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RESEARCH ARTICLE

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A Cross-Sectional Observational Study of Thrombocytopenia in Sick Neonates

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ABSTRACT

Aim: The aim of this study was to assess thrombocytopenic neonates for the causes most likely to be associated to their low platelet count.

Methods: An algorithm was designed to enroll the neonates with thrombocytopenia and then with the help of clinical assessment and laboratory investigations, assess them for the most probable cause of thrombocytopenia in them. The enrolled neonates were firstly classified based on the severity of thrombocytopenia; i.e Mild, Moderate and Severe. After, clinical assessment and laboratory investigations, the thrombocytopenic neonates were then associated with probable causes of thrombocytopenia. The study also assessed the degree of bleeds in thrombocytopenic patients. We studied the prevalence of thrombocytopenia in the present study, which included the proportion of severity of thrombocytopenia as well.

Results: The duration of enrolment of this study was a time period of 1 year and 7 months. In this period a total of 6,237 neonates were admitted, out of which 1,154 neonates were included in this study, as their platelet count was less than 1,50,000/µL. The prevalence of thrombocytopenia in our setup which is a tertiary care centre was 18.5%. The severity of thrombocytopenia was also assessed, that showed 38.3% of patients to be mild thrombocytopenic, followed by moderate (34%) and severe (27.8%) thrombocytopenic neonates. The study also assessed the thrombocytopenic neonates for the probable cause leading to a decrease in the platelet count, in which it was observed that Neonatal Sepsis was the most prevalent cause that led to neonatal thrombocytopenia in our setup, followed by Birth Asphyxia, prematurity and IUGR.

Background: Neonatal thrombocytopenia can be defined as a platelet count less than 150000/µL at birth. Thrombocytopenia presented in the first 72 hours of life, is due to placental insufficiency and reduction in the production of platelets, and are usually mild or moderate. When presented after 72 hours of life, it is due to sepsis or Necrotizing Enterocolitis (NEC), and is severe and long lasting.

ARTICLE HISTORY

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Introduction

The incidence of neonatal thrombocytopenia, varies upon the population studied. Various studies are done to find the prevalence of thrombocytopenia in different population ranging from 0.5%-2% and a higher incidence (22-35%) of severe thrombocytopenia was seen in premature neonates [1,2].

Although there is a vast number of causes of neonatal thrombocytopenia, including rare inherited causes, only a few are commonly encountered in neonatal practice and are therefore most clinically relevant. The spectrum of thrombocytopenia includes, on the one hand, the extremely sick premature neonate with profound thrombocytopenia secondary to sepsis in whom the impact of a major haemorrhage may be catastrophic but whose survival will depend mainly on successful treatment of infection, and, on the other hand, severe isolated thrombocytopenia in a term neonate who is otherwise well and for whom the clinical outcome may solely depend on the impact of the thrombocytopenia [3].

Neonatal thrombocytopenia is a common clinical problem. Thrombocytopenia presenting in the first 72 hours of life is usually secondary to placental insufficiency and caused by reduced platelet production; Thrombocytopenia presenting after 72 hours of age is usually secondary to sepsis or necrotising enterocolitis. Platelet transfusion remains the only treatment [4-6].

The most frequent cause of early-onset thrombocytopenia is associated with chronic fetal hypoxia, as it occurs in infants born to mothers with pregnancy-induced hyper-tension or diabetes and/or in those with intrauterine growth restriction (IUGR). On the other hand, thrombocytopenia which presents after the first 3 days of life is due to sepsis or necrotizing enterocolitis (NEC) in >80 % of cases [7].

Thrombocytopenia is a common finding in small for gestational age (SGA) neonates and is thought to result from a unique pathophysiologic mechanism related to chronic intrauterine hypoxia [8]. In SGA neonates, early-onset thrombocytopenia is thought to result from increased platelet consumption in the

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placenta due to increased blood flow resistance and/or result from sup-pressed platelet production due to increased red cell production [9]. Not all SGA neonates develop thrombocytopenia, and severity varies, therefore other factors are thought to play an etiological role as well. Several studies on hematologic parameters in SGA neonates have been published [10].

