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Mean platelet volume/count and mortality in extremely low birth weight infants of preeclamptic mothers

Abstract

Purpose: To compare complete blood count (CBC) parameters in extremely low birth weight (ELBW) infants born to mothers with and without preeclampsia and to evaluate whether these parameters could be used to determine the prognosis of infants born to mothers with preeclampsia.

Method: Thirty-eight infants of preeclamptic mothers (IPM) and 77 infants of non-preeclamptic mothers (INPM) were included in the study. The CBC parameters of ELBW infants were evaluated at the sixth hour of life.

Results: The mean hemoglobin level of the IPM group was higher than the INPM group (16.4 ± 2.4 vs 15.3 ± 2.4 ; $p=0.02$). The mean platelet count of the IPM Group was significantly lower than the INPM group (168 ± 65 vs 206 ± 78 ; $p=0.008$). Overall and 7th day of life survival of infants were not different between the groups, but there was a correlation between platelet count of the IPM group and mortality in the first 7 days of life and overall mortality ($r=-0.38$, $p=0.023$ and $r=-0.36$, $p=0.029$). A cut-off point of $<100,000/\text{mm}^3$ had significant predictive value for mortality (sensitivity of 84%, specificity of 91%). Also, MPV/platelet count correlated significantly with overall mortality and mortality in the first 7 days of life in infants of preeclamptic mothers ($p=0.05$, $r=0.319$; $p=0.04$, $r=0.336$, respectively). A cut-off point of >0.4 had significant predictive value for mortality (sensitivity of 91%, specificity of 66%).

Conclusion: Hemoglobin and platelet counts were statistically different in ELBW infants born to preeclamptic mothers compared with non-preeclamptic mothers. Although the survival was not different between the two groups, platelet count and MPV/platelet count ratio were significantly correlated with overall mortality and mortality in the first 7 days of life in infants of preeclamptic mothers.

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Preeclampsia is new-onset hypertension of a pregnant woman with proteinuria with or without edema. Infant perinatal mortality is increased in women with preeclampsia and primarily results from the need for early delivery as prematurity remains the most important threat to the infants of hypertensive mothers [1,2]. Damaged trophoblastic invasion of the maternal vessels and uteroplacental ischemia are the major factors in the pathophysiology of preeclampsia. There are also studies suggesting that platelets play a major role in the pathogenesis of preeclampsia [3,4]. There are many studies on platelet indices in preeclampsia in pregnant women and it has been suggested that these parameters have a prognostic significance in determining the severity of preeclampsia [5]. Conversely, there are some studies suggesting that whole blood platelet aggregation fails to detect differences between preeclampsia and normal pregnancy [6]. Among very low birth weight neonates, pre-eclampsia and intrauterine growth restriction are associated with a lower platelet mass [7]. Mean platelet volume (MPV), a readily available marker of platelet activation, is used in the assessment of prothrombotic and pro-inflammatory potentials in several clinical conditions [8]. Recently there has been much interest in this index as an indicator of platelet reactivity, and thus a predictor of clinical outcomes. There are limited data on hematologic parameters, especially platelet reactivity, of extremely low birth weight (ELBW) (birth weight < 1000 g) infants born to preeclamptic mothers. The aim of this study is to shed light on this issue.

We aimed to compare complete blood count (CBC) parameters, especially platelet count and mean platelet volume (MPV), in ELBW infants of preeclamptic and non-preeclamptic mothers. We also aimed to evaluate whether hematologic parameters, especially platelet count and indices, could be used to determine the prognosis and mortality of ELBW infants of preeclamptic mothers.

Materials and Methods

This study was carried out with a total of 115 ELBW infants who were followed for 2 years in a tertiary neonatal intensive care unit of Turkey at the Zekai Tahir Burak Maternity Teaching Hospital situated in Ankara. Thirty-eight of the infants were ELBW infants born to preeclamptic mothers (IPM) and 77 were ELBW infants born to non-preeclamptic mothers (INPM). In the diagnosis of preeclampsia, medical history, obstetric examination and laboratory tests were used. After the 20th week, blood pressure measured at least twice at 6-h intervals and found to be higher than 140/90 mmHg, or average arterial pressure higher than 105 mmHg, proteinuria

higher than +1 in spot urine or higher than 300 mg in 24 h were taken into consideration [9].

