Review Article

Clinical Feature of Neonatal Sepsis: Role of Variation in Platelate Indices and Thrombocytopenia

Shachi Dixit, Shikha Jain*

Assistant Professor, Department of Pathology, World College of Medical Science & Research, Jhajjar, Haryana, India

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Abstract

Diagnosis of neonatal septicemia may be difficult as the early signs of sepsis may be subtle and different at different gestational ages. Platelet indices are helpful in the diagnosis as well as follow-up of sepsis including assessing the response of antimicrobial treatment if interpreted cautiously. However, these platelet indices are not appropriate always. The important platelet indices available for clinical utility include mean platelet volume (MPV), platelet distribution width and plateletcrit that are related to morphology and proliferation kinetics of platelets. Thrombocytopenia is a common hematological abnormality in neonates with sepsis. Abnormal MPV can aid diagnosing the cause of thrombocytopenia. Low MPV associated with thrombocytopenia has been found to result in clinical bleeding. Until recently, the mechanism of neonatal thrombocytopenias are unclear. As a result, classifications based on mechanism have proved of little practical help to neonatal paediatricians because of overemphasis of rare conditions of known mechanism. The studies addressing the importance of these platelet indices and thrombocytopenia may provide insights for the early diagnosis of neonatal sepsis and therapy that would reduce the mortality rate. This review presents the details about the thrombocytopenia and its mechanism as a diagnostic measure for neonatal sepsis.

Keywords: Thrombocytopenia, Platelet indices, Neonatal sepsis, Diagnosis.

Introduction

The neonatal period is most susceptible for infection than any other period of life due to exposure to a large number of organisms and weak neonatal host defences system against micro-organisms from blood and tissues[1]. The systemic response to infection in the newborn infant is called as Neonatal Sepsis. This is commonest cause of the mortality in infants[2]. The definition of early onset sepsis (EOS) is variable from <3 days (American Academy of Pediatrics [AAP] definition) to <7 days (Centers for Disease Control and Prevention [CDC] definition based on epidemiology studies)[3]. The incidence of neonatal sepsis in India was 30/1,000, as per the Neonatal Perinatal Database (NNPD)[4]. Fatal septicemia may occur with little warning and hence the timely diagnosis of sepsis in neonates is critical as the illness can be rapidly progressive and in some instances fatal. Sepsis should not be regarded as a homogenous entity, as it neglects the pathogenic and clinical differences between the various causative micro-organisms and clinical syndromes and presentations of neonatal sepsis. Clinical features of sepsis are nonspecific in neonates and hence Early diagnosis of neonatal septicemia is a vexing problem[5]. Although blood culture is the "Gold Standard" for the diagnosis of sepsis, reports are available after 48-72 hours and they may be affected by intrapartum antibiotic administration to the mother. Therefore, a complete blood cell count with differential count is widely used, either singly or in conjunction

*Correspondence
Dr. Shikha Jain
Assistant Professor, Department of Pathology, World College of Medical Science & Research, Jhajjar, Haryana, India.
E-mail: dixit.shachi@gmail.com

with other tests or clinical findings as a diagnostic tool for neonatal sepsis. Haematologic values at birth encompass broader ranges of normal than at any other time in life due to the dynamic nature of the developmental processes that precede and follow birth[6].

Diagnosis challenges

Neonatal sepsis presents a diagnostic challenge to the neonatologists due to non-specific clinical features and a lack of objective evaluation. It may mimic noninfective conditions, such as inborn error of metabolism, birth asphyxia, and even respiratory distress syndrome in preterms. Nonetheless, over-diagnosis and initiating unwanted empirical antibiotics may pose the threat of drug resistance, increasing the hospital stay and cost of treatment. Even with diagnosis with sophisticated biomarkers curtail sepsis mortality by timely intervention is challenging[7]. Early diagnosis may reduce antibiotic abuse and help in rationalising a unit policy for the rationale use of antibiotics. The current gold standard microbiological blood culture screen many produce false-negatives because of low yield when a lesser amount of blood is collected, in addition to high turnover time[8]. Additional haematological tests used traditionally, such as white blood cell count (WBC), absolute neutrophil count (ANC), immature to total neutrophil (I/T) ratio, and C-reactive protein (CRP) measurement, also have a poor sensitivity and specificity and may need serial monitoring[9]. For better prediction of sepsis, recent evidence suggests the use of age-specific nomograms rather than fixed normal ranges of WBC, ANC, and I/T ratio[10]. Thus, diagnostic tests that are rapid and accurate in guiding the management of septic newborns are needed.

