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Original Research Article

Mean platelet volume: predictor of mortality and an adjunct to C-reactive protein in the diagnosis of neonatal sepsis

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Abstract

Objectives: To determine the role of Mean Platelet Volume as an adjunct to CRP levels in the diagnosis of Neonatal Sepsis.
Design: Hospital based prospective analytical study
Setting: Special Care Newborn Unit of Medical College Hospital
Participants: 200 preterm and term neonates admitted in the hospital [100 cases (group I and II) and 100 controls (group III)]
Procedure: Neonates were evaluated clinically for sepsis and relevant laboratory investigations done. Based on clinical and laboratory findings, neonates were classified into Group I (clinical sepsis), Group II (culture proven sepsis) and Group III (healthy controls). MPV and serial CRP levels were analyzed in all three groups to determine their role in diagnosis of neonatal sepsis.
Results: Mean MPV was 10.47(0.69) fL in group I, 10.51(0.97) fL in group II and 8.67(0.65) fL in group III (p value of cases versus controls <0.001). Cases with positive serial CRP had mean MPV 10.80(0.77)fL compared to cases with single positive CRP [mean MPV=9.61(0.92)fL] and negative CRP [mean MPV=8.83(0.77)fL)] (p<0.001). MPV alone was 68% sensitive and 98% specific in diagnosis of neonatal sepsis. Serial CRP and MPV combined had sensitivity and specificity of 81% and 98%. Cases with mortality had mean MPV 10.81(0.98) fL while mean MPV of survivors was 9.47(1.14) fL (p value <0.001).
Conclusions: MPV is significantly increased in neonatal sepsis. High MPV is a risk factor for mortality. MPV when combined with serial CRP measurement has an increased sensitivity in diagnosing neonatal sepsis.
Keywords: Neonatal Sepsis, CRP, Mean Platelet Volume.

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1. Introduction

Neonatal infections are estimated to cause about 1.6 million deaths worldwide. Furthermore, 40% of all sepsis related neonatal deaths occur in developing countries [1]. Clinical features in neonatal sepsis are often non specific and subtle. Hence investigations have to be relied upon to confirm or rule out the diagnosis of sepsis. Growth of microorganisms in blood culture remains the gold standard for the diagnosis; however blood culture takes time, causing a delay in the initiation of treatment. Moreover, blood culture may not be positive in all cases of neonatal sepsis, owing to various factors such as previous treatment with antibiotics, low-level bacteremia, inadequate sample etc.

The diagnosis of "Clinical sepsis" is made when clinical features are suggestive of sepsis, along with positive laboratory results, but without a positive blood culture. Consequently, several laboratory tests have been investigated that can support a culture proven diagnosis of sepsis, as well as help in diagnosing sepsis in the absence of a positive blood culture.

This study was planned to determine the correlation of Mean Platelet Volume and CRP levels with neonatal sepsis. Studies have shown that CRP is raised in neonatal sepsis. CRP is an acute phase reactant that is increased in inflammatory conditions. However, it is not a sensitive test at birth since an inflammatory response with release of IL-6 is required for increase in CRP

concentration [2,3]. So it has a poor sensitivity for neonatal sepsis. Besides, it is also elevated in non-infectious inflammatory conditions including maternal fever, fetal distress, stressful delivery, perinatal asphyxia, meconium aspiration, and intraventricular hemorrhage [4,5].

Studies have shown that thrombocytopenia is an early but non-specific marker of sepsis, however the mechanism that focuses on platelet kinetics is still unclear [6,7]. This study proposes that mean platelet volume, along with CRP levels, is raised in neonatal sepsis. And the combination of these two parameters can be used in early diagnosis of neonatal sepsis, thereby facilitating early treatment.

2. Method

After obtaining ethical approval from Institutional Ethical Committee and written informed consent from parents of all the newborns included in the study, all newborns were evaluated for clinical findings of sepsis. Newborns with birth weight <1500 grams, chromosomal abnormalities, previous treatment with IV antibiotics, surgery in past one week, presence of birth asphyxia or meconium aspiration were excluded from the study.

Blood samples were drawn at admission, before administration of IV antibiotics. Following parameters were assessed: Total Leukocyte count (TLC), Absolute Neutrophil Count (ANC), Platelet count, Mean Platelet Volume (MPV) and micro ESR. Qualitative Serial CRP estimation (Serum CRP concentration >0.6mg/dL cut off for positive result) was done at an interval of 24 hours using slide agglutination method.

Blood culture was obtained for all patients. CSF culture and Urine culture etc. were obtained as per the clinical indications. Based on the clinical evaluation and laboratory results, newborns were classified into three groups: Group I (clinical sepsis), Group II (culture proven sepsis) and Group III (healthy controls). Mean Platelet Volume and CRP levels were determined in each group. Data analysis was done using SPSS software version 23.0. *P* value of <0.05 was considered to be statistically significant.

