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ORIGINAL ARTICLE

Effectiveness of early systemic inflammatory indices in predicting advanced intraventricular hemorrhage in preterm infants

Efectividad de los índices inflamatorios sistémicos precoces para predecir la hemorragia intraventricular severa en prematuros

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What do we know about the subject matter of this study?

Systemic inflammatory indices are effective parameters in predicting adverse clinical outcomes in inflammation-mediated diseases. Systemic inflammatory indices have been found to be associated with intracerebral hemorrhage in adults. The relationship between systemic inflammatory indices and intraventricular hemorrhage (IVH) in premature infants is not yet fully known.

What does this study contribute to what is already known?

An effective marker to predict IVH has not been defined. In our study, we evaluated for the first time if six systemic inflammatory indices could predict advanced IVH in premature babies. Our results showed that any systemic inflammatory indices had the power to predict IVH. We hypothesize that the reason why systemic inflammatory indices were not found to be diagnostic markers for IVH may be because inflammation was not the only factor in IVH in preterm infants.

Abstract

Some systemic inflammatory indices have been reported to be associated with intracerebral hemorrhage in adults. However, the relationship between systemic inflammatory indices and intraventricular hemorrhage (IVH) in premature neonates is still not completely understood. **Objective**: To evaluate the relationship between systemic inflammatory indices obtained on the first day of life in premature infants and the development of severe IVH. **Patients and Method**: Premature newborns < 32 weeks of gestational age were included. Eligible patients were divided into 2 groups: Group 1: without IVH or grade I and II hemorrhage, and Group 2: grade III and IV HIV. Demographic characteristics, clinical outcomes, monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), pan-immune inflammation value (PIV), and Systemic inflammation response index (SIRI) were compared between groups. **Results**: A total of 1176 newborns were included in the study, 1074 in Group 1 and 102 premature babies in Group 2. There was no difference between the groups in terms of the count of leukocytes, neutrophils, monocytes, lymphocytes and platelets ($p > 0.05$). The values of NLR, MLR, PLR, PIV, SII and SIRI were similar in both groups ($p > 0.05$). **Conclusion**: While the relationship between inflammation, hemodynamics and IVH is still under discussion, our results show that systemic inflammatory indices have no predictive value for IVH.

Keywords:
Cerebral Intraventricular Hemorrhage;
Preterm Newborn;
Hematologic Tests

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Introduction

The cause of intraventricular hemorrhage (IVH) in preterm infants is primarily due to the fragile structure of the germinal matrix vessels. Postnatal hemodynamic changes and inflammation may lead to IVH with bleeding in fragile germinal matrix vessels in preterm infants[1]. Despite advances in neonatal care, IVH remains a common complication, particularly in premature infants less than 32 weeks of gestation. The incidence of IVH increases with decreasing gestational age and birth weight[2]. IVH increases the risk of lifelong disability and mortality[1]. Male gender, caucasian race, absence of antenatal steroid use, mechanical ventilation (MV), respiratory distress, pulmonary hemorrhage, pneumothorax, chorioamnionitis, asphyxia, sepsis and patent ductus arteriosus (PDA) are other additional risk factors for IVH[3,4].

Although some risk factors have been identified in the occurrence of IVH, an effective biomarker that can be used to predict the severity of IVH has not been identified so far. It has been reported that inflammatory cytokines and chemokines are elevated as markers of neuroinflammation in cerebrospinal fluid (CSF) in premature infants with posthemorrhagic hydrocephalus[5].

Unfortunately, testing costs for cytokines and chemokines are high and not readily available in most hospital laboratories. Markers routinely studied from peripheral blood samples instead of invasively obtained CSF may be less invasive for IVH predictivity. Therefore, it is necessary to find new markers that are more cost-effective, faster, less invasive, safe and effectiving in predicting IVH. In this respect, systemic inflammatory indices may be candidates that meet the mentioned criteria. Systemic inflammatory indices are effective parameters in predicting adverse clinical outcomes in inflammation-mediated diseases[6]. Neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation (SII) levels have predictive value for clinical outcomes and mortality in diseases involving the central nervous system in adults such as intracranial hemorrhage, primary intraventricular hemorrhage, cerebral/cerebellar hemorrhage, and delayed cerebral ischemia[7-11]. There are few studies on the relationship between neonatal diseases and systemic inflammatory indices. Systemic inflammatory indices have been reported to be useful diagnostic markers for neonatal hypoxic ischemic encephalopathy (HIE), sepsis, retinopathy of prematurity (ROP), and PDA[12-15]. The relationship between IVH and systemic inflammatory indices is not fully known yet.

