

Platelet indices in neonatal sepsis: A review

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Abstract

Thrombocytopenia is a common hematological abnormality in neonates with sepsis. The autoanalyzers now-a-days readily provide platelet indices along with platelet counts without any additional cost. However these indices are not given proper weightage often. 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. Studies in adult patients reported their role in the diagnosis of severe sepsis and prognosis of adverse clinical outcomes including mortality. Abnormal MPV can aid diagnosing the cause of thrombocytopenia. Low MPV associated with thrombocytopenia has been found to result in clinical bleeding. Other indices, however, are less studied. The studies addressing the importance of these platelet indices in neonatal sepsis are limited. The current review gives an overview of potential utility of important platelet indices in neonatal sepsis.

Key words: Sepsis; Platelet indices; Thrombocytopenia; Bleeding; Neonate

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Core tip: Sepsis in neonates often results in thrombocytopenia and changes in platelet indices. The important platelet indices such as mean platelet volume (MPV), platelet distribution width and plateletcrit are related to morphology and proliferation kinetics of platelets. All these indices are readily available with no additional cost while performing routine blood counts using autoanalyzers. Studies in adult patients reported the potential role of platelet indices in the diagnosis of severe sepsis and prognosis of adverse clinical outcomes including mortality. Abnormal MPV can aid diagnosing the cause of thrombocytopenia. Low MPV associated with thrombocytopenia has been found to result in clinical bleeding. The current review gives an overview of potential utility of important platelet indices in neonatal sepsis.

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INTRODUCTION

Neonatal sepsis is often accompanied by thrombocytopenia and late onset sepsis remains an important cause of thrombocytopenia in neonates^[1-5]. Although important platelet indices are readily available while obtaining routine complete blood counts (CBC), they are less studied. 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 role of platelet indices in sepsis has been reported in adult studies. Such studies reported their role in the diagnosis of sepsis and severe sepsis^[6,7]. In addition, these indices have been found to be useful in the prognosis of adverse clinical outcomes including mortality^[6-8]. Guclu *et al*^[6] reported that MPV and PDW were significantly different between sepsis patients and control group. They concluded that patients having PDW greater than 18% have higher risk for death. Gao *et al*^[7] reported usefulness of MPV in predicting adverse outcome in septic shock patients. Usefulness of continuous monitoring of MPV and thereby identifying the change in MPV 72 h after admission in stratifying mortality risk in patients with severe sepsis and/or septic shock was reported by Kim *et al*^[8]. Furthermore, Becchi *et al*^[9] reported the usefulness of MPV trend in sepsis patients along with platelet count.

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. An increased proportion of young platelets may result in increased MPV. A significant increase in MPV from baseline values in neonatal sepsis has been reported by Guida *et al*^[2]. O'Connor *et al*^[3] described changes of MPV in neonates with Coagulase negative *Staphylococcus* sepsis. In the subsequent sections, the changes of platelet indices during neonatal sepsis and clinical utility of three important indices have been discussed.

PLATELET INDICES

CBC tests with automated hematology analyzers are one of the most commonly ordered tests during neonatal sepsis work up. These analyzers rapidly measure the platelet count and also the platelet indices. 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. In automatic CBC profiles, MPV, PDW and PCT are a group of platelet indices determined together. These indices are related to morphology and proliferation kinetics of platelets and hence have a definite clinical utility in patients with 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). The latter

indices are studied very rarely. P-LCR often correlates to MPV but is more sensitive to changes in platelet size^[7]. The IPF rises in patients with peripheral consumption or destruction of platelets. It is normal or low in patients with marrow failure.

The MPV is the arithmetic mean volume of the platelets derived from the platelet histogram on automated Coulter counters. It is expressed in femtoliters (fL). The platelet volume is regulated by cytokine dependent megakaryocyte ploidy and platelet number^[10,11]. In the settings of decreased platelet production such as sepsis, 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. The average MPV is 7.2–11.7 fL in healthy human subjects. The paucity of gestational age-based normative data has limited the clinical utility of MPVs in neonatal medicine. Wiedmeier *et al*^[12] reported that MPVs are rather constant from 22 to 42 wk of gestation with a slight but statistically significant decrease between the earlier vs later gestations. They also provided 5th and 95th centile for MPV for different gestations.

