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# A Study of Thrombocytopenia in Sick Neonates in a Tertiary Care Centre

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**Abstract:** Thrombocytopenia is the most common haematological abnormality in sick newborns occurring in almost one third of NICU admissions. To study the incidence of thrombocytopenia in sick neonates and its relation with various clinical problems of neonates. This observational prospective study was conducted at the Neonatal Intensive Care Unit of a tertiary care centre over one year. 272 sick neonates, irrespective of birth weight and gestational age, were evaluated for thrombocytopenia. Their clinical problems were also evaluated in relation to the thrombocytopenia. Data was analyzed using SPSS version17. Descriptive statistics were given as the mean, standard deviation, and percentage. A $\chi^2$-test was used for analysis of qualitative data. A non-parametric test was used for analysis of two independent quantitative variables. The incidence of thrombocytopenia was observed at 35.30 % of the studied sick neonates. Mean age of thrombocytopenic cases was 92.86 [+_143.75] hrs and 61.5% of these cases had early onset thrombocytopenia. The thrombocytopenic cases showed significant association ($p<0.05$) with factors such as small for gestational age, prematurity, septicemia, perinatal asphyxia and preeclampsia. The mortality was considerably higher in thrombocytopenic sick newborns ($p< 0.05$) and mortality showed a direct correlation in cases who had septicemia, and were small for gestational age ($p< 0.05$) . Since every third sick neonate in our study had thrombocytopenia and its related complication which could lead to mortality, we strongly emphasize the need to monitor platelet counts in all sick neonates so as to improve the probabilities of survival.
**Keywords:** thrombocytopenia, sick neonate

## INTRODUCTION

Thrombocytopenia is a significant cause of morbidity and mortality in the sick pre-and full-term babies [1]. It a common clinical problem in neonatal care units. The frequency of neonatal thrombocytopenia has been estimated to range from 1% or more for the healthy full-term infant to 20% of the newborns admitted to NICU [2].

Thrombocytopenia as per various studies has been defined as platelet count of less than 150 x 109/L; it needs investigations and, at times, treatment [3]. Normally the fetal platelet count is above 150 x10 9/L after second trimester of pregnancy and remains fairly constant after that [4-6]. The healthy new-borns have the same platelet count as that of adults. Thrombocytopenia can be mild, moderate, and severe; mild 1 lac to 1.5 lac /cc, moderate 50000 to 1.0 lac/cc and severe less than 50000/cc.

As an important component of blood, platelets are intimately involved in both vascular and clotting aspects of haemostasis. They are subjected to various inherited, congenital and acquired diseases of new-borns [7]. Most infants with thrombocytopenia are ill, premature, and have other disorders including bacteraemia and DIC and in these cases thrombocytopenia is severe even several days after birth [8]. There are a large number of placental and maternal conditions responsible for thrombocytopenia in addition to the various disorders of neonates.

About 30% of the new-borns born to the mothers with idiopathic thrombocytopenic purpura have thrombocytopenia [7, 9]. Thus, neonatal scrutiny for thrombocytopenia is justified and mandatory when there is a history of bleeding manifestations or low platelet count in the firstborns or the mother. Neonates with severe thrombocytopenia can have bleeding, which might lead to lifelong residual defects such as intracranial haemorrhage or death. Early diagnosis and adequate treatment reduces the fatal complications in both mother and neonates. Although thrombocytopenia is frequent in neonates, the frequency escapes attention

due to infrequent manifestations of clinical symptoms in these cases.

The present study is an attempt to evaluate the prevalence of thrombocytopenia in sick neonate and to study the causative factors in a tertiary level hospital in central India.

## SUBJECTS AND METHODS

This was an observational prospective study, conducted in a Level III Neonatal Intensive Care unit of Department of Paediatrics, Kamla Nehru Hospital, and Gandhi Medical College Bhopal.