Considering the effect of inflammation on IVH and based on previous studies of systemic inflammatory indices, a possible relationship between IVH and systemic inflammatory indices can be expected. The objective of our study is to evaluate whether the NLR, SII values, monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), pan-immune-inflammation value (PIV) and systemic inflammation response index (SIRI) obtained after birth can predict advanced IVH in preterm infants < 32 weeks of gestation. Thus, systemic inflammatory indices can provide the clinician with valuable preliminary information about IVH and IVH-related morbidities.

Patients and Method

Premature infants < 32 weeks of gestation hospitalized in the neonatal intensive care unit between February 2019 and February 2022 were evaluated. Infants with major congenital anomalies and born at ≥32 weeks of gestation were not included in the study. Patients who met the exclusion criteria were excluded from the study. All patients who met the inclusion criteria were included in the study. Data for preterm infants were obtained from a retrospective cohort of hospital medical records. Ethical approval was obtained from the local ethics committee.

Demographical and Clinical Characteristics

Gestational week (GW), birth weight (BW), administration of antenatal steroid, gender, cesarean section, chorioamnionitis, Apgar scores (at 1st and 5th minutes), duration of MV, early onset sepsis (EOS), late onset sepsis (LOS), small for gestational age (SGA), IVH, respiratory distress syndrome (RDS), PDA, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), ROP, duration of hospitalization data, and mortality were recorded.

Definition of IVH and Preterm Morbidities

Sepsis starting within the first 3 days of postnatal life was defined as EOS and sepsis occurring after the 3rd day of postnatal life was defined as LOS[16]. If a preterm baby needed surfactant due to respiratory failure, it was defined as RDS[17]. Infants diagnosed with PDA based on clinical and Doppler echocardiography findings and treated either medically or surgically were recorded as hemodynamically significant PDA[18]. According to clinical and laboratory findings, premature infants with moderate or advanced (stage ≥ 2) NEC were recorded[19]. Preterm infant requiring < 30% oxygen in the postmenstrual age of 36th week was defined as moderate BPD, and infants who needed positive pressure respiratory support or ≥ 30% oxygen were defined as severe BPD[20]. Infants with ROP who were scanned following the retinal examination scanning protocol and required laser treatment were registered[21].

In our unit, preterm infants <32 weeks of gestational were scanned by cranial ultrasonography (USG) for IVH on the 1st, 3rd, 7th and 15th-30th days of life and before discharge. According to cranial USG findings, the severity of IVH was defined with the IVH staging system defined by Volpe. After staging, grade I and II were defined as mild IVH, grade III and IV advanced IVH[22]. IVH classification according to cranial USG findings is shown in table 1. Patients without IVH and grade I and II IVH were included in Group 1, and patients with grade III and IV were included in Group 2 (advanced IVH). Demographic characteristics, clinical outcomes and laboratory parameters in both groups were compared.

Complete Blood Count Analysis

Peripheral venous blood samples were taken for complete blood count from each preterm infant within the first hour after birth. After the venous blood samples were taken into an ethylenediaminetetraacetic acid (EDTA) tube, complete blood count was performed with Cell-Dyn 3700 automatic hemocytometer (Abbott, Abbott Park, IL, USA). Leukocyte count (10^3 μ/L), neutrophil (N) count (10^3 μ/L), monocyte (M) count (10^3 μ/L), lymphocyte (L) count (10^3 μ/L) and platelet (P) count (10^3 μ/L) values were obtained.

Evaluation of Systemic Inflammatory Indices

N, M, L, and P count were used in the calculation formulation of Systemic inflammatory indexes. The formulas used when calculating the systemic inflammatory indexes are given below.

NLR=N/L, PLR=P/L, MLR=M/L, SII=P x N/L, SIRI=N x M/L, and PIV=P x N x M/L[12].

Ethics

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee (24/2019).