Haematological Indices

Traditionally, the following parameters (Table 1) have been used as the initial markers of neonatal sepsis, either individually or in combination:

Table 1: Traditional markers for the diagnosis of Neonatal Sepsis

Markers	Features	Disadvantages	Ref
Total leukocyte count (TLC).	Since, few reserves of white blood cells in the neonatal bone marrow remaines, leukopenia can represent an overwhelming infection. Neutrophil indices are more reliable if obtained after 6–12 hours, thus delaying the diagnosis.	Poor predictive value in EOS	24,25
Absolute Neutrophil Count	In neonates this is varying from <1,800/µL at birth to <7,800/µL at 12–14 hours of age, and falling again to <1,800/µL at 72 hours.		
Immature to Total Leukocyte Ratio (I/T) ratio	I/T ratio is calculated as 'immature polymorphs/mature plus immature neutrophils' and is the most sensitive indicator of sepsis. Values >0.27 in term and >0.22 in preterm neonates are significant.	Less specific	
Platelet count	Thrombocytopenia has been seen quite often in sepsis, especially fungal sepsis. Increased mean platelet volume (>8.6 fL) has been studied recently as a marker of EOS and a predictor for mortality, especially in preterm neonates	Low positive predictive value	

Platelet indices and Clinical Utility

The platelet indices have gained more importance in the recent studies. Among many platelet indices, the indices related to morphology and platelet kinetics such as mean platelet volume (MPV), platelet volume distribution width (PDW) and plateletcrit (PCT) are studied in sepsis. The other indices include mean platelet component, mean platelet mass, platelet component distribution width, platelet large cell ratio (P-LCR) and immature platelet fraction (IPF).These indices are related to morphology and proliferation kinetics of platelets and hence have a definite clinical utility in patients with sepsis. Platelet indices are biomarkers of platelet activation. These indices are of diagnostic and prognostic value without any added costs in a variety of settings including sepsis. The role of platelet indices in sepsis has been reported in adult studies. Such studies reported their role in the diagnosis of different grades of sepsis[11,12]. In addition, these

indices have been found to be useful in the prognosis of adverse clinical outcomes including mortality[13].

MPV

The MPV is the arithmetic mean volume of the platelets derived from the platelet histogram and most studied platelet index in neonatal sepsis expressed in femtoliters (fL). The average MPV is 7.2–11.7 fL in healthy human subjects. Continuous monitoring of MPV and identifying the change in MPV 72 h is Usefulness in reducing mortality risk in patients with severe sepsis and/or septic shock[13]. An increased proportion of young platelets may result in increased MPV. Young platelets that are bigger and more active enter the circulation and hence MPV levels increase. Increased MPV indicates increased platelet diameter. Therefore, increased MPV is useful clinically as a marker of production rate and platelet activation. During conditions of rapid platelet turnover, increased MPV signifies the release of larger, younger platelets into the circulation. Neonatal sepsis showed a significant increase in MPV from baseline values[14] such as in coagulase negative Staphylococcus sepsis infection[15].MPVs are rather constant from 22 to 42 wk of gestation with a slight but statistically significant decrease between the earlier vs later gestations[16]. It is important to understand the pathophysiology of alterations in PV and its inverse relationship with platelet count for the successful clinical application[17].