Neonatal outcomes and hematologic parameters of preeclamptic mothers of ELBW infants were compared to mothers without preeclampsia that were delivered preterm for other indications. The outcomes analyzed included overall mortality, mortality in the first 7 days of life, SGA (small for gestational age), Apgar 1, Apgar 5 and Clinical Risk Index Score for Babies (CRIB score).

All procedures followed were in accordance with the ethical standards of the Responsible Committee on Human Experimentation (Institutional and National) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from parents of all patients for being included in the study.

Sampling and analysis

Venous blood sampling (2 cc) was performed from a peripheral vein or through a central catheter at the sixth hour of life for CBC. The blood sample was collected in dipotassium ethylenedinitrotetraacetic acid tubes. CBC was performed using a twice-daily calibrated Cell-Dyn 3700 automated hemocytometer (Abbott, IL). The MPV and platelet distribution width (PDW) were calculated automatically in the CBC tests. The CBC parameters, including the platelet indices, MPV and PDW, were analyzed within 5 minutes after taking the blood sample. The MPV was calculated using the following formula: $MPV (fL) = Pct (\%) \times 1000 \div PLT (\times 10^3 / \mu L)$, where PLT is the platelet count and is the number of particles between the upper and lower discriminators and Pct is the platelet crit, which was calculated electronically from the raw histogram data. The normal range for MPV was 7–10.7 femtolitre (fl) in our laboratory.

Statistical analysis

The SPSS 16 for Windows® was used for statistics in the study. Normally distributed data are given as mean and standard deviation [SD]; other data are presented as median and range. Demographic percentage and mean outcome measures of the patients were compared between the two groups with Fisher's exact test, Chi-squared test, and Student's t-test, respectively. Abnormally distributed data were evaluated with the Kolmogorov-Smirnov test. A p-value of <0.05 was considered statistically significant.

TABLE 1. Demographic patterns and hematologic parameters of ELBW infants born to preeclamptic and nonpreeclamptic mothers

	IPM Group (Infants of IPM) (n=38)	INPM Group (Infants of NIPM) (n=77)	p
Gestational age (weeks) (mean±SD)	27.5 ± 2.0	26.9 ± 2.4	NS*
Birth weight (g) (mean±SD)	847± 116	836 ± 143	NS
Gender (M/F)	23/15	38/39	NS
SGA (n) (%)	12 /31.5	5 /6.5	0.001
APGAR 1 (median)	4 (1-7)	4 (1-7)	NS
APGAR 5 (median)	7 (3-9)	7 (1-9)	NS
CRIB Score (median)	5 (1-12)	7 (0-19)	0.06
Mortality	12 (31.5%)	26 (34.0%)	NS
Mortality in first 7 days of life	9 (23.6%)	23 (29.9%)	NS
White blood cell (WBC) (×10 ⁹ /l)	15.6±9.4	13.8±8.3	NS
Hemoglobin (g/dl)	16.4±2.4	15.3±2.4	0.02
Hematocrit (%)	49.0±7.1	46.7±10.6	NS
Mean cell volume (MCV) (fl)	116.4±6.1	114.2±6.6	NS
Mean cell hemoglobin concentration (MCHC) (g/dl)	33.6±1.4	33.5±4.0	NS
Red cell distribution width (RDW) (%)	13.0±5.1	13.6±4.6	NS
Platelet (PLT) (×10 ⁹ /l)	168±65	206±78	0.008
Mean Platelet Volume (MPV) (fl)	7.7±0.78	7.9±3	NS
MPV/PLT	0.054±0.031	0.044±0.030	NS
Platelet distribution width (PDW)	9.50±2.81	9.49±2.46	NS

Abbreviations: ELBW, extremely low birth weight; IPM: infants born to preeclamptic mother; NIPM: infants born to non- preeclamptic mother; NS: non-significant

Results

We performed complete blood count parameters of 115 ELBW infants at the sixth hour of life. Thirty-eight of the newborns were infants of preeclamptic mothers. Demographic patterns and hematologic parameters of ELBW infants born to preeclamptic and non-preeclamptic mothers are shown in Table 1.

Gestational age and birth weight of the infants were not significantly different between the groups. The number of infants who were small for gestational age was significantly higher in the IPM group. Apgar 1, Apgar 5 and CRIB scores were not different between the groups. Overall and 7th day of

life survival of infants born to preeclamptic mothers were not different from the infants born to non-preeclamptic mothers.