A total of 272 sick neonates, intra and extramural, irrespective of gestational age and birth weight, admitted in our NICU during the study period of one year, from 1st October 2008 to 31st September 2009 were studied. Sick babies were defined as per the WHO criteria [9]. Sick new-borns having one or more of the following conditions, namely neonatal septicaemia, perinatal asphyxia, hyperbilirubinemia and RDS were included.

Four vital signs namely, age, temperature, respiratory rate, weight for age Z score were taken for identifying the sick new-born. And seven clinical findings, namely, no arousal with minimal stimulation, history of change and activity, history of convulsions, inability to suck, definite lower chest wall in drawing, crepitation's and cyanosis were included.

Amongst these sick new-borns, cases were those new-borns in which the platelet count was less than 1.5 lac/cmm and controls were those new-borns in whom platelet count was equal to 1.5 lac or more/cmm.

New-borns with gross congenital disorders and suspected congenital infections were excluded from the study. The cases were studied in four groups – neonatal sepsis, perinatal asphyxia, neonatal hyperbilirubenemia and respiratory distress and the groups were defined as per the following.

### Neonatal sepsis

These cases were included mainly on the basis of clinical signs, symptoms and various other laboratory parameters suggestive of neonatal sepsis in addition to blood culture.

### Perinatal asphyxia

Perinatal asphyxia was diagnosed on the basis of definite history of delayed cry and resuscitation and clinical examination showing signs of perinatal asphyxia.

### Neonatal hyperbilirubinemia

In all these patients, the level of serum bilirubin was in the phototherapy range or more.

### Respiratory distress

Silverman Anderson Scoring System was used to grade the respiratory distress.

### History and physical examination

All relevant perinatal risk factors, maternal history, neonatal illness, physical examination were noted on a predesigned proforma.

### Gestational age

Gestational age was calculated as the best obstetrical estimate according to the last menstrual period combined with Dubowitz gestational age scoring system.

### Maternal history

Maternal clinical characteristics included, mode of delivery, evidence of preeclampsia, prolonged preterm rupture of membranes (PROM) of one or more weeks of duration; maternal history was taken with special emphasis on previous episodes of skin and mucosal bleed, drug intake, presence of rash or fever in early gestation, consanguinity, family history of bleeding disorders, recurrent infections.

### Physical examination

Complete physical examination was performed in each neonate including gestational age at the time of delivery, birth weight, gender, and assessment of general well-being, activity, vital signs, any skin or mucosal bleed in the form of petechiae, bruises, epistaxis, hematemesis, melaena and hematuria. The infants were also examined for jaundice, pallor, congenital malformations, abdominal distension and hepatosplenomegaly. Complete neurological examination was also performed.

### Investigations

A complete blood count with peripheral film was carried out to evaluate the degree of anemia and underlying infections. The samples were collected carefully with a large bore butterfly needle to allow free flow of blood. EDTA was used as an anticoagulant. The samples were analyzed for the platelet counts as early as possible by blood smear method. At times, depending upon the availability, platelet counts were performed on a cell counter.

In cases of suspected septicemia, the possible work-up for sepsis including C-reactive proteins, the ratio of immature to the mature neutrophils, blood culture, urine complete examination and culture and CSF examination were performed.

Blood grouping, Coomb's test and serum bilirubin was estimated in cases of pathological jaundice and blood group incompatibilities. X ray chest and abdomen was done where indicated. The data was recorded after its proper validation, check for error, coding & decoding and analyzed using the software SPSS 17 for windows (SPSS Inc, Chicago, IL, USA).

