Mean Platelet Volume in Neonatal Sepsis

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Background: The aim of this study was to investigate any changes in mean platelet volume (MPV) in patients with neonatal sepsis (NS). **Methods:** Subjects were stratified into two groups: proven sepsis (Group 1a) and clinical sepsis (Group 1b). The control group (Group 2) consisted of healthy newborns matched for gestational age and birth weight. **Results:** A total of 100 patients with NS (35 with proven sepsis and 65 with clinical sepsis) and 50 healthy controls were enrolled. A comparison of markers of sepsis obtained at baseline revealed white blood cell count (WBC), C-reactive protein (CRP), interleukin-6 (IL-6), and MPV levels to be significantly higher in newborns

with sepsis compared to healthy controls ($P = 0.01$, <0.001 , <0.001 , and 0.001 , respectively). Mean baseline serum levels of CRP and MPV were significantly higher in Group 1a compared to Group 1b ($P = 0.003$, $P = 0.007$, respectively), whereas the difference between group with regards to baseline serum levels of IL-6 and platelet count was statistically insignificant ($P = 0.14$, $P = 0.28$, respectively). **Conclusion:** This is the first study to demonstrate a statistically significant difference with regard to baseline MPV values between patients with sepsis (proven or clinical) and healthy controls. J. Clin. Lab. Anal. 26:493–496, 2012. © 2012 Wiley Periodicals, Inc.

Key words: mean platelet volume; neonatal sepsis; C-reactive protein; interleukin-6

INTRODUCTION

Neonatal sepsis (NS) is a potentially life-threatening clinical condition that requires early intervention. Initial symptoms are generally nonspecific and may mimic several other medical conditions. NS is associated with high morbidity and mortality rates if not treated promptly. Various clinical and laboratory findings may help in making a diagnosis (1, 2). Several acute phase reactants such as C-reactive protein (CRP) and interleukin-6 (IL-6) have proven helpful in the diagnosis of an ongoing infection, the levels of which increase with the degree of inflammation. However, the rate at which each marker begins to show elevations and the time to normalization differs with every marker (3–5).

The measurement of mean platelet volume (MPV) has been available since 1970s and it is routinely done nowadays in clinical practice (6). Although it has been known that MPV in healthy population showed an inverse relationship with platelet count (PC) (7), however, its biological, clinical meaning and inter-relationship with PC

changes in sepsis is still unclear. Previous studies on neonates have reported on significantly higher baseline MPV values in patients with respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (8, 9). The role of MPV in cases of NS has not been extensively investigated before (10). The aim of this study was to investigate any changes in MPV in patients with NS.

MATERIALS AND METHODS

Patient Selection

This prospective study was conducted at Zekai Tahir Burak Maternity Teaching Hospital situated in

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Ankara, with the approval of the local ethics committee. Consecutive newborns evaluated at our hospital between March and July 2011 with a suspicion of NS were screened for eligibility for inclusion in this study. A diagnosis of clinical sepsis required the presence of at least three of the following: bradycardia ($<100/\text{min}$), tachycardia ($>200/\text{min}$), hypotension, hypotonia, seizures, apnea, tachypnea, cyanosis, respiratory distress, poor skin color and perfusion, feeding difficulty, irritability, lethargy in addition to laboratory results showing elevated levels of CRP or IL-6. Patients with culture positivity were accepted as proven sepsis (11).

Patients with sepsis (Group 1) were further divided into two subgroups based on whether they had proven (Group 1a: newborns with positive blood cultures, clinical findings in agreement with the diagnosis, and elevated IL-6 and/or CRP levels during the clinical course) or clinical (Group 1b: newborns with clinical findings of infection, plus a significant rise in IL-6 and/or CRP levels during the clinical course, but with negative blood cultures). The control group (Group 2) consisted of healthy newborns who were admitted to neonatal intensive care unit for other than sepsis. Patients were further subdivided into two groups based on the time of development of sepsis; patients diagnosed within the first 72 hr of life were considered to have early onset NS (EOS), whereas the development of sepsis in newborns older than 72 hr was described as late onset NS (LOS).