Hemoglobin values were significantly higher in the IPM group. Mean cell volumes (MCV), mean cell hemoglobin concentration (MCHC) and red cell distribution width (RDW) were not significantly different in the IPM and IPNM groups. Platelet count was significantly lower in the IPM group than the IPNM group ($p=0.008$) (Table 1). The MPV and mean PDW were not statistically different between the two groups.

There was a correlation between the platelet count of the IPM group and mortality in the first 7 days of life and overall mortality ($r=-0.38$, $p=0.023$ and $r=-0.36$, $p=0.029$) (Figure 1).

TABLE 2. The comparison of survivors and non survivors of IPM

	Non survivors of IPM (n=12)	Survivors of IPM (n=26)	P
White blood cell (WBC) ($\times 10^9/l$)	15.69 ± 16.42	15.66 ± 12.81	0.89
Hemoglobin (g/dl)	16.51 ± 2.61	16.46 ± 2.43	0.66
Hematocrit (%)	49.61 ± 7.75	48.82 ± 6.95	0.84
Mean cell volume (MCV) (fl)	118.66 ± 7.85	115.44 ± 5.066	0.14
Mean cell hemoglobin concentration (MCHC) (g/dl)	33.07 ± 0.87	33.88 ± 1.67	0.12
Red cell distribution width (RDW) (%)	13.2 ± 5.14	12.8 ± 5.24	0.83
Platelet (PLT) ($\times 10^9/l$)	139.75 ± 51	182.84 ± 67	0.04*
MPV (fl)	7.81 ± 1.01	7.65 ± 0.66	0.88
MPV/PLT	0.068 ± 0.045	0.047 ± 0.019	0.03*
PDW	9.92 ± 3.23	9.29 ± 2.62	0.5

FIGURE 1. Comparison of platelet counts of survivors and non-survivors of IPM

Abbreviations: IPM, preeclamptic mothers; PLT, platelet

FIGURE 2. Comparison of MPV/PLT ratio of survivors and non-survivors of IPM

Mean platelet volume (MPV) and platelet (PLT) count and extremely low birth weight infant mortality of preeclamptic mothers (IPM).

A cut-off point of $<100,000/\text{mm}^3$ was found to have significant predictive value for mortality according to receiver-operating characteristics curve analysis. This cut-off point had a sensitivity of 84% and a specificity of 91%.

MPV was significantly correlated with CRIB score and APGAR 1 scores in the IPM group ($p=0.015$, $p=0.045$, respectively). MPV was slightly correlated with APGAR 5 score ($p=0.06$) but MPV was not correlated with overall mortality and mortality in the first 7 days of life in the IPM group ($p=0.491$, $p=0.395$, respectively). MPV/platelet count was weakly correlated with CRIB scores but not correlated with APGAR1 and 5 scores ($p=0.01$, $r=0.248$; $p=0.23$, $r=-0.124$; $p=0.92$, $r=-0.011$, respectively). MPV/platelet count was significantly lower in survivors of the IPM group. MPV/platelet count was significantly correlated with overall mortality and mortality in the first 7 days of life in infants of preeclamptic mothers ($p=0.05$, $r=0.319$; $p=0.04$, $r=0.336$, respectively) (Figure 2). A cut-off point of >0.4 was found to have significant predictive value for mortality according to receiver-operating characteristics curve analysis. This cut-off point had a sensitivity of 91% and a specificity of 66%.

The comparison of survivors and non-survivors of the IPM group is shown in Table 2.

Discussion

The major finding of our study is that hemoglobin and platelet counts were statistically different in ELBW infants born to preeclamptic mothers compared with non-preeclamptic mothers and that platelet count and MPV/platelet count ratio were significantly correlated with overall mortality and mortality in the first 7 days of life in infants of preeclamptic mothers.