Rationale

Thrombocytopenia in the neonatal period is encountered very often; but it is underdiagnosed and incompletely worked up due to inadequate facility. The present study, was focussed to find the prevalence of thrombocytopenia, followed by the assessment of the most likely cause associated to thrombocytopenia in the patients, with the help of clinical assessments and laboratory evaluations for the diagnosis and management of neonatal thrombocytopenia in a tertiary care centre.

Hypothesis

In our study, we are proposing to understand the basic pathophysiology and natural course of neonatal thrombocytopenia, that includes both immune and non-immune causes associated to thrombocytopenia. This will help the neonatologists in better management and diagnosis of thrombocytopenia in the neonates and also formulate appropriate transfusion strategies in high-risk cases.

Methodology

In this study we enrolled the neonates for 1 year and 7 months, and this study was approved by the Institutional Ethics committee.

Sample Population

Inclusion Criteria

- Neonates with platelet count less than 1,50,000/µL were included in the study
- Neonates whose informed consent form was approved by their parents/guardians.

The data was entered and analysed using SPSS and GraphPad Prism, and an algorithm was designed to explain the workflow for achieving the objectives of the study.

Study Design

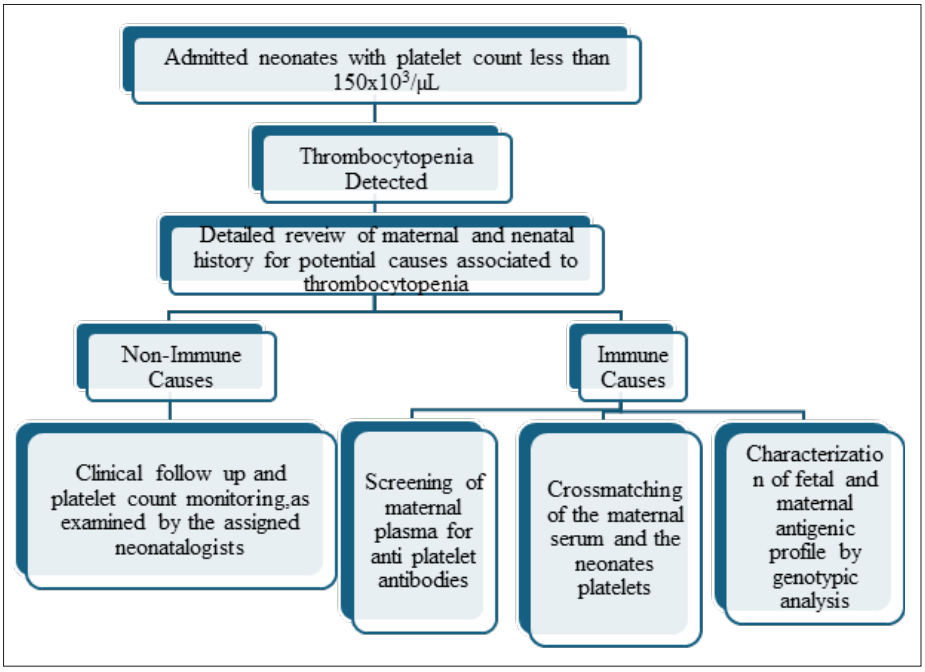

Figure 1: Study Algorithm to Achieve the Objectives of the Study

The study enrolled the neonates who were born in the institute, as well as the neoantes who were referred to our institute from outside. The neonates were enrolled from May 2018 to March 2020. The present study was approved by the institutional ethics committee.

The study enrolled a total of 1,154 thrombocytopenic neonates, which were assessed clinically, as well as with laboratory findings, to ascertain the most probable etiology associated to thrombocytopenia in them. The following algorithm was designed to achieve the objectives of the study, where the admitted neonates with platelet count less than 1,50,000/µL were enrolled in this study. Subsequently, a detailed review of maternal and neonatal history was done to assess the potential causes associated to thrombocytopenia. The potential causes were further categorized as immune and non-immune causes. The non-immune causes were followed up and monitored as examined by the assigned neonatologists and for immune causes; serological and genotypic analysis was done to ascertain the immune cause of thrombocytopenia.The thrombocytopenic neonates, under supervision of an assigned

