A prospective observational study of thrombocytopenia in high risk neonates in a tertiary care teaching hospital

***Anubha Sharma**[1], **Karuna Thapar**[2]

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Abstract

Objective: To study the incidence, associated risk factors and outcomes of thrombocytopenia in a group of high risk neonates admitted to the Neonatal Intensive Care Unit (NICU) of a tertiary care teaching hospital.

Method: A prospective observational study was carried out in the NICU of Sri Guru Ram Dass Institute of Medical Sciences and Research, Amritsar on 100 high risk neonates (intramural + extramural) enrolled consecutively from January to July 2013. Babies of parents who refused to sign the consent form were excluded from the study. Gestational age was calculated by obstetrical estimate according to last menstrual period, combined with ultrasound and/or Ballard scoring. Enrolled neonates were observed prospectively and a platelet count was done at presentation, and subsequently, as and when required. The outcomes of the high risk neonates with thrombocytopenia were assessed. Statistical analysis (Chi square test) was done to find out the association of the risk factors with neonatal thrombocytopenia.

Results: The study population comprised 84 males and 16 females. There were 55 preterm babies and 66 low birth weight babies. There were 11 babies with necrotising enterocolitis, 35 with perinatal asphyxia, 32 with maternal risk factors, 56 with respiratory risk factors, 66 with sepsis, 11 with twin deliveries, 41 with small for gestational age / intrauterine growth retardation (SGA/IUGR), 20 with jaundice, 10 with congenital defects / syndromes and 4 with ABO incompatibility. Incidence of thrombocytopenia among the high risk neonates was 55%. Perinatal asphyxia (P=0.015), maternal risk factors (P=0.006), respiratory risk factors (P=0.035), sepsis (P=0.016) and SGA/IUGR (P=0.008) were significantly associated with thrombocytopenia. During the study period 8 (14.5%) cases with thrombocytopenia died, 5 (9%) developed intraventricular haemorrhage and 11 (20%) had frank bleeding. Of the 55 high risk neonates with thrombocytopenia 21 (38%) received platelet transfusions and of them 11 (52%) showed improved platelet counts and 4 (19%) died.

Conclusion: Thrombocytopenia occurred in 55% neonates admitted to NICU. Perinatal asphyxia, maternal risk factors, respiratory risk factors, sepsis and SGA/IUGR were significantly associated with thrombocytopenia.

(Key words: Thrombocytopenia, neonates, neonatal intensive care unit)

Introduction

A healthy neonate, even a preterm, has the same mean platelet count as adults and a platelet count less than 150,000/cu mm is defined as thrombocytopenia[1]. Thrombocytopenia is present in 1–5% of newborns at birth and severe thrombocytopenia in 0.1–0.5%[2]. Thrombocytopenia develops in 22–35% of all babies admitted to neonatal intensive care units (NICUs), in up to 50% of those admitted to NICUs who require intensive care and in 50% of sick preterms[3]. The various grades of thrombocytopenia are: mild (100,000-150,000 per cu mm), moderate (50,000-100,000 per cu mm) and severe (<50,000 per cu mm). Some authors categorize platelet counts less than 30,000 per cu mm as severe thrombocytopenia[4].

The causes are best differentiated by the time of presentation into fetal, early (<3 days of age) and late onset (3-28 days)[4]. Common fetal causes of thrombocytopenia are alloimmune, congenital infections, aneuploidy and autoimmune[4]. Early onset thrombocytopenia is usually secondary to placental insufficiency [e.g. intrauterine growth retardation (IUGR), diabetes, perinatal asphyxia, disseminated intravascular coagulation (DIC), alloimmunity and autoimmunity, congenital infections, thrombosis, bone marrow replacement, metabolic diseases and

[1]*Senior resident,* [2]*Professor and Head, Department of paediatrics, Sri Guru Ram Dass Institute of Medical Sciences and Research, Amritsar, India*
**Correspondence:* anubha.khera@yahoo.in
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congenital/inherited syndromes][4]. Late onset thrombocytopenia is often secondary to sepsis or necrotising enterocolitis. Thrombocytopenia not explained by other causes, may indicate an underlying thromboembolic event[4]. The most common cause of severe thrombocytopenia in neonates is immune thrombocytopenia from antiplatelet antibodies across placenta[5]. Low platelet count in an otherwise healthy term newborn is due to neonatal alloimmune thrombocytopenia (NAIT) until proven otherwise[4].

The only treatment available for neonatal thrombocytopenia, except for immune thrombocytopenia, is platelet transfusion[6]. Neonates should receive 10-15 ml/kg of cytomegalovirus safe or leukoreduced platelets and they are at increased risk for transfusion-associated graft versus host disease[7]. There are limited Indian prospective studies to identify risk factors associated with neonatal thrombocytopenia and its clinical outcome.