A cut-off point of platelet count $<100,000/\text{mm}^3$ was found to have significant predictive value for mortality with a high sensitivity and specificity. MPV/platelet count ratio with a cut-off point of >0.4 was also found to have significant predictive value for mortality, with a high sensitivity and specificity. The role of platelet indices and platelet count as novel prognostic markers in different diseases, especially preeclampsia, is of much interest. Studies comparing the MPV and platelet numbers of preeclamptic mothers with normal pregnancies have shown variable results; whereas some studies found no statistically significant difference between preeclamptic women and control groups for platelet and MPV values, other studies found lower platelet numbers and higher MPV values in preeclamptic women. Altınbas *et al.* showed that MPV levels were higher in pregnant women than in a control group; however, MPV did not differ either between

pregnant women with mild and severe preeclampsia or between pregnant women with preeclampsia and non-preeclamptic [10]. On the other hand, von Dadelszen *et al.* found that the MPV to platelet ratio was more sensitive than MPV alone in predicting preeclampsia-related adverse maternal outcome [11]. The data are conflicting but more data are accumulating. There are data on the importance of these parameters predicting preeclampsia but little data for infants of preeclamptic mothers. In particular, data on platelet count and indices of ELBW infants are limited.

In addition, the underlying mechanism of these parameters as prognostic factors has not been fully elucidated. Akcan *et al.* studied the relationship between thrombocytopenia and MPV in babies of preeclamptic mothers but no significant correlation was found between MPV and platelet count [1]. There are no data in the literature on the relationship between platelet indices and mortality in ELBW infants of preeclamptic mothers. In our group, MPV and PDW were not significantly correlated with overall mortality and mortality in the first 7 days of life in infants of preeclamptic mothers. In addition, MPV was significantly correlated with CRIB score and APGAR 1 scores in the IPM group. Platelet count and MPV/platelet count was significantly correlated with overall mortality and mortality in the first 7 days of life in infants of preeclamptic mothers. A cut-off point of MPV/platelet count >0.4 was found to have significant predictive value for mortality with a sensitivity and specificity. This correlation may reflect the role of platelet count in survival. On the other hand, it has been emphasized that MPV is highest in babies with thrombocytopenia and that MPV increases with the decrease in platelets among the groups [1]. This result suggested to us that thrombocytopenia seen in the babies of preeclamptic mothers may be related to destruction of platelets. Also, while thrombocyte count decreases, MPV can increase. This can lead to an elevation of the MPV/platelet ratio, since there was a correlation between platelet count in the IPM group and mortality in the first 7 days of life and overall mortality ($r=-0.38$, $p=0.023$ and $r=-0.36$, $p=0.029$). A cut-off point of $<100,000/\text{mm}^3$ was found to have significant predictive value for mortality according to receiver-operating characteristics curve analysis, with a high sensitivity and specificity.

Hemoglobin values were significantly higher in the IPM group. Because of compensatory mechanisms such as increased systemic oxygen-carrying capacity, erythropoietin in infants born to preeclamptic mothers and the preponderance of SGA infants in the IPM group, an elevation of hemoglobin values were to be expected. The pathogenesis of thrombocytopenia

among infants born to mothers with preeclampsia is unknown. One potential mechanism is that preeclampsia, and the resultant fetal hypoxia, has a direct depressant effect on megakaryocyte proliferation [12].

Consistent with the literature [13,14], our study showed that the frequency of SGA infants in the IPM group (31.5%) was higher than in the IPNM group (6.5%).

Our study has some limitations. The diagnosis of preeclampsia was not classified as mild or severe. The severity of preeclampsia might lead to a classification of infants and laboratory findings. Since our center is a referral hospital, most of the mothers were severely preeclamptic; therefore, our results can be accepted as ELBW infants born to severely preeclamptic mothers. The other limitation of our study was the anticoagulant agents used in the collecting tubes may have affected MPV values. However, this effect cannot be avoided. Because of the retrospective data collection and lack of maternal data, information in our study is limited to routine protocol approaches, but nevertheless sheds light on the relationship between platelet indices and prognosis in ELBW infants of preeclamptic mothers. Our study added new data to the literature on platelet count and MPV/platelet count ratio as significant predictors of mortality in ELBW newborns of preeclamptic mothers.

Conclusion

In addition to thrombocytopenia in infants born to preeclamptic mothers, hemoglobin levels were higher than in infants of non-preeclamptic mothers. Platelet count and MPV/platelet count ratio may be used for prediction of mortality in ELBW newborns of preeclamptic mothers. Future studies are needed to evaluate the role these indices may play in the prediction of mortality in this preeclamptic population.

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