neonatologist was then evaluated for potential causes associated to thrombocytopenia. The possible etiologies associated with thrombocytopenia with thrombocytopenia were assigned by the clinical neonatologist based on the full clinical picture, and other laboratory investigations. Multiple etiologies could be assigned to the neonate. The hemogram; which included the hemoglobin, White Blood Cell (WBC) counts, Red Blood Cell (RBC) counts, platelet counts and immature platelet fraction (IPF) was recorded as and when the blood sample was sent for the investigation till the time of the hospital stay of the neonate. The hemogram of the neonate was investigated using an automated cell counter in the pediatric hematology laboratory of the institute named Sysmex, XN-1000, by Transasia, India. Once, the neonate was assigned to the etiology leading to thrombocytopenia, their course of hospital stay was followed throughout, and their clinical and laboratory investigations were recorded, which included, Laboratory Investigations (Urine Examination, Urine culture, cerebrospinal fluid examination, Blood culture), Investigation of any Clinical Bleed, Blood Transfusions and Radiological examinations.

Results

The clinical and laboratory profile of the enrolled neonates were assessed. These neonates were firstly assessed to ascertain the prevalence of neonatal thrombocytopenia in a tertiary care centre. Subsequently, the neonates were classified based on various factors;

- Severity of Thrombocytopenia
- Severity of thrombocytopenia across the etiologies associated to thrombocytopenia.

The total number of admissions during the enrolment period was 6,237, out of which 1,154 neonates were found to be thrombocytopenic, that were included in the study for their clinical and laboratory assessment. The overall prevalence of neonatal thrombocytopenia in our setup was found to be 18.5%.

Further, the neonates were then classified based on the severity of thrombocytopenia, and it was observed that the prevalence of Mild Thrombocytopenia in a teriary care centre was 38.3%, followed by Moderate (33.8%) and Severe (24.5%).

The present study assessed the thrombocytopenic neonates for the clinical cause associated with their low platelet count with the help of a neonatologist and appropriate laboratory workup. Out of 1,154 enrolled neonates, 897 neonates were assessed for the clinical causes, due to non-availability of data and records.

Table 1: Classification of the Enrolled Neonates based on their Associated Etiologies most likely to cause Thrombocytopenia

Associated Etiologies	TOTAL (n=897)
Sepsis	379 (42.25%)
Birth Asphyxia	207(23%)
Prematurity (PMT)	127(14.1%)
Intrauterine Growth Retardation (IUGR)	86(9.5%)
Syndromic	36(4.0%)
Necrotising Enterocolitis (NEC)	30(3.3%)
Rh Isoimmunization	20(2.2%)
Neonatal Alloimmune Thrombocytopenia (NAIT)	10(1.1%)
TORCH	1(0.1%)
Thrombosis	1 (0.1%)

In the study, the most probable casuse associated to neonatal thrombocytopenia was sepsis present in 42.2% of neonates, followed by Birth Asphyxia (23%), Prematurity (14.1%), IUGR (9.5%), Syndromic (4%), Rh Isoimmunization (2.2%), NAIT (1.1%) and TORCH and Thrombosis (0.1%).

Further, we classified the thrombocytopenic neonates based on the proportion of severity of thrombocytopenia in various underlying etiologies (Table 2). It was observed that neonates with sepsis (42.2%), Necrotizing Enterocolitis (NEC) (46.7%), Intra-Uterine Growth Restriction (IUGR) (41.9%) and Neonatal Allo Immune Thrombocytopenia (NAIT) (100%), and neonates with birth asphyxia were majorly presented with Mild Thrombocytopenia (40%).

Table 2: Proportion of Severity of Thrombocytopenia in Various Underlying Etiologies

	Mild Thrombocytopenia	Moderate Thrombocytopenia	Severe Thrombocytopenia	Total
Sepsis	126 (33.2%)	93 (24.5%)	160 (42.2%)	379 (42.2%)
Birth Asphyxia	83 (40%)	56 (27%)	68 (32.8%)	207 (23%)
Necrotizing Enterocolitis	07 (23.3%)	09 (30%)	14 (46.7%)	30 (3.3%)
Intra-Uterine Growth Restriction	28 (32.5%)	22 (25.6%)	36 (41.9%)	86 (9.6%)
TORCH	0	0	01	01 (0.1%)
Syndromic	13 (36.1%)	08 (22.2%)	15 (41.7%)	36 (4.0%)
Thrombosis	0	0	01	01 (0.1%)
Neonatal Alloimmune Thrombocytopenia (NAIT)	0	0	10 (100%)	10 (1.1%)