## RESULTS

A total of 272 neonates were enrolled for this study and 35.3% were diagnosed with thrombocytopenia. Out of these, 61.5% developed thrombocytopenia within first 72 hours of their birth. Severe form of thrombocytopenia was observed in 14.6% of the total thrombocytopenia cases and these severe cases showed a significant association with early onset thrombocytopenia i.e. within 72 hours (P<0.015). The overall mean age of thrombocytopenic cases was similar to those of non-thrombocytopenic cases (P>0.05). Males were predominantly higher but female cases shown a significantly higher incidence of thrombocytopenia (p=0.047). Among the various clinical features studied we observed small for gestational age (p=0.035), prematurity (p=0.001), , neonatal septicemia (p=0.014), perinatal asphyxia (p=0.021) and pre-eclampsia (p=0.03) to be significantly associated with the thrombocytopenic cohort while the other factors such as birth weight, gestational age and respiratory distress syndrome were insignificant in the two cohorts. (Table -1)

The mortality observed was significantly higher among the cases of thrombocytopenia (p=0.0003) (Table -1). Considering this higher mortality we further analyzed the mortality data to check for any association of the factors between the two cohorts viz thrombocytopenic and non-thrombocytopenic and observed that NNH (p=0.008), neonatal septicemia (p=0.004) and SGA (p=0.026) significantly had higher chances of mortality as compared with the non-thrombocytopenic cohort while cases who were having HIE, pre maturity and pre-eclampsia showed better survival (Table-2).

It was found that a significant linear trend of mortality according to level of thrombocytopenia was present which suggests that as the level of thrombocytopenia increases towards the severity there were more chances of mortality (Graph -1).

**Table–1: Confounding factors in Thrombocytopenia**

| **Factors** | **Thrombocytopenic** (n=96) | **Non thrombocytopenic** (n=176) | **Significance** (p, OR, 95% CI) |
|---|---|---|---|
| Age (in hours) | 92.86 ± 143.75 | 89.83 ±136.48 | P=0.5681 [-31.71 – 37.77] |
| Sex (M/F) | 58/38 | 127/49 | P=0.047, OR=0.58 [0.34–0.99] |
| Birth Weight (in grammes) | 2150 ±0.65 | 2210 ±0.65 | P=0.2338 [-0.22 - 0.10] |
| Gestational Age (in weeks) | 36.19 ± 3.16 | 36.39 ±3.08 | P=0.3062 [-0.97 - 0.57] |
| SGA | 31.3% | 19.9% | P=0.0357, OR=1.83 [1.04–3.22] |
| Maturity (Preterm) | 43.8% | 24.4% | P=0.001, OR=2.40 [1.41 – 4.07] |
| Hyperbilirubinemia | 17.7% | 30.7% | P=0.01, OR=0.48 [0.264–0.893] |
| Neonatal septicemia | 55.2% | 39.8% | P=0.0145, OR=1.86 [1.13–3.08] |
| Perinatal asphyxia | 34.4% | 21.6% | P=0.0218, OR=1.90 [1.09–3.29] |
| RDS | 7.3% | 3.4% | P=0.1515, OR=2.22 [0.76–6.52] |
| Pre-eclampsia | 14.6% | 6.8% | P=0.0374, OR=2.33 [1.04–5.19] |
| Mortality | 27.1% | 10.2% | P=0.0003, OR=3.26 [1.69–6.28] |

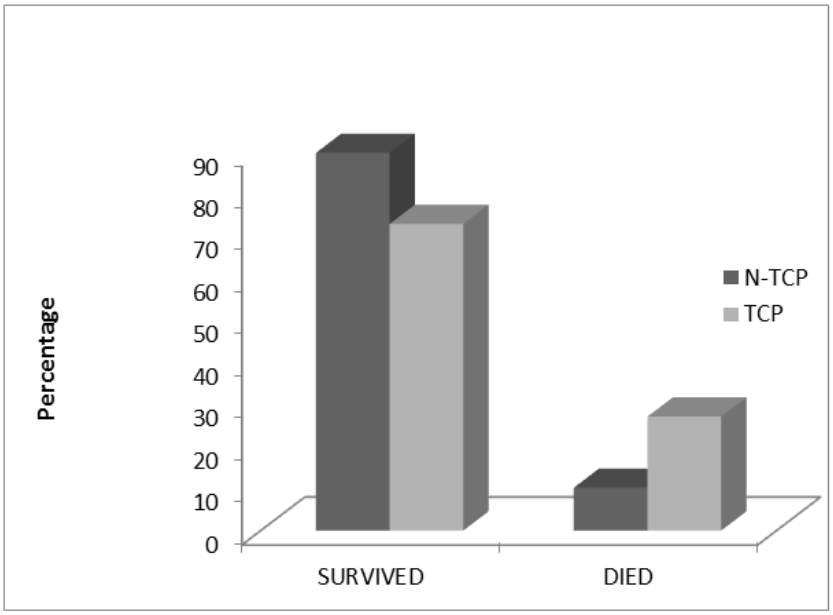
**Table–2: Association of various factors in relation to mortality**