Objective

To study the incidence, associated risk factors and outcomes of thrombocytopenia in a group of high risk neonates admitted to the Neonatal Intensive Care Unit (NICU) of a tertiary care teaching hospital.

Method

A prospective observational study was carried out at Level III NICU of Sri Guru Ram Dass Institute of Medical Sciences and Research, Amritsar from January to July 2013, a period of six months. A total of 100 high risk neonates (intramural + extramural) admitted to the NICU during this period formed the study group. The inclusion criteria were:

- Frank bleed.
- Brown or red respiratory tract aspirate.
- A neonate suddenly presenting with decline in haemoglobin and bulging fontanelle / lethargy/ tone changes / pupillary changes suggesting intraventricular haemorrhage (IVH) in a preterm baby, subarachnoid haemorrhage (SAH) or subdural haemorrhage (SDH) in a term baby.
- Positive maternal history viz. pregnancy induced hypertension (PIH), leaking per vagina, infections (Dengue, TORCH etc.), drug history, diabetes, systemic lupus erythematosus (SLE), idiopathic thrombocytopenic purpura (ITP), bleeding per vagina (BPV).
- Positive family history of thrombocytopenia (in any sibling / bleeding tendency in the family).
- Prematurity, intrauterine growth retardation (IUGR) / small for gestational age (SGA), twin deliveries.
- Neonates presenting with jaundice.
- Neonates with a history of perinatal asphyxia
- Neonates presenting with respiratory distress syndrome (RDS), necrotising enterocolitis (NEC) or meconium aspiration syndrome (MAS).
- Neonates presenting with refusal to feed, fever and lethargy or involvement of more than two organ systems suggestive of septicaemia (or sclerema).
- Neonates with positive blood cultures, peripheral blood films suggestive of sepsis, higher total leucocyte counts than recommended for age, raised C-reactive protein (CRP), positive cerebrospinal fluid (CSF) study, conjugated hyperbilirubinaemia
- Syndromic babies (Down, Turner etc.) and neonates with congenital malformations and congenital diseases.
- Neonates undergoing any surgical interventions.
- Neonates receiving mechanical ventilation and neonates with central line in situ
- Sick newborns and with multiple NICU admissions.

The cases were enrolled consecutively after taking written, informed consent from one or both parents after completely explaining the study details to them. Babies of parents who refused to sign the consent form were excluded from the study.

Gestational age was calculated by obstetrical estimate according to last menstrual period, combined with ultrasound and/or Ballard scoring if required. Enrolled neonates were observed prospectively and platelet counts were done at presentation and subsequently as and when required. Platelet count of less than 150,000/cu mm was taken as the cut off point for determining thrombocytopenia. All neonates who fulfilled the criteria for admission were shifted to the special care neonatal unit for observation and management. Platelet count was done daily or repeated earlier in sick neonates. Treatment consisted of transfusion of random donor platelet concentrates (RDPCs), when required. Platelet transfusion guidelines were followed[4]. After

completion of data collection, statistical analysis (Chi square test) was done to find out the association of the risk factors with neonatal thrombocytopenia.

Results

In our NICU, the incidence of thrombocytopenia was 55% among the high risk neonates. Mild thrombocytopenia (100,000-150,000 per cu mm) was observed in 16.4% neonates, moderate thrombocytopenia (50,000-100,000 per cu mm) in 36.4% and severe thrombocytopenia (<50,000 per cu mm) in 47.5%. Early onset thrombocytopenia (<3 days of age) was seen in 51% and late onset thrombocytopenia (3-28 days) in 49%. The associations between gender, prematurity (<37 weeks gestation), low birth weight (<2.5kg), NEC, perinatal asphyxia, maternal risk factors (PIH, 'leaking' per vagina, BPV, diabetes, infection, autoimmune disorders etc.), respiratory risk factors (RDS, MAS, transient tachypnoea of the newborn etc.), sepsis, twin delivery, SGA/IUGR, jaundice, congenital defects/syndromes, ABO incompatibility and neonatal thrombocytopenia in the study population, along with their statistical significance, are shown in Tables 1-13.

