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May Platelet Indexes Be Effective in Intracranial Hemorrhage of Preterm Infants?

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Abstract

Objective: Preterm newborns are at increased risk of developing morbidities including germinal matrix hemorrhage and intraventricular hemorrhage. In this study, we aimed to examine the efficacy of platelet parameters on germinal matrix hemorrhage and intraventricular hemorrhage in preterm newborns.

Methods: A total of 54 preterm infants between 23 and 36 gestational weeks, and followed-up with germinal matrix hemorrhage and intraventricular hemorrhage in our neonatal intensive care unit were included in our study. Patients' demographic data such as age and gender, birth weight, intrauterine growth retardation, blood transfusion, platelet transfusion, duration of hospitalization, and outcomes were recorded. The infants were divided into 2 groups according to Volpe's germinal matrix hemorrhage and intraventricular hemorrhage classification as mild stage germinal matrix hemorrhage and intraventricular hemorrhage (group 1) and severe stage germinal matrix hemorrhage and intraventricular hemorrhage (group 2).

Results: The mean birth weight of all infants was 1005.74 ± 432.01 g in all infants. The mean gestational week was found as 27.15 ± 2.99 in all infants. Platelet transfusion was performed in 8 (25%) patients in group 1 and 17 (77.27%) patients in group 2, and the difference was statistically significant ($P < .001$). The mean platelet count was found as 187 798.15 ± 77 259.93, the mean platelet volume as 7.55 ± 1.12, and the mean platelet mass index as 1489.44 ± 591.06 in all infants. There was no significant difference between the groups in terms of mean platelet volume, platelet count, and platelet mass index. There was no statistically significant correlation between the platelet indices and any grade germinal matrix hemorrhage and intraventricular hemorrhage.

Conclusion: No statistically significant difference was found between the patients with mild stage germinal matrix hemorrhage and intraventricular hemorrhage and severe stage germinal matrix hemorrhage and intraventricular hemorrhage in terms of platelet count, mean platelet volume, and platelet mass index. In addition, no significant correlation was observed between these indices and any grade germinal matrix hemorrhage and intraventricular hemorrhage.

Keywords: Preterm, intracranial hemorrhage, platelet mass index, platelet count, mean platelet volume

Introduction

Preterm birth is an important factor that contributes to morbidity and mortality. Preterm newborns are at high risk of developing morbidities such as germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH), sepsis, necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia (BPD) during their stay in neonatal intensive care unit (NICU).[1] Germinal matrix hemorrhage and intraventricular hemorrhage in preterm infants is an acquired pathology that has a significant impact on mortality, morbidity, and long-term neurodevelopmental outcomes.[2]

The risk of developing GMH-IVH increases especially in gestational week below 33 weeks. It can lead to hypotension, hypovolemia, and mortality in preterm infants.[3] The GMH-IVH in preterm infants is caused by hemorrhage from fragile blood vessels in the germinal matrix.[4] Massive GMH-IVH can frequently result in progressive ventricular expansion and hemorrhagic infarction in these infants. These complications are associated with motor and cognitive neurodevelopmental sequelae in later periods.[5] Although the incidence of GMH-IVH has decreased since the 1980s, it remains a significant problem due to increased survival rates among very low birth weight infants.[6]

Platelets are among the non-nucleated cells produced in the bone marrow and derived from megakaryocytes. Platelets play an important role in achieving hemostasis and inflammation. The activation of platelets has a lower effect in early gestational life and platelet dysfunction is common in preterm infants.[7] The platelet count (PC) is associated with gestational age and is between 150 and 450 × 10^3/μL from the 22nd gestational week.[8] Platelet volume (PV) increases in preterm infants with respiratory distress syndrome (RDS), indicating that PV may be an indicator of platelet consumption, thrombosis, infection, or severity of disorders.[9] Changes in mean platelet volume (MPV) have been investigated in several disorders.[10,11] A high MPV value has been reported as a risk factor for the development of BPD during the first days of life in extremely preterm infants.[12]

The platelet mass index (PMI) is associated with platelet functioning and is a novel index used in NICUs. The PMI is calculated by multiplying the mean PC by MPV and maybe a better inflammatory indicator in preterm infants.[1] In addition, studies have reported that PMI is more significant data in GMH-IVH than

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other platelet indices.[3,13] However, there is no consensus in the literature on the utility of platelet parameters in the evaluation of GMH-IVH in preterm infants. Therefore, the objective of this study was to investigate the efficacy of platelet parameters on GMH-IVH in preterm infants.