PDW is an indicator of volume variability in platelets size and reflects the heterogeneity in platelet morphology^[10,11]. 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.

PCT is the volume occupied by platelets in the blood as a percentage and calculated according to the formula, $PCT = \text{platelet count} \times \text{MPV}/10000$. Under physiological conditions, the amount 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%.

MECHANISMS OF THROMBOCYTOPENIA AND ALTERATIONS IN PLATELET INDICES DURING SEPSIS

Because thrombocytopenia is a commonly encountered hematologic complication in neonates with sepsis, the mechanisms for thrombocytopenia have been explored. The measurement of circulating megakaryocyte precursors provides a good indicator of megakaryocytopoiesis, and hence platelet production in neonatal sepsis^[13]. Thrombopoietin (Tpo) is the principal physiologic regulator of megakaryocytopoiesis and platelet production. The circulating Tpo levels were found to be high in the face of low platelet counts in neonates with sepsis^[14]. Immune cells recognize pathogens through Toll-like Receptors (TLRs). The TLRs allow platelets to recognize bacterial proteins during sepsis and regulate platelet immunity and function^[15]. Two TLRs, TLR2 and TLR4, have been shown to augment platelet activation and alter its function from hemostatic regulator to immune sentinel. Furthermore,

septic neonates up-regulate Tpo production, leading to increased megakaryocytopoiesis and platelet release^[16]. As platelet indices are biomarkers of platelet activation, in the settings of sepsis, these indices also change accordingly.

MPV

Among platelet indices MPV is the most commonly studied platelet index in neonatal sepsis. During conditions of rapid platelet turnover, increased MPV signifies the release of larger, younger platelets into the circulation. Although MPV varies with gestational age and chronologic age, construction of rigorous normal curves for values of the MPV is difficult in premature infants. Wiedmeier *et al*^[12] found MPVs being rather constant from 22 to 42 wk of gestation. However, it is wiser to obtain the baseline values of MPV for comparison with subsequent values during neonatal sepsis.

A statistically significant increase in MPV with neonatal sepsis from baseline values (mean change in MPV 0.30 femtoliters; 95%CI: 0.12–0.47) was reported by Guida *et al*^[2]. They reported this abnormality while studying platelet counts in 154 blood culture proven neonatal sepsis. The study involved Gram negative, Gram positive and fungal infections in neonates. They did not observe any organism-specific changes in MPV. O'Connor *et al*^[3] reported increased MPV during coagulase-negative Staphylococcal sepsis in neonates even though platelet counts were normal.

The relationship between platelet count (PC) and MPV was studied by Becchi *et al*^[9]. The results were expressed as means and frequency distributions. They reported a negative correlation (95%CI; $r = -0.34$; $P < 0.0001$) between PC and MPV with an inverse trend during sepsis course.

Catal *et al*^[17] found a positive correlation between MPV and other inflammatory markers, IL-6 and CRP in neonatal sepsis. A MPV value of 10.35 fL was identified as the cut off value in patients probably resulting in sepsis with a sensitivity of 97.8% and specificity of 78.7% (AUC = 0.949; $P < 0.001$), and a MPV value of 10.75 fL was determined as the cut off value at diagnosis in patients possibly resulting in death with a sensitivity of 95.2% and a specificity of 84.9% (AUC = 0.944; $P < 0.001$).

Mitsiakos *et al*^[18] reported that platelet mass levels could play an important role in predicting the occurrence of intracranial hemorrhage in neonates with sepsis.

The effects of different infectious agents on platelet count and indices in neonatal sepsis were studied by Akarsu *et al*^[19]. They studied these values at baseline and at least 10 d after the onset sepsis. A MPV of > 9.5 fL and PDW of > 16.8 were considered high. Of 86 sepsis episodes involving Gram negative and Gram positive bacteria, 39.5% were found to be associated with thrombocytopenia, 13.9% with an elevation in baseline MPV and PDW, 11.6% with an elevation in baseline MPV and 72.1% with an elevation in baseline PDW. Neonates with MPV over 10.8 fL and/or PDW over 19.1 were found to

have significantly increased bacteremia. Although there was an increase in MPV and PDW from baseline, there were no differences between different organism groups.