PDW-This is an indicator of volume variability in platelets size and reflects the heterogeneity in platelet morphology[18]. It increases when there is platelet anisocytosis. The PDW reference intervals range from 8.3% to 56.6%. Under physiological conditions, there is a direct relationship between MPV and PDW; both usually change in the same direction. PDW changes in neonatal sepsis and reported 72.1% increase in the PDW during neonates with sepsis[19]. Perreported higher levels of PDW along with higher MPV during sepsis episodes on consecutive days among non-survivors[20].

PCT

It is the volume occupied by platelets in the blood as a percentage and calculated according to the formula, PCT = platelet count × MPV/10000. Under physiological conditions, the number of platelets in the blood is maintained in an equilibrium state by regeneration and elimination. The normal range for PCT is 0.22%-0.24%. Of the several platelet indices PCT is studied less often in neonatal sepsis. The variation in MPV affects PCT. There is a significant overlap of PCT between thrombocytopenic patients and patients with normal platelet counts. Role of platelet mass in predicting the occurrence of intracranial hemorrhage in neonates with sepsis has been reported[21].

Thrombocytopenia

Neonatal sepsis is often accompanied by thrombocytopenia defined as Thrombocytopenia, defined as a platelet count below $150x10^9$/L and late onset sepsis remains an important cause of thrombocytopenia in neonates[14,15,22].

Thrombocytopenia affects 18–35% of all patients admitted to the Neonatal Intensive Care Unit. Recently, there has been wide interest in thrombocytopenia and especially the correlation between platelet count and clinically significant bleeding. The importance of the relationship between thrombocytopenia and sepsis was emphasized by identifying thrombocytopenia as one ofthe most predictive, independent risk factors for sepsis-associated mortality in very low-birth weight neonates[23]. This deserves further clarification of the diagnostic and prognostic meaning of thrombocytopenia in sepsis. Different congenital and inherited thrombocytopenias can be present in the fetus or neonate as follows[24]

- Thrombocytopenia (with abnormal platelet function) Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, X-linked thrombocytopenia, Chediak-Higashi syndrome, Quebec platelet disorder

Some giant platelet syndromes (e.g. Montreal syndrome)

- Thrombocytopenia(without marked thrombo-cytopathy)

Fanconi's anaemia, TAR syndrome, Amegakaryocytic thrombocytopenia

Giant platelet syndromes (e.g. May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome)

Autosomal dominant thrombocytopenia

Mechanism of thrombocytopenia in Neonatal sepsis

A combination of increased destruction and inadequate production of platelets during sepsis-induced thrombocytopenia of the neonate may result in release of young platelets into the circulation. One of the major sources of thrombocytopenia in neonates is sepsis and thrombocytopenia may quickly become very severe with the lowest platelet count reached within 24–48 hours after onset of infection[25]. In neonatal sepsis, endothelial damage activates reticule-endothelial removal of platelets and this fall in platelet production cause thrombocytopenia, with a causative role for serum thrombopoietin levels[26]. Different pathological mechanism that cause thrombocytopenia in sepsis are highlighted in the figure 1.