Material and Method

The protocol of this retrospective study was approved by the local ethics committee of our hospital (Date: 03/03/2021, No: 61). No informed consent was needed as the study was designed as retrospective. The study was performed following the relevant ethical principles of the Declaration of Helsinki and its later amendments.

A total of 54 preterm infants aged between 23 and 36 gestational weeks and followed-up with GMH-IVH in our NICU were included in this study. Infants with metabolic disorders such as asphyxia neonatal immune thrombocytopenia hypoglycemia/hyperglycemia, metabolic acidosis, and congenital anomalies and infants with missing platelet values were excluded from the study.

Patients' demographic data such as age and gender, birth weight, 1st and 5th minute Apgar scores, intrauterine growth retardation, blood transfusion, number of transfusions, platelet transfusion, duration of hospitalization, and outcomes were recorded. In addition, maternal age, antenatal steroid use, early membrane rupture, chorioamnionitis, oligohydramnios, diabetes mellitus, hypertension, and preeclampsia were also recorded.

GMH-IVH values were examined in 4 grades (Table 1).[14]

Grade I and grade II patients were assigned to group 1 (mild stage GMH-IVH) and grade III and grade IV to group 2 (severe stage GMH-IVH). The results were compared between the 2 groups. In addition, correlations between platelet parameters (PC, MPV, and PMI) and GMH-IVH were examined.

The blood samples were drawn from the peripheral or umbilical veins of the infants and collected in ethylenediaminetetraacetic acid tubes. Complete blood count was performed on the first day of life and between 3rd and 7th days in all infants. The MPV and PC values were measured using the Horiba Medical ABX Micros ES 60 device (Montpellier, France). The PMI index was calculated according to the following formula:

$PMI = (PC \times MPV)/10^3$

Statistical Analysis

Statistical analysis of this study was performed using the Statistical Package for Social Sciences v 25.0 (IBM SPSS Corp., Armonk, NY, USA) software. Normal distribution of the variables was examined using the Kolmogorov–Smirnov test. Independent sample *t*-test was used in comparison of the continuous variables between the 2 groups, while Chi-square test was used in the comparison of qualitative variables. Continuous variables were expressed as mean ± SD, while categorical variables were given as frequency (n, %). Correlations between the platelet parameters and GMH-IVH were examined with Pearson's correlation analysis. $P < .05$ values were considered statistically significant.

Table 1. GMH-IVH Grades

GMH-IVH Grades	
Grade I	Germinal matrix bleeding
Grade II	Bleeding filling 10%-50% of ventricular area
Grade III	Bleeding filling >50% of ventricular area
Grade IV	Periventricular hemorrhagic infarction

GMH-IVH, germinal matrix hemorrhage and intraventricular hemorrhage.

Results

A total of 54 preterm infants followed-up in our NICU were enrolled in the study. The newborns were divided into 2 groups according to Volpe's GMH-IVH classification as mild stage GMH-IVH (group 1) and severe stage GMH-IVH (group 2). Accordingly, 32 (59.26%) infants were in group 1 and 22 (40.74%) were in group 2. Distribution of GMH-IVH groups is shown in Figure 1.

The mean birth weight of all infants was 1005.74 ± 432.01 g in all infants. The mean birth weight was found as 1141.69 ± 491.04 g in group 1 and 808.00 ± 214.38 g in group 2. The mean birth weight was statistically significantly higher in group 1 ($P = .004$).

The mean gestational week was found as 27.15 ± 2.99 in all infants. The mean gestational week was found as 28.41 ± 2.92 in group 1 and 25.32 ± 2.01 in group 2. The mean gestational week was statistically significantly higher in group 1 compared to group 2 ($P < .001$).

Of all infants, 24 (44.44%) were girls and 30 (55.56%) were boys. There were 16 (66.67%) girls and 8 (33.33%) boys in group 1, and 16 (53.33%) girls and 14 (46.67%) boys in group 2. There was no statistically significant difference between both groups in terms of gender ($P = .407$).