Table 1. Intraventricular hemorrhage grading using cranial ultrasonography

Grade	Findings
I	Germinal matrix hemorrhage (no or minimal hemorrhage in the ventricle)
II	IVH filling 10-50% of the ventricle at the parasagittal section
III	IVH filling more than 50% of the ventricle and causing ventricular enlargement
IV	Periventricular echodensity

IVH, Intraventricular hemorrhage.

Statistical Analysis

Statistical Package for Social Sciences (SPSS), version 20.0 (SPSS Inc, Chicago, IL, USA) analysis package software was used for statistical analysis of patient data. Histogram and Kolmogorov-Smirnov test were used to analyze the distribution of the variables. Fisher's Exact test or Pearson Chi-Square test was used for the analysis of categorical variables. The Mann-Whitney U test or t test was used for the analysis of continuous variables. The results were presented as median and interquartile range (IQR) and frequency. A P value of < 0.05 was considered statistically significant.

Results

According to the inclusion criteria of our study, 1176 premature infants were eligible. 1074 preterm infants were included in Group 1 and 102 preterm infants were included in Group 2. GW (28.4 (2.1) weeks) and BW (1080 (350) g) in Group 1 were significantly higher than GW (27.2 (1.6) weeks) and BW (910 (263) g) in Group 2 ($p < 0.001$ and $p < 0.001$, respectively). Apgar scores at 1st and 5th minutes were higher in Group 1 compared to Group 2 ($p < 0.001$ and $p < 0.001$, respectively). Duration of MV, duration of hospitalization, and the frequency of RDS, PDA, NEC, BPD, and ROP were higher in Group 2 that in Group 1 ($p < 0.05$). Antenatal steroid administration, chorioamnionitis, gender, cesarean section, EOS, LOS, SGA and mortality were similar in both groups ($p > 0.05$) (table 2).

There was no difference between the groups in terms of leukocyte, neutrophil, monocyte, lymphocyte, and platelet count ($p > 0.05$). NLR, MLR, PLR, PIV, SII, and SIRI values were similar in both groups ($p > 0.05$). The results are shown in table 3.

Discussion

In premature infants, IVH can cause serious adverse outcomes such as seizure, hydrocephalus, neurologic sequelae and impaired neurodevelopmental complications. Until now, an effective marker to predict IVH has not been defined. In our study, we evaluated for the first time that six systemic inflammatory indices could predict advanced IVH in premature babies, but it was found that any systemic inflammatory indices did not have the power to predict IVH. Moreover, the frequency of other preterm morbidities such as RDS, PDA, NEC, BPD, and ROP increased in infants with advanced IVH due to lower GW and BW in addition to prolonged hospitalization and MV.

IVH is a complication that can be seen at a rate

Table 2. Demographic characteristics and clinical outcomes in the intraventricular hemorrhage

Characteristics	Group 1 (No, grade I and II IVH) (n = 1074)	Group 2 (Grade III and IV IVH) (n = 102)	P value
Gestational week, weeks[a]	28.4 (27.1-29.1)	27.2 (27.0-28.5)	< 0.001*
Birth weight, g [a]	1080 (910-1312)	910 (795-1237)	< 0.001*
Antenatal steroid, n (%)	798 (74.3)	71 (69.6)	0.097
Chorioamnionitis, n (%)	119 (11.1)	14 (13.7)	0.311
Male gender, n (%)	525 (48.8)	58 (56.8)	0.054
Cesarean section, n (%)	905 (84.2)	89 (87.2)	0.394
Apgar 1st min, [a]	6 (4-6)	5 (3-6)	< 0.001*
Apgar 5th min, [a]	8 (6-9)	6 (4-8)	< 0.001*
Small for gestational age, n (%)	86 (8.0)	9 (8.8)	0.385
Duration of Mechanical Ventilation, days, [a]	1 (0-3)	6 (2-8)	< 0.001*
Early onset sepsis n (%)	41 (3.8)	6 (5.8)	0.069
Late onset sepsis n (%)	242 (22.5)	24 (23.5)	0.251
Respiratory distress syndrome n (%)	646 (60.1)	92 (90.1)	< 0.001*
Patent ductus arteriosus n (%)	394 (36.7)	49 (48.1)	0.024*
Necrotizing enterocolitis n (%)	16 (1.5)	10 (9.8)	<0.001*
Bronchopulmonary dysplasia , n (%)	185 (17.2)	35 (34.3)	< 0.001*
Retinopathy of prematurity , n (%)	89 (8.2)	26 (25.5)	< 0.001
Duration of hospitalization, days, [a]	53 (26-61)	76 (42-99)	0.032*
Mortality, n (%)	161 (14.9)	19 (18.6)	0.125

[a]median (interquartile range) *P < 0.05 was considered statically significant. IVH intraventricular hemorrhage.

