Mean Platelet Volume in Early Onset Neonatal Sepsis

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Abstract

Introduction: Sepsis is a serious life-threatening condition and a leading cause of morbidity and mortality in neonates. The absence of fast and reliable biomarker causes unnecessary admitted owing to suspected neonatal sepsis and applied antibiotic. Mean platelet volume (MPV) has been used in diagnosis, follow-up, and prediction of neonatal morbidity and mortality such as BPD, Sepsis. In this study, we aimed to contribute to the research about whether or not MPV can be used in the diagnosis of neonatal sepsis.

Methods: This retrospective cohort study was conducted in neonatal intensive care unit of Izmir Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey and Acıbadem Hospital, Istanbul, Turkey between March 2018-April 2019. During these twelve months, 287 neonates with EOS were admitted to these two units. Seventy neonates with early onset neonatal sepsis 65 healthy neonates were enrolled in the study.

Result: The diagnostic cut-off values of the CRP and MPV for EOS were 7.2 mg/L, 9.8 fL, respectively. Sensitivity, specificity, PPV and NPV of CRP, MPV and CRP+MPV were 87.9% vs. 74.6% vs. 88.6%; 81.3% vs. 57.1% vs. 82.3%; 82.4% vs. 63.4% vs. 83.3%; 87% vs. 69.2% vs. 87.8%, respectively.

Conclusion: The combined use of CRP and MPV may be useful in the early diagnosis of neonatal sepsis. Our study provides evidence of the benefit of MPV, which can be combined with other markers in the diagnosis of neonatal sepsis.

Abbreviations: EOS: Early-Onset Sepsis; CRP: C-Reactive Protein; SD: Standard Deviation; WBC: White Blood Cell; ANC: Absolute Neutrophil Count; LR+: Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CRP: C-Reactive Protein; RPR: Red Cell Distribution Width to Platelet Ratio

Introduction

Sepsis is a serious life-threatening condition and a leading cause of morbidity and mortality in neonates [1]. Diagnosis of neonatal sepsis is unclear because of its clinical findings are subtle and nonspecific [2]. Therefore, there are two diagnosis related to sepsis; Suspected sepsis and Proven sepsis [3]. Suspected sepsis is a diagnosis assigned to neonates with clinical findings suggestive of sepsis, meaning that there aren’t any positive blood cultures, but the results of additional laboratory tests are positive. Proven sepsis is a diagnosis assigned to the isolation of a pathogenic bacterium from a blood culture. The difficulty of detecting these two diagnoses is that there is not urgently reliable biomarkers to differentiate between suspected or proven sepsis and non-infected neonates [4]. On the other hand, blood culture has been considered as the gold standard for diagnosis of sepsis, but this analysis is still slow and limited by false negative results [5]. CRP is one of the most studied and most used laboratory tests for diagnosis of neonatal sepsis to date. Whereas, CRP increase 10-12 hours after the onset of sepsis and in several conditions [6]. The absence of fast and reliable biomarker causes unnecessary admitted owing to suspected neonatal sepsis and applied antibiotic. Recently, complete blood count (CBC) parameters were used as biomarkers of inflammation and infections. Mean platelet volume (MPV) has been used in diagnosis, follow-up, and prediction of neonatal morbidity and mortality such as BPD, Sepsis [7]. In this study, we aimed to contribute to the research about whether or not MPV can be used in the diagnosis of neonatal sepsis.

Methods

This retrospective cohort study was conducted in neonatal intensive care unit of Izmir Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey and Acıbadem Hospital, Istanbul, Turkey between March 2018-April 2019. During these twelve months, 287 neonates were admitted to these two units. 217 neonates excluded from the study because of SGA, IUGR, perinatal asphyxia, congenital anomaly, congenital heart disease,
chromosomal anomaly, preeclampsia, lack of data. Seventy neonates with early onset neonatal sepsis 65 healthy neonates were enrolled in the study. 42 of the 70 neonates with EOS who enrolled the study group were suspected sepsis and 28 of the 70 neonates with EOS were proven sepsis. The diagnosis of suspected EOS was made by maternal history, clinical findings, laboratory findings, and blood culture. The following clinical findings were used as indicators of EOS: (1) temperature instability (hypothermia, hyperthermia); (2) respiratory alterations (tachypnea, intercostal or subcostal retractions, apnea, cyanosis); (3) cardiovascular alterations (bradycardia, tachycardia, poor perfusion, hypotension); (4) neurologic alterations (poor feeding, hypotonia, lethargy, seizures); and (5) gastrointestinal alterations (feeding intolerance, abdominal distension). The Laboratory findings included CBC, peripheral blood spread, C-reactive protein (CRP), and blood culture. The following laboratory findings were used as indicators of EOS: (1) White blood cell (WBC) count <5,000/mm³ or > 20,000/mm³; (2) Absolute neutrophil count (ANC) <1,000/mm³ or > 17,000/mm³; (3) Immature/total neutrophil ratio > 0.2; (4) Platelet count <150,000/mm³; (5) CRP values > 10 mg/L. Newborns with two or more clinical findings in addition to two or more laboratory findings were diagnosed with EOS and sepsis treatment was applied in our units. Neonates with confirmed pneumonia or other inflammatory conditions, CNS malformations, metabolic disorders, chromosomal abnormalities, intrauterine growth restriction, or birth asphyxia were excluded from the study. Sixty-five healthy neonates with no symptoms, signs, or risk factors for infections who had been hospitalized for physiological jaundice in our units were enrolled as controls. Serum CRP level for control groups was negative (CRP <10 mg/L). Maternal risk factors, demographic information, natal characteristics and laboratory findings of neonates included in the study were collected from patient files. Informed consent was obtained from the parents of all the neonates.