The mean maternal age was found as 29.39 ± 5.98 years. The mean maternal age was found as 29.91 ± 5.76 years in group 1 and 30.09 ± 6.36 years in group 2. No statistically significant difference was found between the groups in terms of maternal age ($P = .480$). Platelet transfusion was performed in 8 (25%) patients in group 1 and 17 (77.27%) patients in group 2, and the difference was statistically significant ($P < .001$). The clinical parameters of the groups are given in Table 2.

The mean PC was found as 187 798.15 ± 77 259.93, the mean MPV as 7.55 ± 1.12, and the mean PMI as 1489.44 ± 591.06 in all infants. A comparison of the platelet parameters between the groups is given in Table 3.

As seen in Table 3, there was no statistically significant difference between the 2 groups in terms of MPV, PC, and PMI values. Correlations of the platelet parameters with GMH-IVH grades were examined using Pearson's correlation analysis. Accordingly, no statistically significant correlation was found between the platelet parameters and GMH-IVH (Table 4).

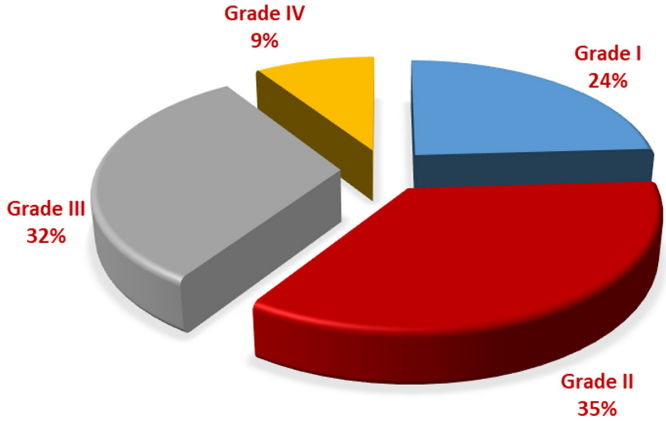

Figure 1. Distribution of GMH-IVH grades. GMH-IVH, germinal matrix hemorrhage and intraventricular hemorrhage.

Table 2. Clinical Features of the Patients

	Group 1(n = 32)		Group 2(n = 22)	
Parameter	**n**	**%**	**n**	**%**
IUGR	5	15.63	1	4.54
Antenatal steroids				
None	16	50.00	11	50.00
1 or 2	16	50.00	11	50.00
Early membrane rupture	7	21.88	7	31.82
Chorioamnionitis	9	28.13	1	4.54
Oligohydramnios	3	9.38	5	22.73
Maternal DM	1	3.13	0	0.00
Maternal hypertension	3	9.38	2	9.09
Preeclampsia	7	21.88	2	9.09
Blood transfusion	17	53.13	20	90.91
Platelet transfusion	8	25.00	17	77.27

IUGR, Intrauterine growth retardation; Maternal DM, Maternal Diabetes Mellitus.

Discussion

Several predisposing factors have been implicated in the development of GMH-IVH in preterm infants.[3,15] Low Apgar score, RDS, hypercapnia, hypoxia, patent ductus arteriosus, sepsis, thrombocytopenia, and coagulopathy have been associated with the development of GMH-IVH.[16,17]

Table 3. Comparison of the Platelet Parameters Between the Groups

	Group 1 (n = 32)		Group 2 (n = 22)		
Parameter	**Mean**	**SD**	**Mean**	**SD**	***P***
Platelet count	183 040.63	78 111.40	194 718.18	77 287.71	.590
Mean platelet volume	7.57	1.30	7.52	0.89	.886
Platelet mass index	1520.81	620.09	1452.36	566.98	.694

Table 4. Correlations Between the Platelet Parameters and GMH-IVH

		GMH-IVH	MPV	PC	PMI
GMH-IVH	Pearson correlation	1	−0.038	0.094	−0.074
	Significance (2-tailed)		0.800	0.497	0.619
	N	54	54	54	54

GMH-IVH, germinal matrix hemorrhage and intraventricular hemorrhage; MPV, mean platelet volume; PC, platelet count; PMI, platelet mass index.

