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Intracranial hemorrhage in premature infants: investigation of etiology and mortality

Prematüre bebeklerde intrakranial kanama: etiyoloji ve mortalitenin araştırılması

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Abstract

Purpose: Advancements in neonatal care have increased the survival rates of premature infants, but intracranial hemorrhage (ICH) continues to be a concerning issue in neonatal intensive care units (NICU). This study sought to evaluate the risk factors associated with ICH in preterm infants born before 29 weeks of gestation, with a particular focus on the preventive measures.

Materials and methods: In a perinatology center with a 61-bed level-4 unit, this retrospective cohort study was conducted in the neonatal intensive care unit. Digital hospital records were scanned for infants born ≤$29^{0/7}$ weeks and hospitalized between 2021-2023. We categorized the study population into three groups based on the increasing severity of ICH according to the first week transfontanelle ultrasonography findings. Demographic, perinatal characteristics, cord blood gas values, platelet count, platelet mass were recorded as laboratory parameters. Clinical interventions, follow-up data and transfusion of blood products, mechanical ventilation requirements, inotrope use within the first 72 hours, length of hospital stay, mortality data were recorded.

Results: A total of 96 patients (female/male: 39/57) were enrolled in the study. A significant difference in mean gestational age was observed among patients in Group 1 (no-ICH, n=50), Group 2 (mild, n=25), and Group 3 (severe, n=21) (p<0.001). Additionally, antenatal corticosteroid therapy was notably less frequent in Groups 2 and 3 (p=0.044). Cord lactate and the rate of metabolic acidosis were significantly higher in Group 3 (p=0.026, <0.001). The platelet count and platelet mass were significantly lower in Group 3 compared to the other two groups (p=0.014, p=0.023).

Conclusion: Our findings emphasize reduced antenatal corticosteroid use, higher metabolic acidosis rates, increased transfusion needs, and lower platelet mass as prominent risk factors, reaffirming the multifactorial nature of ICH. We believe these measures can be integrated into clinical protocols within the framework of an "ICH prevention bundle".

Keywords: Newborn, intracranical hemorrhage, prematurity, platelet mass.

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Öz

Amaç: Yenidoğan bakımındaki ilerlemeler prematüre bebeklerin hayatta kalma oranlarını artırmış olsa da yenidoğan yoğun bakım ünitelerinde (YYBÜ) görülen intrakraniyal kanama (iKK) önemli bir sorun olmaya devam etmektedir. Bu çalışmada, 29. gebelik haftasından önce doğan prematüre bebeklerde İKK risk faktörlerini değerlendirmeyi, önleyici stratejileri öne çıkarmayı amaçladık.

Gereç ve yöntem: Bu retrospektif kohort çalışması, perinatoloji merkezinde bulunan 61 yatak kapasiteli, 4.seviye YYBÜ'de yürütülmüştür. Dijital hastane kayıtları, ≤$29^{0/7}$ gebelik haftasında doğan ve 2021-2023 yılları arasında hastaneye yatırılan bebekler için tarandı. Çalışma popülasyonu, ilk hafta yapılan transfontanel ultrasonografi bulgularına göre İKK'nın giderek artan şiddetine dayanarak üç gruba ayrıldı. Demografik ve perinatal özellikler ile birlikte, kordon kan gaz değerleri, platelet sayısı, platelet kütlesi laboratuvar parametreleri kapsamında kaydedildi. Klinik müdahaleler, takip verileri, kan ürünü transfüzyonu, mekanik ventilasyon gereklilikleri, ilk 72 saat içinde inotrop kullanımı, hastanede kalış süresi ve ölüm oranı gibi bilgiler analiz edildi.