Table 3. Systemic inflammatory indices in the intraventricular hemorrhage

Parameters [a]	Group 1 (No, grade I and II IVH) (n = 1074)	Group 2 (Grade III and IV IVH) (n = 102)	P value
Leukocyte count (10^3 µ/L)	11.00 (6.5-15.3)	13.40 (7.9-16.4)	0.745
Platelet count (10^3 µ/L)	231 (85-303)	189 (96-286)	0.053
Neutrophil count (10^3 µ/L)	2.22 (1.31-3.92)	2.64 (1.88-4.42)	0.344
Monocyte count (10^3 µ/L)	0.66 (0.40-0.79)	0.70 (0.51-0.97)	0.216
Lymphocyte count (10^3 µ/L)	7.14 (0.42-9.76)	8.66 (0.45-10.90)	0.363
Neutrophil to lymphocyte ratio	0.31 (0.18-0.55)	0.31 (0.17-0.60)	0.069
Monocyte to lymphocyte ratio	0.09 (0.05-0.12)	0.10 (0.05-0.13)	0.226
Platelet to lymphocyte	33.6 (23.6-51.5)	25.9 (20.7-48.4)	0.057
Pan immune inflammation value	46.7 (16.0-109.0)	41.9 (15.1-81.4)	0.242
Systemic immune inflammation index	74.0 (36.9-124.6)	49.5 (23.8-11.3)	0.190
Systemic inflammation response index	0.25 (0.11-0.72)	0.41 (0.18-0.81)	0.109

[a]median (interquartile range) IVH, intraventricular hemorrhage.

of approximately 20% in premature babies especially in babies under 32 weeks of gestation[23]. Basically, the main reasons blamed for IVH mechanism in premature infants are immature vascular structures and a fragile germinal matrix structure[4,23]. After germinal matrix bleeding, there is an inflammatory response, microglial activation, release of cytotoxic inflammatory mediators, increased capillary permeability, and accumulation of leukocytes from the peripheral blood to the bleeding area[23]. Therefore, a surge in chemokine and cytokine levels in the CSF in premature infants with IVH is seen as evidence of this situation[5]. In peripheral blood evaluation, while leukocyte, neutrophil, monocyte, and lymphocyte count is not associated with advanced IVH, low platelet count may be associated with increased risk of IVH[24]. On the contrary, low neutrophil count has been reported to increase the risk of advanced IVH[25]. It is thought that cytokines evaluated in the peripheral blood on the first day after birth may be associated with infection rather than IVH[26].

Due to the conflicting results in the literature on biomarkers in the prediction of advanced IVH, the search for an effective parameter in the prediction of IVH in peripheral blood is still ongoing. In this regard, systemic inflammatory indices can be a predictive indicator for IVH. Furthermore, NLR, MLR, PLR and SII can be an effective, inexpensive, and rapidly accessible parameter both for diagnosis and for determining clinical outcomes in different types of intracranial hemorrhage in adults[7-11]. Based on these data, our study evaluated the relationship between six systemic inflammatory indices and IVH in preterm infants. Our results showed that NLR, MLR, PLR, PIV, SII, and SIRI values did not have predictive value for advanced IVH. After these results, the following question comes to mind: Systemic inflammatory indices, which can be an effective diagnostic and prognostic indicator for intracranial bleeding in adults? Why they are not effective predictive parameters for IVH in preterm infants?. The possible reason for this is that cranial hemorrhage in adults and cranial hemorrhage in premature infants develop due to different pathophysiological mechanisms[23].