Table 1: ***Association of gender and neonatal thrombocytopenia***

Sex	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Male	84	45 (53.6)	39 (46.4)	0.511
Female	16	10 (62.5)	06 (37.5)	
Total	100	55	45	

Table 2: ***Association of prematurity and neonatal thrombocytopenia***

Prematurity	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	55	32 (58.2)	23 (41.8)	0.480
Absent	45	23 (51.1)	22 (48.9)	
Total	100	55	45	

Table 3: ***Association of low birth weight and neonatal thrombocytopenia***

Low birth weight	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	66	38 (57.6)	28 (42.4)	0.471
Absent	34	17 (50.0)	17 (50.0)	
Total	100	55	45	

Table 4: ***Association of necrotising enterocolitis and neonatal thrombocytopenia***

Necrotising enterocolitis	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	11	09 (81.8)	02 (18.2)	0.058
Absent	89	46 (51.7)	43 (48.3)	
Total	100	55	45	

Table 5: ***Association of perinatal asphyxia and neonatal thrombocytopenia***

Perinatal asphyxia	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	35	25 (71.4)	10 (28.6)	0.015
Absent	65	30 (46.2)	35 (53.8)	
Total	100	55	45	

Table 6: ***Association of maternal risk factors and neonatal thrombocytopenia***

Maternal risk factor	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	32	24 (75.0)	08 (25.0)	0.006
Absent	68	31 (45.6)	37 (54.4)	
Total	100	55	45	

Table 7: ***Association of respiratory risk factors and neonatal thrombocytopenia***

Respiratory risk factor	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	56	36 (64.3)	20 (35.7)	0.035
Absent	44	19 (43.2)	25 (56.8)	
Total	100	55	45	

Table 8: ***Association of sepsis and neonatal thrombocytopenia***

Sepsis	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	66	42 (63.6)	24 (36.4)	0.016
Absent	34	13 (38.2)	21 (61.8)	
Total	100	55	45	

Table 9: ***Association of twin delivery and neonatal thrombocytopenia***

Twin delivery	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	11	07 (63.6)	04 (36.4)	0.542
Absent	89	48 (53.9)	41 (46.1)	
Total	100	55	45	

Table 10: ***Association of SGA/IUGR and neonatal thrombocytopenia***

SGA/IUGR	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	41	29 (70.7)	12 (29.3)	0.008
Absent	59	26 (44.1)	33 (55.9)	
Total	100	55	45	

Table 11: ***Association of jaundice and neonatal thrombocytopenia***

Jaundice	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	20	09 (45.0)	11 (55.0)	0.315
Absent	80	46 (57.5)	34 (42.5)	
Total	100	55	45	

Table 12: ***Association of congenital defects/syndromes and neonatal thrombocytopenia***

Congenital defect/syndrome	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	10	04 (40.0)	06 (60.0)	0.315
Absent	90	51 (56.7)	39 (43.3)	
Total	100	55	45	

Table 13: ***ABO incompatibility and neonatal thrombocytopenia***

ABO incompatibility	Number	Thrombocytopenia (%)	No thrombocytopenia (%)	P value
Present	04	01 (25.0)	03 (75.0)	0.218
Absent	96	54 (56.3)	42 (43.7)	
Total	100	55	45	

Umbilical catheterisation was carried out in 3 high risk neonates but none of them developed thrombocytopenia. In our study there were 10 ELBW babies (birth weight <1000g) and all of them (100%) had severe thrombocytopenia (platelet count <50,000/cu mm). 42.4% of septic neonates had positive blood cultures. 40.2% of the septic thrombocytopenic neonates had early onset sepsis and 59.8% late onset sepsis. Organisms isolated from the blood of septic babies in order of frequency were: *Staphylococcus aureus*, *Klebsiella*, *Enterobacter*, *Escherichia coli*, *Coagulase negative Staphylococcus aureus*, *Pseudomonas*, *gram-positive cocci* and *Candida*. The outcomes of the 55 high risk neonates with thrombocytopenia are shown in Table 14.

Table 14
Outcome of high risk thrombocytopenic neonates

Outcome	No. (%)
Deaths	08 (14.5)
Intra ventricular haemorrhage	05 (09.1)
Bleeding	11 (20.0)
Discharge on request	07 (12.7)
Left against medical advice	09 (16.4)
Uneventful/improved with treatment	15 (27.3)
Total	55

Of the 55 high risk neonates with thrombocytopenia 21 (38%) received platelet transfusions and of them 11 (52%) showed improved platelet counts, 4 (19%) died, 4 (19%) left against medical advice and 2 (10%) were discharged on request. All 5 babies with IVH were less than 28 weeks in gestation. The 11 bleeding neonates either bled frankly through feeding tube, oral cavity, endotracheal tube and/or nose or had frank haematuria.