| Factor | TCP (n=96) | | N-TCP (n=176) | | Significance |
|---|---|---|---|---|---|
| | Died (n=26) | Survived (n=70) | Died (n=18) | Survived (n=158) | |
| HIE (n1=33, n2=38) | 6 (18.2) | 27 (81.8) | 3 (27.1) | 35 (72.9) | P=0.1938, OR=2.59 [0.64 – 10.33] |
| PRETERM (n1=42, n2=43) | 14 (33.3) | 28 (66.7) | 10 (23.3) | 33 (76.7) | P=0.3021, OR=1.65 [0.64 – 4.22] |
| NNH (n1=27, n2=54) | 7 (25.9) | 20 (74.1) | 3 (5.6) | 51 (94.4) | P=0.008, OR=5.95 [1.50 – 23.22] |
| NNS (SEPSIS) (n1=53, n2=70) | 16 (30.2) | 37 (69.8) | 7 (10.0) | 63 (90.0) | P=0.004, OR=3.89 [1.49 – 10.08] |
| SGA (n1=33, n2=38) | 9 (30.0) | 21 (70.0) | 3 (8.6) | 32 (91.4) | P=0.026, OR=4.57 [1.17 – 17.39] |
| PREECLAMPSIA (n1=14, n2=12) | 2 (14.3) | 12 (85.7) | 3 (25.0) | 9 (75.0) | P=0.4895, OR=0.5 [0.08 – 3.14] |

**Table–3: Mortality in relation to Severity of Thrombocytopenia**

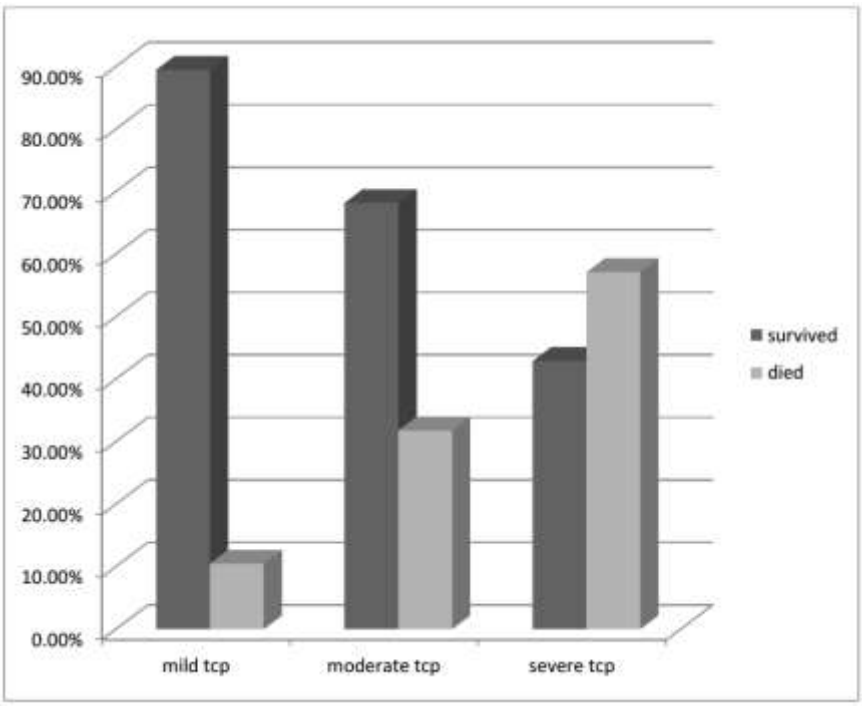
| Outcome | Mild | Moderate | Severe | Normal | Total |
|---|---|---|---|---|---|
| Died | 4 10.5% | 14 31.8% | 8 57.1% | 18 10.2% | 44 16.2% |
| Survived | 34 89.5% | 30 68.2% | 6 42.9% | 158 89.8% | 228 83.8% |
| Total | 38 (100%) | 44 (100%) | 14 (100%) | 176 (100%) | 272 (100%) |