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Bulgular: Çalışmaya 96 hasta (kadın/erkek: 39/57) dahil edildi. Gebelik haftası ortalamaları açısından Grup 1 (İKK olmayan, n=50), Grup 2 (hafif İKK, n=25) ve Grup 3 (şiddetli İKK, n=21) arasında istatistiksel olarak anlamlı bir fark bulundu (p<0.001). Ayrıca, Grup 2 ve Grup 3'te antenatal kortikosteroid tedavisinin uygulanma oranı anlamlı derecede daha düşüktü (p=0.044). Kordon laktatı ve metabolik asidoz oranı Grup 3'te anlamlı derecede yüksekti (p=0.026, <0.001). Trombosit sayısı ve trombosit kütlesi değerleri Grup 3'te diğer iki gruba kıyasla belirgin şekilde daha düşük çıktı (p=0.014, p=0.023).
Tartışma: Bulgularımız, azalmış antenatal kortikosteroid kullanımı, yüksek metabolik asidoz oranları, artan transfüzyon ihtiyaçları, düşük trombosit kütlesi gibi önemli risk faktörlerini vurgulamakta, İKK'nın çok faktörlü yapısını yeniden doğrulamaktadır. Bu bulguların "İKK önleme paketi" çerçevesinde klinik protokollere entegre edilebileceğini düşünüyoruz.

Anahtar kelimeler: Yenidoğan, intrakraniyal kanama, prematürite, trombosit kütlesi.

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Introduction

Intracranial hemorrhage (ICH) affects mortality and long-term neurodevelopmental outcomes in premature infants. In recent years, advancements and innovations in neonatal care have significantly improved the survival rates of premature infants across different levels of immaturity. However, ICH remains a persistent challenge in neonatal intensive care units (NICUs) [1].

In addition to the degree of prematurity and low birth weight, gestational hypertension, the presence of maternal infection, placental abruption, mode of delivery, low APGAR score, postnatal resuscitation, and transport history, problems such as pneumothorax, coagulopathy, pulmonary hemorrhage, hemodynamically significant patent ductus arteriosus (hsPDA), metabolic acidosis, and sepsis during intensive care monitoring increase risks for ICH. Intracranial hemorrhage often begins within the first 48 hours of life, in the periventricular germinal matrix, a region rich in glial and neuronal precursor cells in the developing brain tissue of premature infants. In preterm infants, the fragile vascular structure of the germinal matrix, fluctuations in cerebral blood flow, and abnormalities in platelet and coagulation functions also pose risks for ICH. Given that ICH originates in the perinatal period and may continue to evolve throughout the first postpartum week, prevention strategies must comprehensively address each of these critical phases [2]. Certain interventions such as antenatal steroid (ANS) treatment and cesarean delivery have been shown to be effective in reducing the risk of severe ICH. Additionally, delaying the timing of cord clamping, which ensures better blood volume, is presumed to reduce the incidence of ICH [3].

This study, conducted in our institution, aimed to evaluate the risk factors influencing ICH in premature infants born before 29 weeks of gestation, while emphasizing the preventive strategies.

Materials and methods

Conducted at the NICU of Umraniye Training and Research Hospital, this retrospective cohort study took place in a level 4 perinatology center with a 61-bed capacity. Digital hospital records were scanned for preterm infants with a gestational age of ≤$29^{0/7}$ weeks, hospitalized between 2021 and 2023.

Infants with major congenital anomalies, including central nervous system malformations, complex congenital heart defects, and chromosomal abnormalities, were excluded. Neonates without a transfontanelle ultrasonography (TFUS) within the first week postpartum or those transferred from other institutions after the first week of life were also excluded.

Patients' records were reviewed and recorded on a data sheet for each patient to evaluate a wide array of factors associated with ICH. Gestational age, birth weight, head circumference, length, gender, SGA, and IUGR were recorded as fundamental demographic

parameters. Perinatal characteristics, including maternal age, multiple pregnancies, in vitro fertilization (IVF), inborn/outborn status, mode of delivery, fifth-minute APGAR score, ANS and magnesium therapy, presence of chorioamnionitis, premature rupture of membranes (PPROM), oligohydramnios, placental abruption, preeclampsia, and multiparity, were also evaluated from the records. Cord blood gas pH and lactate levels, metabolic acidosis, hypocapnia, hypercapnia, lowest platelet count, mean platelet volume (MPV) and platelet mass (multiplying the platelet count by the MPV) were recorded as laboratory parameters [4]. Additionally, clinical interventions were documented, including details of neonatal resuscitation at birth, placement of an umbilical venous catheter, transfusion of any type of blood products (erythrocyte, thrombocyte suspensions or fresh frozen plasma) during the first week, medical and/or surgical PDA closure or any other surgical operations. Clinical follow-up data encompassed surfactant therapy, mechanical ventilation requirements, high-frequency oscillatory (HFO) ventilation, inotrope use within the first 72 hours, positive blood cultures in the first 72 hours, diagnosis of hsPDA, necrotizing enterocolitis (NEC), length of hospital stay, and mortality.