3. Results

A total of 200 preterm and term newborns were enrolled in this study, out of which 100 cases and 100 controls were taken. Among these 100 cases, 45 cases were in clinical sepsis group (Group I) and 55 cases were in culture proven group (Group II). Baseline characteristics of cases and controls are mentioned in table 1.

Table 1: Distribution of baseline characteristics

S. No.	Parameter	Cases (sepsis positive)			Group III (Healthy Controls)
		Group I	Group II	(I + II) Cases	
1.	Birth Weight (grams)	2297.3±579.4	2260.5±520.9	2277.1±545.5	2288.3±505.2
2.	Gestational Age (weeks)	36.89±2.3	36.89±1.9	36.89±2.1	36.65±2.6
3.	Post Natal Age at presentation (days)	5.64±5.5	6.93±8.0	6.28±6.75	3.04±3.4

CRP was serially positive in a significantly higher proportion of cases (66%) as compared to single CRP positive newborns (15%) (P<0.001). MPV values observed in various groups and its association with mortality is depicted in table 2 and figure 1 respectively. In the Culture Proven Sepsis group, 87.27% neonates had growth of gram-negative bacilli, common organisms being *Klebsiella (32.7%), E. coli (18.1%) and Acinetobacter (14.5%)*, while 12.72% neonates had gram-positive sepsis. No significant difference was found in mean MPV among cases with various microorganisms (p >0.05).

Table 2: Mean MPV in various groups

Study Groups	Mean MPV (fL)	Group I vs. II	Group (I+II) vs. III
Group I	10.47 ± 0.69	p = 0.81	p<0.001
Group II	10.51 ± 0.97		
Group III	8.67 ± 0.65		

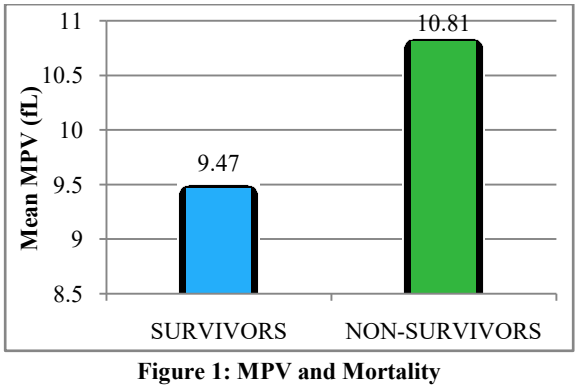

Figure 1: MPV and Mortality

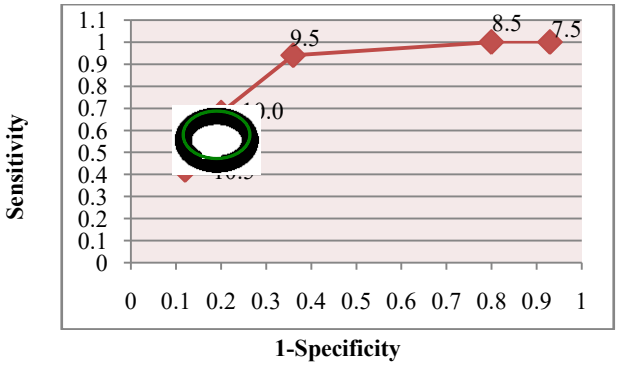

Figure 2: Receiver Operating Characteristic Curve (ROC) for MPV

Area Under Curve	Standard Error	Asymptomatic Sig.	95%Confidence Interval	
			Lower Bound	Upper Bound
0.944	0.015	<0.001	0.915	0.974

Diagnostic cut off of MPV for neonatal sepsis was estimated to be 10.0 fL.

Sensitivity, Specificity, PPV and NPV of MPV alone was 68%, 98%, 97.14% and 75.38% respectively. Sensitivity, Specificity, PPV and NPV of combination of serial CRP and MPV was 81%, 98%, 97.59% and 83.76% respectively.