Prematurity	40 (31.5%)	48 (37.8%)	39 (30.7%)	127 (14.1%)
Rh Isoimmunization	8 (40%)	9 (45%)	3 (15%)	20 (2.2%)
TOTAL	305 (34%)	245 (27.6%)	(38.7%)	897

Discussion

About 20% of the neonates, that are admitted in the Neonatal Intensive Care Unit, present with a platelet count of less than 150x103/µL. The prevalence and the causative factors associated to thrombocytopenia for their clinical assessment and understanding the associated sequalae for their better management; is a challenging task for the neonatologists, thus it becomes imperative to understand the clinical and the laboratory abnormalities associated with these thrombocytopenic life-threatening situations [11]. The appearance of platelets occurs in the fetal life by 5-6 weeks after conception. A platelet counts less than 150x103/µL is defined as thrombocytopenia, irrespective of the gestational age of the neonate. There are multiple etiologies that can cause low platelet count in the neonates and it can either happen before 72 hours (Early onset Sepsis) or after 72 hours (Late Onset Sepsis) [12].

In the present study, we came across 6,237 neonatal admissions, out of which 1,153 neonates were presented with neonatal thrombocytopenia, giving a prevalence of 18.5% in our study. Further, the present study also classified thrombocytopenic neonates based on the severity of thrombocytopenia into Mild (100-150x10^3/µL), Moderate (50-100x10^3/µL) and Severe (<50x10^3/µL).

Factors Affecting Neonatal Platelet Count

Etiologies as a Risk Factor Associated to Neonatal Thrombocytopenia

The occurrence of neonatal thrombocytopenia can be associated with various maternal, perinatal and neonatal causes. The primary clinical conditions in the literature responsible for thrombocytopenia in early neonatal life are early and Late Onset Sepsis, and Intra Uterine Growth Restriction, Birth Asphyxia and Necrotizing Enterocolitis, which varied across different centers all over the globe with facilities for neonatal care [13].

Most likely the neonates who develop thrombocytopenia; do so because of the poor in-utero environment, leading to impairment in megakaryocytopoiesis at birth, along with worsening of thrombocytopenia, when the neonate is exposed to concurrent stress of consumption of platelets.

Neonates with NEC and sepsis show a natural trend of rapid onset of thrombocytopenia and progression followed by recovery; indicating a combination of consumption of platelets, followed by impairment in the production of platelets, which recovers after institution of appropriate therapeutic interventions [14].

It is considered as a general agreement that the neonates with weight less than 750grams at birth, are at an increased risk of developing thrombocytopenia. In such neonates, the most commonly encountered causative factors are, Late Onset Sepsis (LOS) and Necrotizing Enterocolitis (NEC).

Another Randomized Controlled Trial on prevention of sepsis and NEC in VLBW neonates confirmed a statistically significant association between thrombocytopenia (Platelet count less than 80000/µL) and LOS. In about 5.6% of all the VLBW neonates having sepsis, had low platelet count on one or the other occassions [15].

Another study done by Boutaybi et al, showed that neonates who are near term r term, with perinatal asphyxia, are at an increased risk of developing early onset thrombocytopenia (51%) [16]. It has also been reported that the platelet survival is decreased significantly due to acute severe hypoxia, while few studies show that there is impairment in the platelet production due to hypoxia, by altering the megakaryocyte structural and functional characteristics [16].

In the present study, we studied the clinical causes associated with thrombocytopenia in each thrombocytopenic neonate, and we tried to categorize them based on etiologies.It was seen that sepsis (29.4%) was the most prevalent cause that lead to low platelet count in the neonates overall, followed by Birth Asphyxia (22.7%) and Prematurity (13.9%).

Neonatal Thrombocytopenia Associated to Sepsis

In a study done by E. Resch et al; Sepsis was found to be associated to Neonatal thrombocytopenia in 47% of the neonates, which was considerably higher than studies done by Ulusoy et al (30%), and Von Lindern et al (36%) [17].

Another study done in Maharashtra by K Tirupathi et al, observed sepsis to be the most common neonatal risk factor found in neonates that is associated t thrombocytopenia (48.5%) [18].