When the ductus diameter exceeded 1.5 mm, along with a left atrial inner diameter/aortic root (La/AO) ratio >1.4, and confirmation of a left-to-right shunt via Doppler echocardiography, a PDA was classified as 'hemodynamically significant [5]. The treatment regimen for hsPDA consisted of either ibuprofen or paracetamol. PDA closure was deemed successful upon the absence of a detectable PDA shunt, verified through Doppler echocardiography within 24–72 hours following treatment [6, 7].

According to our NICU protocols, bedside TFUS is performed at predefined intervals, such as on the 3rd day, 1st week, 2nd week and 4th week of life. For neonates born before 28 weeks of gestation, initial screening is conducted within 24 hours of birth, with subsequent imaging at corrected gestational age up to 36 weeks postmenstrual or at discharge if earlier [8]. All of the bedside TFUS's are performed by a pediatric radiologist with an Esaote Mylab Seven (201236) portable ultrasonography device using a 13 MHz linear probe, applying preheated gel for imaging. Coronal and sagittal views from the anterior and mastoid fontanelles are obtained. Volpe's criteria is used for ICH evaluation [9]:

Stage 1: Germinal matrix hemorrhage.

Stage 2: Bleeding involving <50% of the ventricle.

Stage 3: Bleeding involving >50% of the ventricle.

Severe hemorrhage with periventricular hemorrhagic infarction.

We categorized the study population into three groups based on the severity of ICH:

Group 1: Patients without ICH.

Group 2: Mild ICH group including, patients with Stage 1 or Stage 2 germinal matrix hemorrhage.

Group 3: Severe ICH group including, patients with Stage 3 germinal matrix hemorrhage and/or periventricular hemorrhagic infarction.

The patients demonstrating worsening or hemispheric asymmetry over time were placed into a group according to the highest grade.

Ethical approval for the study was granted by the Umraniye Training and Research Hospital Ethics Committee on 27.02.2025, under reference number B.10.1.TKH.4.34.H.GP.0.01/22. The study adhered to the principles outlined in the Declaration of Helsinki.

Statistical analysis

Using SPSS statistical software for Windows (ver. 15.0; SPSS Inc., Chicago, IL, USA), statistical analyses were performed. Continuous values were expressed as mean ± standard deviation (SD) or median and range, based on the homogeneity of the distribution assessed via the Kolmogorov-Smirnov test. For continuous variables following a normal distribution, the Student's t-test was applied, whereas the Mann-Whitney U and Kruskal-Wallis tests were used for those without a normal distribution. Categorical data, presented as numbers (n) and frequencies (%), were analyzed using the $\chi 2$ test. A p-value <0.05 was considered statistically significant.

Results

In this retrospective study, we evaluated the digital data of patients hospitalized between 2021 and 2023 in a 61-bed quaternary NICU. Initially, the data of 105 patients were obtained from hospital digital records; however, three were excluded due to congenital anomalies, one was transferred to our hospital from an external center after the first week, and five lacked TFUS within the first week of life, rendering them ineligible for inclusion. The final cohort consisted of 96 patients (female/male: 39/57), who were allocated into three predefined groups. Group 1 included 50 patients (52%), Group 2 comprised 25 patients (26%), and Group 3 consisted of 21 patients (22%). The demographic parameters—including gestational age, birth weight, head circumference, length, gender, SGA, and IUGR—of these 96 infants are summarized in Table 1.