$\chi$2trend = 25.840; P<0.0001




($\chi$2=13.016; P<0.001)

**Fig–1: Correlation between thrombocytopenia and mortality**




$\chi^2_{trend}$ = 25.840; P<0.0001

**Fig–2: Showing mortality in relation to severity of thrombocytopenia**

**DISCUSSION**

Incidence of thrombocytopenia in our study, amongst sick newborns was 35.29%. This was comparable to the incidence of thrombocytopenia as reported from different other studies. According to I Roberts, N A Murray *et al.* thrombocytopenia develops in 22–35% of all babies admitted to NICUs and in up to 50% of those who require intensive care. Considerable proportions (20%) of these episodes of thrombocytopenia were severe [11]. In a prospective study of 807 cases by Castle and colleagues, 22% incidence of thrombocytopenia has been reported in sick neonates in NICUs [12].

In one study conducted by Kaplan *et al.* in France in the year 1992, they reported overall incidence to be 20-40% of all nicu admissions [13]. In our study it was observed that 61.5% cases showed onset in <72 Hrs of their age and 38.5% of cases were found with late onset.

Murray and coworkers also found that in 75% of cases, the low platelet count is either present at birth or develops by 72 hours of life .Most of the patients are preterm neonates born after pregnancies complicated by placental insufficiency and/or fetal hypoxia. Increased platelet consumption and/or sequestration are the major mechanisms in about 25–35% of episodes of neonatal thrombocytopenia [9, 11].

In our study, mean birth weight of thrombocytopenic babies was 2.1466 +_.65 kg and mean gestational age was 36.19 +_ 3.16 weeks. Sandhya Sivakumar *et al.* from Pondicherry, India in 2006 found in their study mean birth weight of thrombocytopenic babies to be 2.15 kg and mean gestational age of 37.4 weeks[14].

In our study we found that higher percentage of thrombocytopenia is associated with male gender (60.4%). Bhatt YR et al also reported in their studies higher number thrombocytopenic cases are associated with male gender (47.7%) [15]. In our study mean age of thrombocytopenic babies was 92.86 hrs ±143.751.

As regards degree of thrombocytopenia, in our study we found mild thrombocytopenia was present in 38(39.58%) cases, moderate in 44 45.83%) cases and severe thrombocytopenia was present in 14 (14.58%) cases. According to I Roberts, N A Murray, considerable proportions (20%) of neonates admitted to nicu are severely thrombocytopenic [11].

Lea Bonifocio found in their study the following distribution 12(12.8%) mild, 34(36.2%) moderate and 48(51%) severe thrombocytopenic cases [16]. Mohammad Al Ghamdi, Khalid Al Umran, have reported in their studies that out of 2592 neonates admitted to NICU during the study period, neonatal thrombocytopenia was diagnosed in 366 (14%). Mild to moderate thrombocytopenia was the diagnosis in 294 (80%) and severe in the rest [17].

Prematurity was the most important risk factor for thrombocytopenia in our study. Incidence of thrombocytopenia in premature babies was 49.41% in comparison to full term babies in whom incidence of thrombocytopenia was 28.87%. Many authors have also found in their studies prematurity to be an important risk factor for developing thrombocytopenia.