4. Discussion

Platelets are not only centrally involved in hemostasis, but also in antimicrobial defense and inflammation. Sola-Visner and coworkers demonstrated that thrombopoiesis is up-regulated in neonatal sepsis. They observed that in neonates with sepsis, thrombopoietin (TPO) concentrations and circulating megakaryocyte progenitors were elevated, suggesting an up-regulation of thrombopoiesis mediated by TPO[7]. Mean Platelet Volume is a measurement of average size of platelets. It has been shown to correlate with platelet function and activation. Normally, this value has inverse relationship to platelet count and it increases, as more young platelets are present in the circulation due to increased destruction of platelets [6]. Thus, MPV can help to differentiate consumptive from hypoplastic thrombocytopenia. A higher MPV value is indicative of increased platelet activity and thus more intense inflammation. It is possible that the rise in MPV in septicemia is caused by an increased production of larger and/or younger platelets as a reaction to septicemia-related platelet destruction. However, the presence of an increased MPV at diagnosis indicates that the production of larger platelets cannot be the only cause for the MPV increase in septicemia. A sudden onset rather suggests an external influence on the circulating platelets. In patients with acute bacterial infection increased levels of β-thromboglobulin have been found, indicating *in vivo* activation and release of platelets. It has been postulated that in vivo activation and release can be the cause for the direct MPV increase in septicemia, presuming that activated and released platelets, which are less dense, are also larger [8].

In the present study, role of Mean Platelet Volume was studied as an adjunctive test, in addition to serum CRP levels for the diagnosis of neonatal sepsis. Nuntnarumit *et al* have reported previously that serial levels of CRP at cut off >5mg/L measured at 24-48 hours interval had very high sensitivity, specificity, positive predictive value, and negative predictive value for proven sepsis of 100 per cent, 94 per cent, 91.6 per cent and 100 per cent respectively [9]. Serial CRP has also been reported to be significantly associated with mortality in neonatal sepsis [10]. Thus, we studied MPV in conjunction with serial CRP in the diagnosis of neonatal sepsis.

In this study, mean MPV in control group was 8.67 ± 0.65 fL. Kir-Young Kim *et al* determined the value of MPV in 54 healthy newborns and found a mean value of MPV as 8.21 ± 0.65 fL[11]. In addition, mean MPV was significantly higher in cases as compared to controls in the present study. Lelie and coworkers demonstrated that MPV was increased in 13 of 25 patients with proven septicemia but in none of 25 patients with localized bacterial infection and negative blood cultures [8].

Another study in neonates by Aydin *et al* found that the neonates with culture positive sepsis had the highest CRP levels, lowest platelet counts and lowest uric acid levels when compared to clinical sepsis and healthy controls. MPV had a sensitivity and specificity in diagnosing neonatal sepsis in their study of 54 % and 82% respectively. When combined with CRP its sensitivity and specificity increased to 89% and 79% respectively [12]. They had observed and proposed a diagnostic cut off for MPV of 10.4. The present study proposes a diagnostic cut off of 10.0 for MPV as per the ROC curve. Moreover, in the present study, newborns with mortality had a significantly higher MPV than the survivor group ($p<0.001$). Thus, high MPV was found to be a significant predictor of mortality in neonatal sepsis.

Previous studies have reported the association of high MPV with mortality in patients with severe sepsis/shock [13,14]. Guida *et al.* also demonstrated significant increase of MPV among cases of neonatal sepsis in very low birth weight babies from baseline values. In their study however, there was no significant difference between MPV and PDW of the cases who died and the cases who survived [15].

Oncel *et al* investigated changes in MPV in patients with neonatal sepsis. A comparison of markers of sepsis obtained at baseline revealed WBC, CRP, Interleukin-6 and MPV levels to be significantly higher in newborns with sepsis compared to healthy controls. Mean baseline serum levels of CRP and MPV were significantly higher in proven sepsis group compared to clinical sepsis group, whereas the difference between these groups with regards to baseline serum levels of IL-6 and platelet count was statistically insignificant [16].

Therefore, to conclude, MPV is a good diagnostic tool to aide in the diagnosis of neonatal sepsis. It increases sensitivity of CRP in the diagnosis at a cut off of 10.0 fL. Also, a high MPV is associated with higher risk for mortality in a case of neonatal sepsis.

The study has a few limitations. The cases and controls are not accurately age matched. The cases were recruited at mean age of 6th postnatal day as compared to controls that were recruited at mean age of 3rd postnatal day. This is due to variable age of presentation of cases. Neonates who presented with late onset sepsis presented at a later postnatal age, while early onset sepsis presented at a lesser postnatal age. On the other hand, most controls were recruited in the postnatal wards, hence their post natal age at recruitment coincided with the usual duration of hospital stay in the setting of normal maternal and neonatal outcomes. Furthermore, as this study excluded conditions with false positive CRP (eg. Birth asphyxia, meconium aspiration syndrome etc.) , MPV could not be assessed in such patients. Hence, more studies are required to study these aspects.

What is already known?

- Serum CRP is raised in Neonatal Sepsis and Serum CRP is a component of sepsis screen.

What the study adds?

- Neonatal Sepsis is associated with an increase in Mean Platelet Volume (MPV).
- MPV, when combined with serial CRP measurement, aids in diagnosing neonatal sepsis.
- High MPV is a predictor of mortality in neonatal sepsis.

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