Table1. Demographic characteristics of infants within three groups

	Group 1 (n:50)	Group 2 (n:25)	Group 3 (n:21)	*p* value	Test value
Gestational week, wk, (mean ± SD)	26.3±1.3	26.4±1.6	24.8±1.6	<0.001*,**	14.491
Birth weight, g, (mean ± SD)	858.9±238.7	930.6±278.5	757.6±229.2	0.068	5.362
Head circumference, cm, (mean ± SD)	24.2±2.6	23.9±2.0	23±2.9	0.107	4.461
Length, cm, (mean ± SD)	32.9±4.3	33.9±2.9	32.4±3.5	0.308	2.356
Gender					
Male, n, (%)	28 (56%)	15 (60%)	14 (66.7%)	0.704	0.703
Female, n, (%)	22 (44%)	10 (40%)	7 (33.3%)		
SGA, n (%)	8 (16%)	0	4 (%19)	0.084	4.955
IUGR, n, (%)	9 (18%)	1 (4%)	2 (9.5%)	0.201	3.204

*: Indicates comparisons between Group 1-3, *p*<0.001
**: Indicates comparisons between Group 2-3, *p*:0.002
SGA: Small gestational age, IUGR: Intrauterine growth restriction
Kruskal Wallis, Mann Whitney U test and Chi-Square test

The ANS rate was observed to be significantly lower in Group 2 (32%) and Group 3 (33.3%) compared to Group 1 (58%) (*p*=0.044). No significant difference was found between the groups in terms of other perinatal risk factors evaluated in the study. The perinatal characteristics of the patients are presented in Table 2.

When the laboratory values of the patients were examined, it was found that the cord lactate value and the rate of metabolic acidosis were significantly higher in Group 3 (*p*=0.026). The platelet count and platelet mass value were significantly lower in group 3 compared to the other two groups (*p*=0.014, *p*=0.023, respectively) (Table 3).

A significant difference was found between the groups in terms of resuscitation at birth (*p*=0.029), transfusion requirements within the first week of intensive care follow-up, and the rates of hsPDA requiring medical treatment. The comparisons of the interventions and treatments applied to the patients in the NICU are presented in Table 4.

Surfactant therapy was administered to 54.5% of those who received ANS and to 82.7% of those who did not receive it (*p*=0.004). Infants with severe intraventricular hemorrhage required more surfactant therapy, more respiratory support, and had higher rates of hemodynamically significant patent ductus arteriosus and mortality compared to other groups (Table 5). No significant difference was found in mortality, NEC, or the need for mechanical ventilation in the first 72 hours among those who received antenatal steroids. The comparisons related to the clinical follow-up of the patients are presented Table 5.

Table 2. Perinatal period characteristics of the patients

	Group 1 (n:50)	Group 2 (n:25)	Group 3 (n:21)	*p* value	Test Value
Multiple pregnancy, n (%)	15 (30%)	3 (12%)	4 (19%)	0.194	3.285
IVF, n (%)	7 (14%)	1 (4%)	2 (9.5%)	0.405	1.809
Outborns, n (%)	2 (4%)	2 (8%)	0	0.399	1.837
Vaginal delivery, n (%)	17 (34%)	8 (32%)	13 (61.9%)	0.060	5.628
5th minute APGAR Score <7, n (%)	15 (30%)	9 (36%)	10 (47.6%)	0.366	2.012
Antenatal steroid, n (%)	29 (58%)	8 (32%)	7 (33.3%)	0.044*	6.230
Antenatal magnesium therapy, n (%)	32 (64%)	12 (48%)	11 (52.4%)	0.129	7.124
Chorioamnionitis, n (%)	7 (14%)	2 (8%)	6 (28.6%)	0.144	3.873
PPROM, n (%)	17 (34%)	3 (12%)	7 (33.3%)	0.114	4.351
Oligohydramnios, n (%)	5 (10%)	1 (4%)	1 (4.8%)	0.565	1.142
Placental abruption, n (%)	3 (6%)	3 (12%)	1 (4.8%)	0.565	1.142
Preeclampsia, n (%)	13 (26%)	5 (20%)	4 (19%)	0.753	0.567
Multiparity, n (%)	27 (54%)	8 (32%)	9 (42.9%)	0.188	3.345