Bhat YR *et al.* reported in their studies that prematurity (67.4%) is significantly associated with thrombocytopenia [15]. Mehta P, Vasa R, Neumann L *et al.* studied one-hundred twenty-nine high-risk infants with thrombocytopenia and 238 control infants without thrombocytopenia and found that thrombocytopenia was more common in babies less than 37 weeks of gestation and in sick babies compared to healthy babies[17].

Beiner ME, Simchen MJ *et al.* studied risk factors for neonatal thrombocytopenia in preterm infants, and found in their studies that thrombocytopenic infants had a significantly lower average gestational age at delivery (30.5 vs. 31.6 weeks, p = 0.002) and lower birth weight (1208 vs. 1597 g, p = 0.0001) [18].

Oren H, Iren G, Oren B also studies the risk factors for neonatal thrombocytopenia and found that thrombocytopenia developed in 18.2% of the preterm neonates and 0.8% of the term neonates. In our study small for gestational age were also found to be significantly associated with neonatal thrombocytopenia. Incidence of thrombocytopenia in SGA group was 46.15% as compared to AGA group in which incidence was 31.88% with a p value of <.05 .

In various other studies different authors have also found SGA as a significant risk factor for neonatal thrombocytopenia. Beiner Me *et al.* studied three hundred and five preterm infants, between 27 and 35 weeks of gestation, classified as SGA or AGA. There were significantly more SGA infants in the thrombocytopenic group (40.9 vs. 17%, p = 0.0001) [18].

Lea bonifocio also found SGA as a significant risk factor for thrombocytopenia with a p value of <.0001[16]. S Sivakumar *et al.* reported in their studies that incidence of thrombocytopenia is more in SGA (38%) group of neonates as compared to AGA (24%) group [14].

In our study we also studied the relation of various clinical conditions on thrombocytopenia. We noted various morbidities to have an effect on the incidence of thrombocytopenia. Sepsis was present in 55.2% of our cases with a p value of <.05. It is an important risk factor for developing thrombocytopenia in neonates. In various other studies different authors have also found sepsis as a major risk factor for thrombocytopenia.

Murray and coworkers found that about 90% of cases of severe thrombocytopenia presenting after the first few days of life were due to late-onset bacterial sepsis, necrotizing enterocolitis, or both [20].

Aman I, Hassan KA, Ahmad TM. Studied thrombocytopenia in sick neonates and found that the neonatal infections were the most common cause of thrombocytopenia. Out of 152 neonates with sepsis, 62 had low platelet counts (40.78%) [21].

Lea bonifocio *et al.* also reported that sepsis and NEC were associated with severe thrombocytopenic events in preterm babies [16]. In our study 33 out of 96 cases were diagnosed as having perinatal asphyxia with incidence of thrombocytopenia 46.47% with a p value of 0.022 showing a significant association of perinatal asphyxia with thrombocytopenia.

Many studies also show perinatal asphyxia as a significant risk factor for development of thrombocytopenia. M Salonvaara *et al.* studied the effects of gestational age and prenatal and perinatal events on the coagulation status in premature infants and found that platelet counts in infants with birth asphyxia are low, which may further increase the vulnerability of the haemostatic system [22].

Biran V, *et al.* from Department of Neonatology, , University of Paris, studied effect of perinatal asphyxia on platelet count and found that these babies presented biological features compatible with HUS, such as fragmentocytes (approximately 2%), thrombocytopenia (<50,000/mm(3), and anemia (<8 g/dl)[23].

As regards maternal clinical conditions in our study we found that preeclampsia is significantly associated with neonatal thrombocytopenia. We found the incidence of thrombocytopenia in babies of preeclampsia mother was 53.8%, $\chi 2=4.33$; P<0.05, OR = 2.33, 95% CI (0.96-5.67). This shows a significant association of babies of preeclamptic mother with neonatal thrombocytopenia.