Evaluation of the platelet function in preterm infants poses a diagnostic difficulty because the laboratory investigations are performed with small amounts of blood samples. The effects of platelet parameters on several diseases including RDS, anemia of prematurity, spontaneous closure of ductus arteriosus, and thrombocytopenia have been reported in the literature.[7,18,19]

In a meta-analysis and systematic review by Grevsen et al.[20] it has been stated that neonates with PC < 100 × 10^9/L during the first week of life had an increased incidence of GMH-IVH, but whether reduced platelet function is associated with the risk of IVH in premature infants remains to be investigated. In this study, we investigated the effects of platelet parameters (PC, MPV, and PMI) on GMH-IVH grades, which have been relatively infrequently studied in the literature, in preterm infants. We could not find any correlation between them. In our study, the mean birthweight of the infants was found as 1005.74 ± 432.01 g. In a study by Korkmaz et al.[3] the mean birthweight was reported as 1163.1 ± 217.3 in very low birth infants. In another study by Okur et al.[1] the mean birthweight of very preterm infants was found as 994 ± 212. Within this context, our finding is within the range reported in previous studies.

In our study, the mean gestational week was found as 28.41 ± 2.92 in infants with grade I and grade II GMH-IVH and 25.32 ± 2.01 in infants with grade III and IV GMH-IVH, and the difference was statistically significant ($P < .001$). In a study by Korkmaz et al.[3] the mean gestational week was found as 29.6 ± 2.0 in infants with grade I and II GMH-IVH and 29.2 ± 2.0 in infants with grade III and IV GMH-IVH. No significant difference was found between the 2 groups.[3] The difference between the studies may be because of the measurement time and sample size.

Platelet transfusion has been associated with not only increased mortality but also comorbidities including GMH-IVH.[21] The use of platelet mass-based NICU guidelines has been correlated with increased hemorrhagic problems and lower rates of platelet transfusions.[18] Reduced platelet activity has been associated with more intracranial hemorrhage. A lower PMI index shows that platelet function affects the cascade of inflammation. In addition, low platelet activity has been reported to be correlated with the severity of GMH-IVH (22). In the present study, platelet transfusion was carried out in 8 (25%) infants in group 1 (grade I and grade II) and 17 (77.27%) patients in group 2 (grade III and grade IV), and the difference was statistically significant ($P < .001$). In a study by Kasap et al.[19] it was reported that the use of PMI may reduce the rate of platelet transfusion.[19]

Studies have reported that clinical findings such as GMH-IVH which shows decreased platelet activity increases as PMI decreases and in contrast, GMH-IVH decreases as PMI rises.[3] In the study by Korkmaz et al.[3] PC and MPV values showed no significant difference between the 2 groups, while PMI value measured between 5 and 7 days was statistically significantly higher in both grade I and grade II GMH-IVH groups ($P = .01$). In a study by Kahvecioglu et al.[18] it was reported that PMI measured during 3-7 days of life may be useful as a predictor for GMH-IVH. In our study, no significant difference was found between the groups in terms of PC, MPV, and PMI values (for all, $P > .05$).

In a study by Chen et al.[23] PC was associated with any grade GMH-IVH, while MPV and PMI showed no significant difference. In a study by Mitsiakos et al.[13] it was reported that GMH-IVH in preterm infants cannot be explained only by platelet indices, and further studies are warranted to enlighten the associations between platelet indices, IVH, and outcomes. On the other hand, in a study by Lupton et al.[24] it was reported that a reduced PC does not play a major role in the pathogenesis of GMH-IVH in preterm

infants.[24] Likewise, in our study, we could not find a statistically significant correlation among MPV, PC, PMI, and any grade GMH-IVH. However, further more comprehensive studies with larger series of patients are needed to enlighten these relationships.

The major limitations of this study are its retrospective design and a relatively small number of patients. In addition, a healthy control group without GMH-IVH could be included in the study. Finally, advanced statistical calculations could not be performed due to limitations in the selection of the subjects. However, given the scarcity of studies investigating the relationship between platelet parameters and GMH-IVH in the literature, we think that the results of our study will be guiding for further comprehensive studies on this issue.

Conclusion

No statistically significant difference was found between the patients with mild stage GMH-IVH and severe stage GMH-IVH in terms of PC, MPV, and PMI. In addition, no significant correlation was observed between platelet parameters and any grade GMH-IVH. However, further studies are needed to support these findings.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the University of Health Sciences, Zeynep Kamil Women and Children's Diseases Training and Research Hospital (Date: 03/03/2021, Number: 61).

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