IVF: In vitro fertilization, PPROM: Preterm Premature rupture of membranes, ChiSquare test, *p<0.05

Table 3. Laboratory results of the patients

	Group 1 (n:50)	Group 2 (n:25)	Group 3 (n:21)	*p* value	Test Value
Cord pH, mean ± SD	7.29±0.15	7.28±0.13	7.24±0.18	0.621	0.953
Cord lactate, median (min-max)	2.7 (1.1-19)	3.3 (1.9-11)	4 (1.1-12.5)	0.026*	7.270
Metabolic acidosis in the first 72 hours, n (%)	11 (22%)	8 (32%)	15 (71.4%)	<0.001**, &	15.969
Hypocapnia in the first week, n (%)	16 (32%)	10 (40%)	10 (47.6%)	0.443	1.629
Hypercapnia in the first week, n (%)	14 (28%)	9 (36%)	12 (57.1%)	0.066***	5.425
Lowest platelet count in the first week, mean ± SD, (x10^3/mm^3)	173.4±82.7	178.5±64.3	125.1±79.6	0.014****, &&	8.487
MPV value, mean ±SD, (fL)	10.1±0.9	10±1.3	10.3±0.9	0.174	3.503
Platelet mass, mean ± SD, (x10^3/µL)	1723.9±795	1773.9±674	1286.5±790	0.023*****, &&&	7.575

Indicates comparisons between Group 1-3, *p:0.046, **p<0.001, ***p:0.04, ****p:0.034, *****p:0.018
Indicates comparisons between Group 2-3, &p:0.018, &&p:0.021, &&&p:0.01
ICH: Intracranial hemorrhage, MPV: Mean platelet volume, Kruskal Wallis, Mann Whitney U test and Chi-Square test

Table 4. Interventions applied to patients

	Group 1 (n:50)	Group 2 (n:25)	Group 3 (n:21)	*p* value	Test value
Resuscitation at birth, n (%)	34 (68%)	21 (84%)	20 (95.2%)	0.029*	7.103
Intubation at birth, n (%)	26 (52%)	15 (60%)	16 (76.2%)	0.166	3.593
Compression at birth, n (%)	6 (12%)	1 (4%)	2 (9.5%)	0.534	1.256
Umbilical venous catheter, n (%)	50 (100%)	23 (92%)	20 (95.2%)	0.152	3.761
Erythrocyte transfusion in the first week, n (%)	8 (16%)	4 (16%)	17 (81%)	<0.001	32.830
Fresh frozen plasma transfusion in the first week, n (%)	19 (38%)	8 (32%)	15 (71.4%)	0.013	8.612
Platelet suspension transfusion in the first week, n (%)	2 (4%)	3 (12%)	5 (23.8%)	0.043	6.310
Medical PDA treatment, n (%)	21 (42%)	14 (56%)	19 (90.5%)	<0.001	14.123
PDA ligation, n (%)	2 (4%)	1 (4%)	3 (14.3%)	0.227	2.962
Operation, n (%)	8 (16%)	4 (16%)	8 (38.1%)	0.088	4.856

*: Indicates comparisons between Group 1-3, *p*:0.032. ICH: Intracranial hemorrhage. Mann Whitney U test and Chi-Square test

Table 5. Clinical follow-up results of patients

	Group 1 (n:50)	Group 2 (n:25)	Group 3 (n:21)	*p* value	Test Value
Surfactant requirement, n (%)	28 (56%)	20 (80%)	19 (90.5%)	0.007*	10.008
Mechanical ventilation (first 72 hours), n (%)	26 (52%)	19 (76%)	19 (90.5%)	0.004	11.177
HFO (first 24 hours), n (%)	8 (16%)	1 (4%)	3 (14.3%)	0.321	2.273
Inotrope requirement (first 72 hours), n (%)	11 (22%)	5 (20%)	9 (42.9%)	0.137	3.981
Blood culture positivity (first 72 hours), n (%)	3 (6%)	3 (12%)	2 (9.5%)	0.659	0.835
hsPDA, n (%)	22 (44%)	15 (60%)	19 (90.5%)	0.001	13.181
NEC, n (%)	5 (10%)	2 (8%)	5 (23.8%)	0.300	4.879
Length of hospital stay, median (min-max)	78 (1-333)	81 (5-350)	80 (4-203)	0.827	0.381
Mortality, n (%)	7 (14%)	2 (8%)	8 (38.1%)	0.018**	8.078