### Statistical Analyses

Statistical analyses were performed using SPSS for Windows statistical package, version 22.0 (SPSS, Chicago, IL, USA). The differences between groups regarding non-parametric quantitative data were assessed by Mann-Whitney’s U-test. The chi-squared test was used for testing significant differences of qualitative variables. The sensitivity, specificity, and optimal salivary CRP cut point were determined using the receiver operating characteristic (ROC) curve. For all statistical analysis, the level of statistical significance was set at p < 0.05.

### Result

A total of 70 neonates with EOS and 65 healthy neonates were included in this study. The patients were classified into three groups; suspected sepsis (n=42) and proven sepsis (n=28) and control group (n=65). No statistical differences were detected between three groups with respect to gestational age, birth weight, gender and delivery mode (Table 1). WBC, ANC, Platelet count, MPV and CRP values were higher in suspected and proven sepsis groups in comparison with the control group (p < 0.05) (Table 2). CRP levels of the suspected, proven sepsis and control groups were 23.5 ± 5.7; 37.1 ± 6.6; 3.4 ± 0.9 mg/L, respectively. MPV levels of the suspected, proven sepsis and control groups were 10.4 ± 2.2; 10.8 ± 3.1; 8.4 ± 1.7, respectively (Table 2). The diagnostic cut-off values of the CRP and MPV for EOS were 7.2 mg/L, 9.8 fl, respectively. Sensitivity, specificity, PPV and NPV of CRP, MPV and CRP and MPV combination were 87.9% vs. 74.6% vs. 88.6%; 81.3% vs. 57.1% vs. 82.3%; 82.4% vs. 63.4% vs. 83.3%; 87% vs. 69.2% vs. 87.8%, respectively (Table 3).

### Table 1: Demographic characteristics of infants included in the study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Suspected Sepsis (n=42) Group 1</th>
<th>Proven Sepsis (n=28) Group 2</th>
<th>Control Group (n=65) Group 3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, week (mean ± SD)</td>
<td>37.2±3.8</td>
<td>38.3 ± 4.4</td>
<td>39.5 ± 5.5</td>
<td>Grup 1-3 &gt;0.05</td>
</tr>
<tr>
<td>BW, g (mean ± SD)</td>
<td>2644±531</td>
<td>2890 ± 623</td>
<td>3278±332</td>
<td>Grup 2-3 &gt;0.05</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (57.1)</td>
<td>13 (46.4)</td>
<td>37 (56.9)</td>
<td>Grup 1-3 &gt;0.05</td>
</tr>
<tr>
<td>Male</td>
<td>18 (42.8)</td>
<td>15 (53.5)</td>
<td>28 (43)</td>
<td>Grup 2-3 &gt;0.05</td>
</tr>
<tr>
<td>Mode of Delivery, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VD</td>
<td>34 (80.9)</td>
<td>19 (67.8)</td>
<td>45 (69.2)</td>
<td>Grup 1-3 &gt;0.05</td>
</tr>
<tr>
<td>C/S</td>
<td>8 (19)</td>
<td>9 (32.1)</td>
<td>20 (30.7)</td>
<td>Grup 2-3 &gt;0.05</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of the hematological parameters of the EOS between three groups.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Suspected Sepsis (n=42)</th>
<th>Proven Sepsis (n=28)</th>
<th>Control Group (n=65)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/L (mean ± SD)</td>
<td>23.5 ±5.7</td>
<td>37.1±6.6</td>
<td>3.4±0.9</td>
<td>Grup 1-3 &lt;0.05 Grup 2-3 &lt;0.05</td>
</tr>
<tr>
<td>WBC 10³/L (mean ± SD)</td>
<td>22.4±6.1</td>
<td>27.8±7.7</td>
<td>15.5±3.9</td>
<td>Grup 1-3 &lt;0.05 Grup 2-3 &lt;0.05</td>
</tr>
<tr>
<td>ANC 10³/L (mean ± SD)</td>
<td>16.7±4.2</td>
<td>19.8±5.2</td>
<td>9.4±3.2</td>
<td>Grup 1-3 &lt;0.05 Grup 2-3 &lt;0.05</td>
</tr>
<tr>
<td>Platelet 10³/L (mean ± SD)</td>
<td>228±55.7</td>
<td>255.2±43.9</td>
<td>291.1±64.2</td>
<td>Grup 1-3 &gt;0.05 Grup 2-3 &gt;0.05</td>
</tr>
<tr>
<td>MPV (fl) (mean ± SD)</td>
<td>10.4±2.2</td>
<td>10.8±3.1</td>
<td>8.4±1.7</td>
<td>Grup 1-3 &lt;0.05 Grup 2-3 &lt;0.05</td>
</tr>
</tbody>
</table>