Beiner ME, Simchen MJ, *et al.* studied the risk factors for neonatal thrombocytopenia in preterm infants they found in their studies that in thrombocytopenic preterm, the rate of preeclampsia was significantly higher (p = 0.002) [17].Burrows RF, Andrew M from Canada in year 1990 studied the effect of preeclampsia on neonatal thrombocytopenia. The rate of neonatal thrombocytopenia was 9.2% in

hypertensive patients, compared with 2.2% in infants of normotensive mothers (P less than .00001).

In the hypertensive group, preterm birth was the major risk factor for neonatal thrombocytopenia. [24] Bhat YR, Cherian CS. From Department of Pediatrics, Kasturba Medical College, Manipal studied 97 neonates born to PIH mothers; 35 (36.1%) had thrombocytopenia; In 20 (20.6%) thrombocytopenia was severe [15]. In our study we found the outcome of thrombocytopenic babies was most worrying as we found strong correlation between thrombocytopenia and mortality of neonates (figure 1).

The rate of mortality in thrombocytopenic group was 27.1 % as compared to mortality in non-thrombocytopenic group which was only 10.2 %.( p value <0.001 and odds ratio=3.26, CI =1.60-6.68).Mortality rate also shows an association with the degree of thrombocytopenia. Mortality rate in mild thrombocytopenia was 10.2%, in moderate thrombocytopenia it was 31.8% and in severe thrombocytopenia it was 57.1% (figure 2).

P value for outcome in relation to degree of thrombocytopenia was P<0.0001, $\chi 2$ trend = 25.840; this is showing a significant linear trend of mortality according to level of thrombocytopenia and suggests that as the level increases towards the severity there are likely chances of higher mortality.

In our study prematurity is significantly associated with mortality with a p value for mortality is <0.000. Mehta P, Vasa R, Neumann L *et al*. studied 129 high-risk infants with thrombocytopenia and 238 control infants without thrombocytopenia. They found that thrombocytopenia was more common in babies less than 37 weeks' gestation and in sick babies compared to healthy babies.

Thrombocytopenic babies had more complications, more hemorrhage, and greater mortality than no thrombocytopenic babies. This study shows that neonatal thrombocytopenia is often associated with high-risk factors and with increased hemorrhage, morbidity, and mortality [9,25]. Nadkarni *et al*. noted a higher mortality rate in preterm hypoxic neonates with thrombocytopenia as compared to term asphyxiated neonates with thrombocytopenia [26].

K.K. Diwakar *et al.* evaluated the role of Intravenous gamaglobulin (IVIG) and platelet transfusion on the improvement and survival of neonates with thrombocytopenia. They found that among the thrombocytopenic infants, 77% (30 /39) died if untreated, as compared to 38 % (21/55) of those given some form of specific therapy (Platelets or IVIG). (RR 0.5, 95 % CI 0.34 – 0.72, p = 0.0005)[27].

Thrombocytopenia is a common finding in sick new-borns. Growth restriction, lower gestational age at delivery, neonatal septicemia and perinatal asphyxia are significantly associated with neonatal thrombocytopenia in newborn babies which may lead to significant morbidity. Other factors that are significantly associated with thrombocytopenia are sepsis, preeclampsia and IUGR babies. Screening these high-risk groups for thrombocytopenia might be beneficial in terms of early diagnosis and management. Early diagnosis and adequate treatment reduces the fatal complications in neonates.

Most of the cases reported with early onset of thrombocytopenia, prematurity and perinatal asphyxia are leading causes of neonatal thrombocytopenia. The mortality was considerably higher among the cases with thrombocytopenia and mortality showed a direct correlation in the thrombocytopenic cases who had septicemia, and were small for gestational age.

Thrombocytopenia a common clinical problem in Neonatal care units, yet it should not be dismissed without consideration of its significance. It can lead to morbidity and mortality in the sick pre-and full-term babies. There is a need to check platelet counts in every sick neonate to reduce the thrombocytopenia related complications and improve survival of neonates.

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