An understanding of the pathophysiology of alterations in platelet volume and the inverse relationship between platelet volume and count hence is a prerequisite for the successful clinical application of platelet volume measurements^[20].

PLATELET DISTRIBUTION WIDTH

Farias *et al*^[21] reported the PDW median of 13.3% with a reference range of 10.0%–17.9% for the 5th–95th percentiles with a confidence interval of 95% for normal individuals. Akarsu *et al*^[19] addressed PDW changes in neonatal sepsis. By considering PDW of > 16.8 as high, they found an elevated baseline PDW in 72.1% of neonates with sepsis. However they did not find any organism specific response in PDW. Catal *et al*^[17] reported higher levels of PDW along with higher MPV during sepsis episodes on consecutive days among non-survivors.

PLATELETCRIT

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 by Mitsiakos *et al*^[18].

LIMITATIONS IN CLINICAL UTILITY OF PLATELET INDICES

Platelet volumes are frequently measured in blood samples collected in ethylenediaminetetraacetic acid (EDTA). Factors affecting platelet counting such as interference from cells or cell fragments, inadequate detection of large platelets or platelet clumps also influence platelet indices that are calculated from the platelet distribution curve^[22]. An overestimation of MPV, a higher PDW and an increase in fraction of large cells may occur if red blood cells are misclassified as platelets. In severe thrombocytopenia, difficulties in obtaining a sufficient platelet distribution curve may limit the calculation of other platelet indices. Concerns have been raised about the recommended anticoagulant for platelet counting, K2 or K3 EDTA, because it affects MPV. Transmission electron microscopy findings suggested more activation of platelets in EDTA samples^[23]. ACD/Na2EDTA has been suggested as an ideal anticoagulant for the study of MPV because it inhibits platelet activation while maintaining the platelets in their normal discoid shape^[24]. The methods of measurement of MPV are also important. EDTA causes an increase in MPV from 7.9% within 30 min to 13.4% over 24 h when measured by impedance and decreases by 10% when determined by an optical method. Because

time delay is likely to affect PDW and other indices sample needs to be processed within 120 min. Pseudo-thrombocytopenia due to agglutination of platelets caused by EDTA should also be kept in mind^[25].

MPV, PDW and PCT are not only altered in sepsis but also in other neonatal pathological conditions^[26-29]. This fact further complicates the clinical utility of platelet indices during neonatal sepsis. Gestational age, prematurity and birth asphyxia having some influence on these indices has been reported by Kannar *et al*^[26]. Premature neonates with sepsis may have other comorbidities such as bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). Higher MPV level was noted in BPD and IVH groups in a study by Bolouki Moghaddam *et al*^[27].

A decreased platelet count and PCT, an increased PDW and no difference in MPV among preterm neonates have been reported by Wasiluk *et al*^[28] while studying samples from umbilical arterial blood. The large platelet count (LPLT) was found to be diminished in preterm neonates (5.23%) in comparison with term neonates (6.12%). They also reported higher MPV, lower LPLT and lower PCT among small for gestation neonates. Higher PDW, lower PCT and higher but not statistically significant MPV in preterm neonates compared to term neonates were reported by Sandeep *et al*^[29].

CONCLUSION

Sepsis in neonates often results in thrombocytopenia and changes in platelet indices. The important platelet indices available for clinical utility include MPV, PDW and PCT. All these indices are readily available with no additional cost while performing routine blood counts using autoanalyzers. Platelet indices are helpful in the diagnosis as well as follow-up of sepsis including assessing the response of antimicrobial treatment if interpreted cautiously. High MPV and PDW have a high specificity for the identification of bacteremia and have a good predictive value. Neonatal studies support their clinical application but limitations should be kept in mind while interpreting results.

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