*: Indicates comparisons between Group 1-3, *p*:0.011
**: Indicates comparisons between Group 2-3, *p*:0.028
ICH: Intracranial hemorrhage, hsPDA: Hemodynamically significant patent ductus arteriosus, Mann Whitney U test and Chi-Square test

Discussion

In this study, key risk factors and prevention strategies for ICH in premature infants were analyzed. While factors such as low gestational age, metabolic acidosis, and reduced ANS administration are well-documented contributors to ICH, our findings highlight the significant role of platelet mass in neonatal hemorrhagic risk. Specifically, infants with severe ICH exhibited markedly lower platelet counts and platelet mass values compared to those with mild or no hemorrhage. Given that platelet mass integrates both platelet count and MPV, it may provide a more comprehensive reflection of hemostatic balance, reinforcing its potential as an early biomarker for neonatal hemorrhagic complications. Furthermore, postnatal resuscitation, increased transfusion requirements, and hsPDA were also observed as contributors to ICH risk. The findings underscore the importance of optimizing hematological parameters alongside the metabolic and circulatory stability in preterm infants to mitigate the severity of ICH. Notably, infants with lower ANS exhibited a heightened need for surfactant therapy, potentially increasing ICH incidence.

Platelet mass, a novel concept utilized in the NICU, is a parameter associated with platelet functionality. Platelet mass may have a greater influence on the hemostatic efficacy of platelet plug formation than platelet count or MPV [10]. In terms of transfusion thresholds, utilizing platelet mass rather than platelet count was associated with a reduction in thrombocyte transfusions without an accompanying increase in the incidence of ICH [11]. Okur et al. [10] demonstrated an association between ICH and low platelet mass in premature infants during the early postnatal period. Zisk et al. [12] identified that in very low birth weight infants, those who developed severe ICH had a lower platelet mass compared to infants without ICH. In the investigation performed by Korkmaz et al. [13], platelet mass was found to have a closer association with high-grade ICH compared to lower-grade ICH when evaluated against other platelet parameters. Chen et al. [14] demonstrated that platelet transfusion is significantly associated with mortality risk, and low platelet counts have a notable impact on both ICH and mortality in preterm infants. Platelet counts and platelet mass were found to be significantly lower in cases with severe ICH compared to those with no hemorrhage or mild ICH, similarly, in our study. These findings highlight the critical role of platelet levels and mass in the pathophysiology of hemorrhagic events and underscore the importance of optimizing transfusion strategies in high-risk neonatal populations.

A wide range of demographic, perinatal, and neonatal factors has been associated with ICH in premature infants [2]. Studies have highlighted low birth weight, ANS absence, severe respiratory distress syndrome, sepsis, metabolic acidosis, and hsPDA as critical determinants of ICH risk [15-17]. Coskun et al. [2] identified low gestational age, low 5-minute APGAR scores, birth at an outside facility, and bleeding diathesis as significant risk factors for ICH. Consistent with these findings, our study demonstrated a strong association between low gestational age and advanced-stage intracranial hemorrhage, although low APGAR scores showed no significant impact.

The PRECIOUS Study (PREterm Cesarean/vaginal birth and IVH/OUtcomeS) highlights the ongoing debate regarding the optimal delivery mode for very preterm infants to mitigate mortality and neurological injury [18]. Although limited evidence points to a protective effect of cesarean delivery against ICH, the study emphasizes the need for robust prospective trials to confirm these findings. Our study observed rates of spontaneous vaginal delivery of 34% in group 1, 32% in group 2, and 61.9% in group 3, with no statistically significant differences among the groups, consistent with these findings. The unpredictable nature of vaginal delivery and the lack of a planned timeline often hinder the completion of antenatal steroid therapy, increasing the vulnerability of premature infants to severe ICH [18].