Laboratory Analyses

The day that a clinical diagnosis of sepsis was made was considered day 1, and venous blood sampling was performed within the first 12 hr after first presentation. Blood sampling was repeated after 5 days after first presentation. From each sample obtained, determination of white blood cell (WBC) count, PC, MPV, CRP, and IL-6 levels were performed immediately.

Blood for complete blood counts was obtained either by venipuncture, by arterial puncture, or through a central catheter. PC and MPV determinations were performed using a twice daily calibrated Cell-Dyn 3700 automated hemocytometer (Abbott, IL).

Serum concentrations of CRP were measured by a Tinaquant CRP (Latex) high sensitive immune turbidimetric assay on a Roche Modular P analyzer (Roche kit, Roche Diagnostics, Mannheim, Germany) according to manufacturer instructions. Plasma levels of IL-6 were determined by IL-6 solid phase, enzyme labeled, chemiluminescent sequential immunometric assay on an IMMULITE 2000 analyzer (Siemens Diagnostic Product Corporation, Los Angeles, CA) as per manufacturer instructions.

Blood Culture

Blood cultures were performed on newborns when NS was suspected. Blood culture was not taken from healthy controls. The Bactec microbial detection system (Becton-Dickinson, Sparks, MD) was used to detect positive blood cultures. Two-blood culture positivity was required to confirm *Staphylococcus epidermidis* sepsis.

Statistical Analyses

All statistical analysis was carried out using SPSS for Windows version 15 (SPSS, Chicago, IL). Comparison of parametric data and nonparametric data between groups was done using Student's *t*-test and Mann-Whitney *U*-test, respectively. Results are given as mean $\pm$ standard deviation and median (min-max). A *P* value under 0.05 was considered significant.

RESULTS

A total of 100 newborns fulfilling the criteria for a diagnosis of sepsis were enrolled in the study. Out of the remaining 100 patients, 35 had proven sepsis (Group 1a) and 65 had clinical sepsis (Group 1b). The control group (Group 2) consisted of 50 healthy controls. The demographic characteristics and laboratory parameters of the study population have been summarized in Table 1. The difference between patients with sepsis (Group 1) and healthy controls (Group 2) with regard to each of maternal age, gestational age, birth weight, gender, mode of delivery was statistically insignificant. However, while none of the healthy controls were born to mothers with premature rupture of membranes (PROM), 18 (18%) of the newborns who developed sepsis were born following PROM and the difference deemed statistically significant ($P = 0.001$).

A comparison of markers of sepsis obtained at baseline revealed WBC, CRP, IL-6, and MPV levels to be significantly higher in newborns with sepsis compared to healthy controls ($P = 0.01$, <0.001 , <0.001 , and 0.001 , respectively). When patients were divided into two groups based on gestational age, no statistically significant difference in terms of baseline WBC, PC, CRP, IL-6, and MPV were observed between preterm infants (<37 gestational weeks; $n = 64$) and term infants (≥ 37 gestational weeks; $n = 36$).

A comparison of patients with sepsis based on the age of diagnosis revealed newborns with LOS ($n = 34$) to have been born at significantly lesser gestational ages (30 ± 4.1 vs. 35.6 ± 4.6 weeks) with lower birth weights (1396 ± 690 vs. 2508 ± 1063 g) than patients with EOS ($n = 66$) ($P < 0.001$ for both). Furthermore, significantly

TABLE 1. Demographic characteristics and laboratory parameters of patients with sepsis and healthy controls