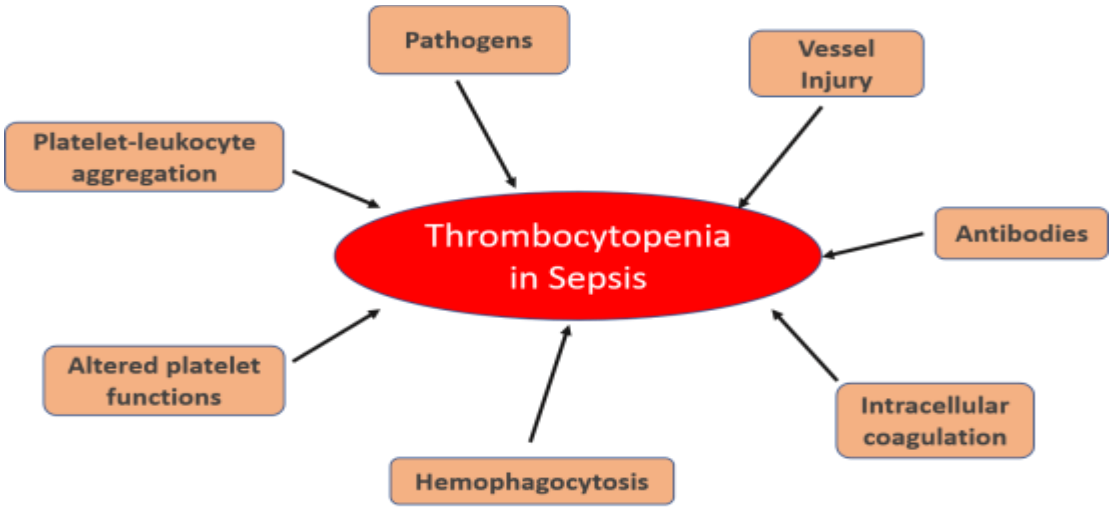

Fig 1:Thrombocytopenia in sepsis

Impaired platelet production

The major mechanism underlying neonatal thrombocytopenia is impaired platelet production. In 75% of all cases, the low platelet count is either present at birth or develops by 72 hours of life[27]. Most of the remaining patients are preterm neonates born after pregnancies complicated by placental insufficiency and/or fetal hypoxia—for example, maternal pre-eclampsia and fetal intrauterine growth restriction. Neonates with this early onset thrombocytopenia have impaired megakaryocytopoiesis and platelet production; megakaryocytes and their precursor and progenitor cells are considerably reduced at birth, and levels of the megakaryocytopoietic cytokine thrombopoietin (Tpo) are therefore elevated[28,29].

Consumption and sequestration

Increased platelet consumption and/or sequestration are the major mechanisms in about 25–35% of episodes of neonatal thrombocytopenia. Overall, 15–20% of neonatal thrombocytopenias present at birth result from transplacental passage of maternal platelet alloantibodies and autoantibodies, [30] and disseminated intravascular coagulation is responsible for a further 10–15% of cases, nearly always in babies who are very ill, particularly in association with perinatal asphyxia and infection[27].

Thrombosis or platelet activation/ immobilisation at sites of inflammation are further examples of neonatal thrombocytopenias principally caused by platelet consumption. In addition, there is evidence that limited splenic sequestration of platelets occurs in sick newborns[31].

Combined mechanisms

A preterm neonate from a mother with pre-eclampsia who develops early bacterial sepsis and a baby with intrauterine growth restriction who develops NEC may both become thrombocytopenic as a result of underlying impaired platelet production (after pre-eclampsia or intrauterine growth restriction) combined with platelet consumption (during sepsis or NEC). Indeed it is likely that most neonates who develop thrombocytopenia do so because their adverse fetal environment causes impaired megakaryocytopoiesis at birth, with a predisposition for thrombocytopenia to worsen when the baby is exposed to concurrent neonatal platelet consumptive "stress". In addition, during sepsis and NEC, the natural history of thrombocytopenia (rapid onset and progression followed by slow recovery over five to seven days) suggests that it probably results from a combination of mechanisms—that is, platelet consumption (rapid onset phase) followed by impaired platelet production (slow recovery phase).

Perspective and Conclusion

Sepsis in neonates often results in thrombocytopenia and changes in platelet indices. It is widely observed neonatal sepsis, develops thrombocytopenia (~50% cases) and severe thrombocytopenia (~20% cases). This may independent of the maternal hypertension, the Gram negative sepsis and intravascular thrombosis. Severe thrombocytopenia usually associated with major hemorrhages and mortality. Mortality is commonly seen in both thrombocytopenia and Gram negative sepsis. The investigation son the exact pathogenesis of thrombocytopenia warrants further research to stratify exact bacteria underlying the cause. Neonatal studies backing their clinical application but limitations should be kept in mind while interpreting results.

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