Adverse neonatal outcomes, particularly prematurity and very low birth weight infants, are significantly influenced by multiple pregnancies as a major risk factor. Jang et al. [19] reported a significantly higher risk of ICH among multiple gestations, underscoring the increased vulnerability of this population to severe neonatal complications. However, our study did not identify statistically significant differences in ICH incidence or severity between groups based on plurality.

Lee et al. [20] demonstrated that ANS administration significantly reduced the incidence of advanced-stage ICH in preterm infants, with protective effects on neonatal mortality and morbidity. Similarly, our study found that preterm infants requiring surfactant therapy exhibited higher rates of ICH, suggesting an indirect relationship between ANS administration and reduced surfactant need. Among our cohort, ANS use was observed in 36 of 86 infants overall and in 8 of 10 infants conceived via in vitro fertilization, indicating that closer monitoring in these pregnancies may contribute to higher ANS administration rates.

Maternal preeclampsia or gestational hypertension has been linked to lower rates of periventricular-intracranial hemorrhage (PV-ICH), potentially due to magnesium sulfate or obstetric management strategies [2, 21, 22]. Lee et al. [21] found lower maternal preeclampsia and ANS use in ICH cases, suggesting a protective effect. However, our study did not identify significant associations between maternal preeclampsia or other antenatal risk factors and ICH, possibly reflecting differences in study populations and underscoring the multifactorial etiology of ICH.

Its complex etiology is further shaped by the inherent fragility of the germinal matrix and the dynamic variations in cerebral blood flow [23]. Metabolic disturbances, such as hypocarbia, hypercarbia, hypoxemia, and acidosis, disrupt cerebral autoregulation in preterm infants, heightening their vulnerability to ICH [21, 24]. Hypercapnia is well-established as a vasodilator that increases cerebral blood flow. Wang et al. [24] identified acidosis as an independent risk factor for ICH, highlighting its role in disrupting cerebrovascular autoregulation. These results highlight the need for further research to elucidate the interaction between hypercapnia and other clinical factors contributing to ICH, as well as to identify potential protective mechanisms for neonates. In our study, metabolic acidosis was significantly more frequent in severe ICH cases, emphasizing its potential contribution. However, our study found no significant association between hypercapnia and severe ICH.

Our findings emphasize reduced ANS use, higher metabolic acidosis rates, increased transfusion needs, and lower platelet mass as prominent risk factors, reaffirming the multifactorial nature of ICH and the importance of addressing modifiable contributors. Schmid et al. [25] demonstrated a 50% reduction in the incidence of ICH among preterm infants with birth weights below 1500 grams following the implementation of preventive measures. Their study, combining retrospective cohort analysis and prospective cohort design, highlights the efficacy of these interventions. Consistent with this, identification of significantly lower ANS administration in infants with severe ICH, alongside metabolic acidosis and reduced platelet mass as key contributors to ICH risk in our study, can underscore the potential preventive strategies.

The findings of this study emphasize the critical importance of targeted interventions to reduce the incidence and severity of ICH in preterm infants. Given the strong association between prematurity and ICH, preventing preterm birth and administering ANS therapy remain pivotal strategies. Optimizing metabolic balance, particularly by addressing acidosis and ensuring timely platelet transfusions, is essential for maintaining hematological stability. This study highlights the critical role of platelet mass as a biological parameter in assessing the risk of neonatal ICH. By integrating platelet count and MPV, platelet mass provides a more comprehensive reflection of hemostatic balance, offering valuable potential for early hemorrhagic risk stratification and management. We believe these measures can be integrated into clinical protocols within the framework of an “ICH prevention bundle,” encompassing precise timing for ANS administration, standardized monitoring of pH, lactate levels and platelet mass. Kolnik et al. [26] reported a 76% reduction in severe ICH following targeted interventions to improve care bundle adherence in preterm neonates. Although this study did not evaluate the efficacy of the ICH bundle, the approach may be considered a potentially beneficial strategy and should be systematically assessed in future research.

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