Parameters	Group 1 (sepsis) (n = 100)	Group 2 (controls) (n = 50)	P-value
Gestational age, weeks ^a	33.7 ± 5.1	32.3 ± 3.9	0.11
Birthweight, g ^a	2130 ± 1087	1905 ± 781	0.19
Male gender ^b	64 (64%)	30 (60%)	0.63
Mode of delivery (caesarean) ^b	51 (51%)	30 (60%)	0.29
PROM ^b	18 (18%)	0 (0%)	0.001
RDS ^b	36 (36%)	14 (28%)	0.32
Hb (g/dl) ^a	15.2 ± 2.9	15.7 ± 2	0.36
WBC on first day (/mm ³) ^a	15,817 ± 7,250	13,028 ± 4,491	0.01
PC on first day (/mm ³) ^a	226,153 ± 106,889	226,060 ± 85,254	0.99
MPV on first day (fl) ^a	8.57 ± 0.67	7.58 ± 0.45	0.001
CRP on first day (mg/ml) ^c	27.4 (0.11–45.2)	0.3 (0.01–4.87)	<0.001
IL-6 on first day (pg/ml) ^c	122.5 (5.3–1000)	4.6 (2–26)	<0.001

^aValues are given as mean ± standard deviation.^bValues are given as percentage.^cValues are given as median (min–max).

WBC, white blood cell count; PC, platelet count; MPV, mean platelet volume; CRP, C-reactive protein levels; IL-6, interleukin 6.

more subjects in the LOS group had proven sepsis compared to the EOS group ($P < 0.001$). Mean baseline serum levels of CRP and IL-6 were higher in patients with LOS than patients with EOS ($P = 0.002$ and $P = 0.02$, respectively). After fifth day, statistically significant elevations of only CRP levels were observed in the LOS group compared to patients with EOS ($P = 0.006$). The observed trend for CRP levels was as to remain elevated for longer and to return to normal later in patients with LOS than those with EOS.

Subgroup comparisons revealed patients with clinical sepsis to have higher baseline WBC levels than proven sepsis, but it was insignificant ($P = 0.26$). Mean baseline serum levels of CRP and MPV were significantly higher in Group 1a compared to Group 1b ($P = 0.005$, $P = 0.007$, respectively). But mean baseline serum levels of IL-6 and PC were not significant ($P = 0.14$, $P = 0.28$, respectively). Mean CRP level on fifth day was significantly higher in patients with proven sepsis compared to those with clinical sepsis ($P < 0.001$), while a similar difference was not observed for WBC, PC, MPV, and IL-6 values on fifth day. Results of subgroup analysis have been summarized in Table 2.

The microorganisms that were isolated from the blood cultures of patients with sepsis were *S. epidermidis* in 16

TABLE 2. Comparison of demographic characteristics, WBC, PC, MPV, CRP, and IL-6 in patients with proven and clinical sepsis

Parameters	Group 1a (Proven sepsis) (n = 35)	Group 1b (Clinical sepsis) (n = 65)	P-value
Gestational age, weeks ^a	31.8 ± 5.4	34.7 ± 4.8	0.009
Birthweight, g ^a	1724 ± 873	2349 ± 1133	0.006
Male gender ^b	19 (54.3%)	45 (69.2%)	0.13
Mode of delivery (caesarean) ^b	14 (40%)	37 (56.9%)	0.10
Sepsis days ^c	9 (1–107)	2 (1–50)	<0.001
WBC on first day (/mm ³) ^a	14,714 ± 6,906	16,410 ± 7,421	0.26
WBC on fifth day (/mm ³) ^a	12,011 ± 2,967	13,480 ± 5,139	0.12
PC on first day (/mm ³) ^a	210,494 ± 96,453	234,584 ± 111,915	0.28
PC on fifth day (/mm ³) ^a	261,238 ± 118,272	275,938 ± 93,046	0.49
MPV on first day (fl) ^a	8.82 ± 0.8	8.44 ± 0.5	0.007
MPV on fifth day (fl) ^a	7.82 ± 0.74	7.67 ± 0.61	0.28
CRP on first day (mg/ml) ^c	34.3 (2.7–45.2)	24 (0.11–45)	0.003
CRP on fifth day (mg/ml) ^c	10.9 (0.05–44.6)	2.7 (0.06–42.8)	<0.001
IL-6 on first day (pg/ml) ^c	144 (5.3–1,000)	98.3 (6.6–1,000)	0.146
IL-6 on fifth day (pg/ml) ^c	5 (2–95)	3.2 (2–52)	0.464

^aValues are given as mean ± standard deviation.^bValues are given as percentage.^cValues are given as median (min–max).