In the present study, we found Sepsis to be one of the most common risk factors which was associated to thrombocytopenia in 29.4% neonates. The proportion of severity of thrombocytopenia in neonates with sepsis was also studied, which showed that 42.2% of the neonates with sepsis had a platelet count less than 50x103/µL, followed by Mild (33.2%) and moderate (29.5%) thrombocytopenia and out of 379 neonates with sepsis, 23 (6%) of them were presented with the episodes clinical bleed.

Neonatal Thrombocytopenia Associated to Birth Asphyxia

A study done by E.Resch et al, also showed Birth Asphyxia to be one of the most common etiology that was associated to neonatal thrombocytopenia [17].

Birth Asphyxia was seen to be prevalent in 20% of the neonates in the study done by K.Tirupathu (Maharashtra) [18].

Another Indian study done by K.N Mishra (Bihar) showed Birth asphyxia to be one of the common causative factors associated to cause thrombocytopenia in the neonates [19].

In the present study, Birth Asphyxia was the second most prevalent causative risk factor for neonatal thrombocytopenia, it was seen to be prevalent in approximately 23% of the neonates with thrombocytopenia that were enrolled in the study.

Thrombocytopenia in neonates with Birth Asphyxia was primarily mild (40%), followed by severe (32.8%) and moderate (27.2%) thrombocytopenia and 11 out of 207 neonates with Birth Asphyxia, had clinical bleed.

Neonatal Thrombocytopenia Associated to Intra-Uterine Growth Restriction (IUGR)

A study done by S.F.Fustolo Gunnink et al, confirmed that neonates who are small for Gestational Age (SGA), present with an early onset thrombocytopenia, and they found out that the prevalence of thrombocytopenia is 2.7 times more in neonates who are SGA than those who are Appropriate for Gestational Age (AGA). This study was also able to find a clear correlation between the weight of the neonate and their platelet count, which emphasized the effect of growth restriction on platelet count at birth [20].

It was also studied that, in growth restricted fetuses, the platelet production is impaired, which is associated to fetal hypoxia and hypoxia can induce increase in erythropoiesis, which results in suppression of platelet production in bone marrow, leading to thrombocytopenia [21].

In the present study, it was observed that the prevalence of IUGR, associated to thrombocytopenia accounted upto 9.5%in our enrolled patients. The infants with IUGR, primarily showed severe thrombocytopenia (41.9%), followed by Mild (32.5%) and Moderate (25.6%) thrombocytopenia.

These neonates also presented episodes of clinical bleed but were relatively less as compared to other underlying illnesses. Out of 86 neonates with IUGR, 3 of them developed clinical bleed (3.5%).

Neonatal Thrombocytopenia Associated to Prematurity

In a study done by Lea Bonifacio et al, showed that prematurity was strongly associated to IVH and Neonatal Mortality [22].

A Study done in Pakistan, also showed that Prematurity was one of the significant causes of Severe thrombocytopenia in the neonate [23].

A study done in Karnataka (2008), showed that Prematurity was reported to be one of the major risk factors associated to thrombocytopenia in the neonates, and also reported that the premature infants were at 2.52 times of the risk to develop thrombocytopenia than the term [24-30].

Conclusion

Neonatal thrombocytopenia can be defined as the platelet count less than 150x103/µL at birth and it is prevalence is observed to be of about 18.5% in our study population. Thrombocytopenia was majorly Mild (100-150x103/µL) in the study population and in the present study, sepsis was observed to be one of the major underlying clinical conditions, which led to thrombocytopenia in the neonates, followed by birth asphyxia, Prematurity and Intra Uterine Growth Restriction.

Neonatal Alloimmune thrombocytopenia was seen to be prevalent in 1.1% of the thrombocytopenic neonates and was 0.1% in the total admission of the neonates during the enrolment period (1 year and 7 months). NAIT and Sepsis can be considered as the clinical conditions which are presented with severe thrombocytopenia and hence can lead to life threatening sequelae such as Intracranial hemorrhage and Pulmonary hemorrhage.

In our study the platelet count of the neonate varied across different underlying etiologies and the variation of the platelet count was seen to be significant. From this information we can conclude that the underlying clinical condition of the neonate plays a significant role in determining the platelet count of the neonate, however, other factors such as gestational age and weight of the neonate should also be considered while predicting the trend of the platelet count of the neonate.

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