Discussion

Up to 30% of NICU patients develop thrombocytopenia at some time during hospital admission[3,8,9]. In our NICU 55% of high risk neonates developed thrombocytopenia. Platelet transfusions are frequently given to NICU patients and may result in unnecessary transfusions[10]. Improved guidelines are required for safe lower limits for platelet transfusions in stable and sick neonates, effective platelet transfusion protocols in sick neonates and improved therapy for conditions precipitating thrombocytopenia[10]. Bhat YR et al showed that 57.7% of thrombocytopenia was associated with the male gender[11]. In our study population there were 84% males but only 53.5% of males developed thrombocytopenia compared to 62.5% of females. Thus gender was not significantly associated with thrombocytopenia (P=0.511). Beiner ME et al showed that 31% of preterm babies developed thrombocytopenia[12]. In our study 58.2% preterm babies developed thrombocytopenia. However, 51.1% term babies also developed thrombocytopenia. Thus the association of prematurity with thrombocytopenia was not significant (P=0.480). Christensen RD et al observed thrombocytopenia in 73% of the extremely low birth weight (ELBW) population, being more common in the neonates with birth weight <800g[13]. In our study 100% of ELBW babies had thrombocytopenia. However, low birth weight as a whole was not significantly associated with thrombocytopenia (P=0.471)

Gupta AK et al found no relation between platelet count and type of delivery[14]. Nursen B et al demonstrated a relationship between the severity of thrombocytopenia and the severity and staging of hypoxic ischaemic encephalopathy[15]. In our study perinatal asphyxia was significantly associated with thrombocytopenia (P=0.015). Maruyama H et al found growth restriction to be a significantly independent risk factor for thrombocytopenia[16]. In our study SGA/IUGR was significantly associated with thrombocytopenia (P=0.008). Bhat YR et al observed that 36% of neonates born to mothers with PIH had thrombocytopenia[17]. In our study maternal risk factors were significantly associated with thrombocytopenia (P=0.006).

Gupta AK et al observed that 81.5% of septic neonates developed low platelet counts[14]. In our study sepsis was significantly associated with thrombocytopenia (P=0.016). Arif SH et al observed that *Klebsiella* was the most commonly isolated organism[18]. In our study the commonest organism isolated was *Staphylococcus aureus* with *Klebsiella* taking second place. Bacterial infection causes damage to vascular endothelial lining, thus accelerating adhesion, destruction, and removal of platelets. Viral infection increases platelet destruction due to loss of sialic acid from platelet membrane, increases platelet aggregation, and decreased production from infected marrow[19]. Sepsis also causes DIC, immune-mediated destruction, and decreased production of platelets from infected marrow[20]. Gupta AK et al observed that 43% of thrombocytopenic neonates had respiratory risk factors[14]. In our study respiratory risk factors were significantly associated with thrombocytopenia (P=0.035).

Burrows RF et al showed that thrombocytopenia occurs in twin pregnancy due to plasma dilution[21]. In our study twin delivery was not significantly associated with thrombocytopenia (P=0.542). Jeremiah ZA et al showed that 19.7% of the babies with low platelet counts had neonatal jaundice as the risk factor[22]. In our study neonatal jaundice was not significantly associated with thrombocytopenia (P=0.315). Roberts I et al observed that 90% of cases of late onset thrombocytopenia were due to necrotizing enterocolitis[6]. In our study NEC was not significantly associated with thrombocytopenia (P=0.058). Roberts I et al showed that babies born with certain congenital syndromes have late onset thrombocytopenia[6]. In our study congenital defects/syndromes were not significantly associated with thrombocytopenia (P=0.315).

Von Lindern JS et al found that 12% of babies with neonatal thrombocytopenia developed IVH[23]. In our study 5 (9.1%) high risk babies with neonatal thrombocytopenia developed IVH and all 5 were less than 28 weeks in gestation. This is understandable since the germinal matrix lacks a fibronectin layer in preterm babies. Bonifacio L et al observed that mucocutaneous bleeding complicated 18.4% of cases with severe and late-onset thrombocytopenia[24]. In our study 11 (20%) of high risk neonates with thrombocytopenia developed bleeding. Von Lindern JS et al showed that out of all included neonates with thrombocytopenia, 29% received a platelet transfusion[23]. In our study 21 (38%) high risk neonates with thrombocytopenia received platelet transfusions.

Platelet transfusions are frequently given to NICU patients with severe thrombocytopenia but no study has assessed whether this is clinically appropriate. Although the widely used liberal triggers for neonatal platelet transfusion reflect available guidelines and represent cautious ('safe') haemostatic practice, they are likely to result in unnecessary transfusion for a significant number of NICU patients. Improved practice requires definition of a safe lower limit for platelet count in stable neonates; effective platelet transfusion strategies for sick neonates; and improved therapies for conditions precipitating severe thrombocytopenia.

Conclusions

- Thrombocytopenia occurred in 55% neonates admitted to NICU.
- Perinatal asphyxia, maternal risk factors, respiratory risk factors, sepsis and SGA/IUGR were significantly associated with thrombocytopenia.

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