WBC, white blood cell count; PC, platelet count; MPV, mean platelet volume; CRP, C-reactive protein levels; IL-6, interleukin 6.

cases (45.7%), *Escherichia coli* in seven cases (20%), *Klebsiella pneumonia* in five cases (14.2%), and *Acinetobacter baumannii* in three cases (8.5%). Growths of *Klebsiella oxytoca* and *Pseudomonas aeruginosa* were observed in two cases each (5.7%). Overall, Gram-positive bacteria were isolated in 16 (45.7%) patients with proven sepsis compared to a Gram-negative growth in 19 (54.3%) patients. Baseline serum levels of CRP and IL-6 were significantly higher in newborns with confirmed Gram-negative sepsis compared to those infected with Gram-positive bacteria ($P = 0.002$ and $P = 0.03$, respectively). On the contrary, baseline serum levels of MPV and PC were not significant in newborns with confirmed Gram-negative sepsis compared to Gram-positive sepsis ($P = 0.13$ and $P = 0.08$, respectively). Changes in serum levels of MPV from baseline and after fifth day are depicted in Figure 1.

Fig. 1. Plots mean platelet volume (MPV) level of patients with sepsis ($n = 100$) and control group ($n = 50$).

DISCUSSION

Some of the studies have shown that increases in MPV are associated with NS. Increased MPV indicates an increased proportion of young platelets in the circulation, because platelets decrease in size as they age, and is suggestive of increased platelet production and/or increased platelet destruction (12, 13).

In a study by Guida et al. (10) on low birth weight (<1500 g) newborns with culture-positive sepsis, thrombocytopenia (<100,000) was observed in 54% of sepsis episodes with 61% of patients having an elevated MPV. In this study, sepsis-related elevations in baseline MPV occurred regardless of the underlying causative agent (76% Gram-positive bacteria, 16% Gram-negative bacteria, 8% fungus), with no ascertainable difference between microorganism groups. Based on our results, 19 (54.3%) patients with proven sepsis had a Gram-negative growth on blood cultures compared to 16 (45.7%) patients with a Gram-positive growth. No fungal growth was observed in any of our patients, and we could not establish a statistically significant association between type of culture growth and MPV values.

In a study on 18 neonates with coagulase-negative staphylococcal sepsis, O'Connor et al. reported on significant elevations in MPV with rapid normalization of values with appropriate treatment of the underlying infection (14). *Staphylococcus epidermidis* was isolated in the blood cultures of all our patients with a Gram-positive growth. We did not observe a significantly higher MPV in these patients compared to those with a Gram-negative growth. However, we managed to demonstrate a marked decrease in MPV on fifth day of treatment.

In another study by Vander Lelie et al. on 25 adult patients with proven sepsis, an elevated MPV was observed in 13 cases with normalization of values 1 week

after initiation of treatment. Elevations were particularly pronounced in patients with invasive infections such as endocarditis and abdominal abscess. Investigators postulated the MPV may be useful as an indicator of invasive bacterial infections and septicemia (15). None of the patients in our study had an invasive infection, and significant reductions in MPV were observed on the fifth day of evaluation.

To the best of our knowledge, this is the first study to demonstrate a significantly higher MPV in patients with sepsis (proven and clinical) compared to healthy controls. We suggest that this finding should be confirmed by more comprehensive clinical studies.

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