Abbreviations: EOS: Early-Onset Sepsis, CRP: C-Reactive Protein, SD: Standard Deviation, WBC: White Blood Cell, ANC: Absolute Neutrophil Count Data were expressed as mean ± SD where Student-t test was applied for comparisons or as number and percentage using Chi-square (X²) test.

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Table 3: Statistical analysis of statistically significant parameters of the study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cutt of value</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>LR+</th>
<th>PPV %</th>
<th>NPV %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP mg/L</td>
<td>7.2</td>
<td>87.9</td>
<td>81.3</td>
<td>8.3</td>
<td>82.4</td>
<td>87</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.8</td>
<td>74.6</td>
<td>57.1</td>
<td>5.9</td>
<td>63.4</td>
<td>69.2</td>
</tr>
<tr>
<td>CRP+MPV</td>
<td>88.6</td>
<td>82.3</td>
<td>83.3</td>
<td>83.3</td>
<td>87.8</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: LR+: Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value; CRP: C-Reactive Protein; RPR: Red Cell Distribution Width to Platelet Ratio.

Discussion

Neonatal sepsis is the most common cause of morbidity and mortality in term and preterm infants [8]. Especially preterm newborns are more susceptible to infections than children of other ages [9]. Neonatal sepsis has been defined as the presence of bacteria in sterile body fluids, namely, blood, urine, cerebrospinal, peritoneal, and pleural fluid [10]. It has been classified as early onset sepsis (EOS) and late onset sepsis (LOS) on the basis of time of onset after neonatal birth [11]. The signs and the clinical manifestations of neonatal sepsis are nonspecific and have varied clinical features [12-15]. The production of microorganism in blood culture still remains the gold standard in the diagnosis of neonatal sepsis, however it takes approximately 48 hours [12,16]. In addition, the lack of growth in blood culture doesn’t always exclude the diagnosis of neonatal sepsis [12,17-19]. Various inflammatory biomarkers have been evaluated with the aim of identifying those with the highest sensitivity, specificity, positive and negative predictive values for sepsis diagnosis [12,16]. As a result, a combination of findings is required to ensure accurate diagnosis of neonatal sepsis. Mean platelet volume (MPV) is a hemogram parameter that is important in the management of septic patients [20]. MPV has been used in diagnosis, follow up and prediction of neonatal sepsis in neonates [21,22]. Also, Cekmez investigated the relationship between MPV and other diseases in preterm infants. According to their study high MPV levels may reflect the presence of a risk factor for the development of NEC, BPD and IVH in extremely preterm infants. On the other hand, as opposed to the findings in our study they didn’t find any association between high MPV levels and development of neonatal sepsis [23].

According to Eberhardt et al. septic patients revealed a correlation between MPV value at admission and the risk of death. Patients who died presented with a higher initial value of MPV (9.6 versus 9.19 fL, p=0.031) [24]. In another study the association between MPV and the disease severity as evaluated by APACHE IV, and APS scores, were shown to be statistically significant (p=0.03, respective p=0.02) [25]. In our study, MPV values showed a significant difference between suspected, proven sepsis and control groups, with a mean of 10.4 ± 2.2 fL, 10.8 ± 3.1 fL and 8.4 ± 1.7 respectively, and showed a significant correlation with CRP. Oncel et al. also reported a higher mean MPV in septic neonates when compared with controls (8.82 ± 0.8 fL and 8.44 ± 0.5 fL, respectively) [21]. On the other hand, Celmek et al. didn’t found any association between high MPV values and sepsis [23]. According to our study, MPV was able to predict diseases neonates and demonstrated diagnostic accuracy with 74.6% sensitivity and 57.1% specificity at a cut-off point of 9.8 fL. Aydın et al. reported that the diagnostic cut-off value for MPV in neonates with sepsis, 10.4 fL, presented sensitivity of 54% and specificity of 82% [26]. Recently, Yao et al. found that optimal cut-off point of MPV for the diagnosis of sepsis was 11.4 fL, with sensitivity of 40.5% and specificity of 88.4% [27]. Omran et al. showed that optimal cut-off point of MPV for the diagnosis of sepsis was 10.2 fL, with sensitivity of 80% and specificity of 80% [28].

Conclusion

In conclusion, the combined use of CRP and MPV may be useful in the early diagnosis of neonatal sepsis. Our study provides evidence of the benefit of MPV, which can be combined with other markers in the diagnosis of neonatal sepsis.

Acknowledgment

None.

Conflict of Interest

No conflict of interest.

References