Intracranial bleeding in adults may be secondary to trauma, vascular diseases, coagulopathy, and thrombocytopenia. There may be a series of immunological changes after bleeding. First neutrophils and monocytes pass to the central nervous system with the activation of the immune system after acute bleeding. Then, slowly activated T lymphocytes and the adaptive immune system come into play[8-11]. The risk of bleeding in the central nervous system may also increase due to increased systemic inflammation. Moreover, brain edema and neurotoxicity may develop due to inflammation. Thus, increased inflammation directly causes negative neurological clinical outcomes[10]. This tight connection between changes in peripheral whole blood cells and intracranial hemorrhage in adults may present systemic inflammatory indices as an indicator[8-11]. Contrary to all these results, Mureşan et al. have determined that there was no relationship between NLR, MLR, PLR, and SII levels and unfavorable clinical outcomes in patients with spontaneous intracerebral hemorrhage in the emergency department[27]. Therefore, the clinical use of systemic inflammatory indices in intracranial hemorrhages in adults is still not fully understood.

In the field of neonatology, NLR and PLR were compared in 17 premature babies with IVH and 54 without IVH, and NLR was found to be similar in both groups in the study of Silahli et al. On the other hand, PLR was reported to be lower in the IVH group[28]. We found that six different systemic inflammatory indices were not associated with advanced IVH of prematurity. The difference between the results of Silahli et al and our study may be due to the high number of patients in our study. We believe that the large number of patients in our study provides more comprehensive information on evaluating the relationship between systemic inflammatory indices and IVH. Furthermore, some inflammatory indices may also be diagnostic and prognostic indicators in intracranial hemorrhages in adults, our results did not find any predictive value of systemic inflammatory indices for IVH. The possible reason for this may be due to the difference in the formation mechanisms of intracranial hemorrhage in adults and premature infants.

In premature infants, the germinal matrix is at the end of the arterial region and is directly connected to the vein of Galen. The terminal vein, which is the main vein of the system, anatomically turns in a U shape around the germinal matrix structure and conditions such as ischemia, reperfusion, and venous congestion in this region can cause injury in the germinal matrix. Therefore, changes in cerebral blood flow have an important role in the pathogenesis of IVH. Under normal conditions, critical changes in cerebral blood flow are not expected due to cerebral autoregulation. However, sudden changes in blood pressure directly affect the brain in premature infants where this compensatory mechanism is not fully developed. Low gestational age, low birth weight, and hypotension impair cerebral autoregulation. Hemodynamic and metabolic changes frequently seen in premature infants may increase the risk of IVH by causing cerebral vasodilation. IVH may occur as a result of the triggering of inflammation and the release of cytokines. However, the effect of inflammation and chorioamnionitis on IVH is still not understood[4]. The role of systemic inflammatory indices in the diagnosis of IVH is unknown due to the un-

certainty of the relationship between the mechanisms of IVH formation and inflammation in preterm newborns.

IVH in preterm newborns is of multifactorial origin, such as inflammation, variability of hemodynamics, and immature fragile germinal matrix. In our results, the reason why systemic inflammatory indices was not found as a diagnostic marker for IVH may be because inflammation was not the only factor in IVH in premature infants. Additionally, considering that the immune system of premature infants is immature, premature infants may not be able to give an adequate immune response to IVH formation. There may be a local response to IVH formation only in the central nervous system, and it may not show a systemic immune inflammatory response originating from IVH. Therefore, no difference could be detected between the groups with and without IVH in terms of both whole blood cells and systemic inflammatory indices. Although we cannot fully explain its pathophysiological mechanism, it could be said that systemic inflammatory indices did not play a role in the diagnosis of IVH. However, these indicators need to be measured prospectively in infants, starting from the mother. Thus, the relationship between these parameters and the hemodynamics of IVH can be better understood. It remains important to conduct prospective studies with large numbers of patients in order to better understand the relationship between inflammation indicators and HIV.

Although the number of patients in our study was high, the results of our study were performed in a single center, which limits the generalization of our findings due to its retrospective nature. Moreover, the results were interpreted based on the data we obtained from a single blood sample. It could not be evaluated by serial sampling of maternal and postnatal neonatal systemic inflammatory indices. The hemodynamic status of our patients could not be evaluated either. Finally, we could not evaluate the relationship between complications that may occur due to IVH and systemic inflammatory indices.

Conclusions

The relationship between systemic inflammation and IVH was not fully understood. Our study was the first in the literature to investigate the diagnostic value of six systemic inflammatory indices for IVH. Our results showed that systemic inflammatory indices had no predictive value for the diagnosis of IVH in premature infants in the early postnatal period. In order to better evaluate our results, prospective studies with a larger number of patients may help to understand the relationship between inflammation and IVH.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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