse calcifications. The baby died despite platelet and blood transfusions on the tenth day of life. The male-female sex ratio in our study was 1.3:1. Majority of the severely thrombocytopenic infants were male babies.<sup>9</sup> Maternal PIH had a significant association with neonatal thrombocytopenia in our study. This is following the study conducted by Burrows et al<sup>41</sup>. In our study maternal PIH was more commonly associated with severe thrombocytopenia whereas in other studies it was associated with mild to moderate forms.<sup>10</sup> This discrepancy once again can be explained by the fact

that these high-risk infants would have succumbed to infections more commonly than other babies leading to severe forms of thrombocytopenia. Other factors like GDM, Rh incompatibility, APH, mode of delivery, and gestational age were not significantly associated with thrombocytopenia in our study, unlike other studies where there is strong documentation for the association of these factors.<sup>11</sup> In our study, 59% of infants presented after 72 hours of life. This finding is in association with other studies which show a well-documented finding that the majority of the severely thrombocytopenic infants presented only after 72 hours of life and the most common etiology in the late-onset sepsis are the acquired causes such as septicemia and associated factors.<sup>12</sup> There was a strong association between septicemia with low platelet counts particularly the severe forms of thrombocytopenia in our study. The P value was found to be 0.02. This is following other studies where septicemia is a well-recognized risk factor for low platelet counts in neonates admitted to NICU.<sup>13</sup> According to Western literature, around 10% of babies with sepsis and severe thrombocytopenia had DIVC. In our study, around 7% of cases had DIVC. The exotoxins and lipopolysaccharide of the bacteria will cause endothelial dysfunction contributing to DIVC.<sup>14</sup> Regarding the incidence of thrombocytopenia among gram-positive and gram-negative sepsis, there are more controversies. While some studies show that there is an association between gram-negative sepsis and thrombocytopenia many other studies fail to show such an association. This may be explained by the pathological variations in the mechanism of sepsis among various organisms.<sup>15</sup> In our study there is a slightly higher incidence of low platelet count as well as mortality among gram-negative sepsis when compared to gram-positive sepsis. Around 44.5% of group I and 34% of group II babies had gram-negative sepsis. In our study, there was a significant association between birth asphyxia and thrombocytopenia.<sup>16</sup> The P value was found to be 0.01. It is in concordance with most other literature

showing a significant association of perinatal asphyxia with low platelet counts. Other factors such as exchange transfusion, hyperbilirubinemia, RDS, and MAS were not significantly associated with thrombocytopenia.<sup>17</sup> Exchange transfusion done using non-fresh blood can lead to thrombocytopenia. Since in our study only fresh whole blood was used for this purpose there was no significant association of exchange transfusion with thrombocytopenia.<sup>18</sup> Several studies showed severely thrombocytopenic infants bleed more frequently than their normal counterparts. In our study mucosal bleed was significantly associated with thrombocytopenia. While 13% of group I infants had some form of bleed, among group II infants around 90% had some form of bleed like G.I. bleeding, pulmonary hemorrhage, and skin bleeding.<sup>19</sup> Other than bleeding the most common sign is prolonged capillary refilling time (>3 sec) this association could be either due to the onset of shock due to septicemia or may be due to bleeding which could have caused shock. The most common symptom other than bleed is not feeding well. It is a nonspecific symptom that is not of much clinical use.<sup>20</sup> The mean duration of hospital stay in group I was 7 days while it was 13 days in severely thrombocytopenic infants. It may be due to the complications and severity of the underlying illness.<sup>21</sup> The mortality rate was significantly high in the severely thrombocytopenic infants which were around 56% when compared to the group I infants in which it was 8% it may be due to the severity of the underlying illness or the incidence of higher complications in severely thrombocytopenic infants. Sepsis was the most common cause of death in both groups.<sup>22</sup> Among sepsis, gram-negative septicemia caused higher mortality when compared to gram-positive sepsis. Outborn babies had higher mortality when compared to inborn babies among group I babies. The mortality pattern was the same among term and preterm infants. Among group II babies, a higher proportion of mortality was seen among preterm when compared to term babies. Also, male babies and outborn babies

had higher mortality. On comparing extramural and intramural babies, there are an increased number of thrombocytopenic infants in extramural cases.<sup>23</sup> About 65% of cases in group I and 76% of cases in group II were born extramural. There is also a higher contribution by the extramural babies to the septicemia group and in the mortality. About half of the extramural asphyxiated babies developed sepsis during their clinical course.<sup>24</sup> The efficacy of the treatment protocol practiced in our NICU is based on the percentage increment in the platelet count after 24 hours of intervention. It was found that though platelet transfusion caused a higher increment in platelet count compared to fresh blood transfusion, the discrepancy was not high. Hence it can be concluded that fresh blood transfusion can be considered a good alternative to platelet transfusion in times of its unavailability. Early onset thrombocytopenia can be prevented by prompt management of its predisposing factors like maternal PIH by regular antenatal visits, thereby filtering the high-risk pregnancies that need tertiary-level care. Early onset sepsis should also be prevented by following strict asepsis while conducting deliveries when handling the newborn and by the use of intrapartum antibiotics in high-risk pregnancies.<sup>25</sup>

## Conclusion

Septicemia is the most common and most important cause of neonatal thrombocytopenia which in its severe form leads to a higher mortality rate. Hence it will be easier and cost-effective to prevent thrombocytopenia and its death by preventing the occurrence of sepsis rather than by treating these dreadful infections with higher antibiotics later in the course of the illness. This can be achieved by following strictly the 5 cleans while conducting deliveries, following strict asepsis routines while handling newborn babies, and educating the mother about the awareness of personal cleanliness during the third trimester and feeding and good child-rearing practices.

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