ORIGINAL INVESTIGATION

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Predictors of Intraventicular Hemorhage in the Neonatal Intensive Care Unit

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ABSTRACT

Aim: To analyze intraventricular hemorrhage (IVH) incidence, clinical features and risk factors in extremely low birth weight infants.

Materials and Method(s): It is a single-center, retrospective cohort in infants delivering neonatal intensive care between 2010 and 2019. Infants of birth weight <1000 grams who had transfontanel-ultrasounds in the first week of life were included. Postnatal transfers, central nervous system anomalies, antenatal-diagnosed hemorrhage, death before obtaining transfontanel-ultrasound and incomplete dataset were excluded from the study. Infants were categorized as mild IVHs (grades 1-2), severe IVHs (grade-3, periventricular-hemorrhagic infarct) and control group. Ante-perinatal characteristics, clinical and laboratory features were recorded. SPSS-23 program utilized analysis for three groups.

Results: Overall IVH incidence was 22.9% in 455 neonates (52.9%, 49%, 31.5%, 13.4%, 6.7% at ≤25, 26, 27, 28 and 29 gestational weeks. Seizure was the first sign in 32.7% of the infants. Neonatal resuscitation, umbilical-cord blood pH, chorioamnionitis, patent ductus arteriosus were associated with developing mild IVH, but did not influence the progression to severe hemorrhage (p=0.782, p=0.109, p=0.566, p=0.111). Gestational age, invasive mechanical ventilation, inotrope-required hypotension was related to high-grade IVHs (p<0.001, p=0.025, p=0.013). The predictive strength of platelets to define IVH was poor at intensive care admission (sensitivity: 74%, specificity: 68.3%). Inotrope-required hypotension and low-umbilical-cord blood pH were determined as independent risk factors of high-grade IVHs (OR: 6.678, 95% CI: 2.557-17.443 and OR: 3.554, 95%CI: 1.089–11.602). Four infants necessitated ventriculo-peritoneal shunting. Mortality was 23.1% in infants developing IVH.

Conclusion: Inotrope-required hypotension is the strongest predisposing factor for high-grade ventricular hemorrhage in extremely low birth weight infants.

Keywords: Intraventricular hemorrhage, prematurity, extremely low birth weight, risk factors

Introduction

Intraventricular hemorrhage (IVH) is a serious complication of the preterm newborn with significant morbidity and mortality (1). The incidence ranges between 20% and 25% in birth weights less than 1500 grams (2,3). High-grade IVHs (grade-3 and periventricular hemorrhagic infarction - PVHI) remain to be a problem in neonatal morbidity (increased risk of cerebral palsy and neurodevelopmental disorders) and develop at a rate of 22% in infants born less than 1000 grams (4-6).

Most IVHs originate from the germinal matrix that consists of a fragile vasculature leading to structural immaturity. Any fluctuations in the cerebral blood flow (CBF) to this site appear to be the major cause of bleeding. Following the initial hemorrhage, production of reactive oxygen species and proinflammatory cytokines increase the permeability of the vasculature. The consequent result is the expansion of hemorrhage in the neighboring white matter and parenchyma. However, the physiopathology is believed to be multifactorial: immature cerebral vessels, fluctuations in the blood flow, platelet abnormalities and coagulopathy contribute to IVH development (2,6-8).

Several predisposing factors have been identified in the development of hemorrhage (5,8). Low Apgar score, instrumental birth delivery, severe respiratory distress syndrome (RDS), air leakage syndromes, hypoxia, hypercapnia, patent ductus arteriosus (PDA), sepsis, thrombocytopenia and

coagulopathy are some of the clinical features associated with IVH (2,9). Thrombocytopenia is common in extremely low birth weight (ELBW: birth weight <1000 grams) infants and platelet infusions are prophylactically used to avoid the risk of bleeding. However, the lack of evidence for platelet transfusion thresholds leads to 15% of transfusion rates and increased risk of transfusion reactions in this vulnerable population (6,10).

Data suggests that wide variations occur in predisposing factors and controversies exit in clinical management and daily transfusion practice (6,10). Each neonatal care center should assess regional risk factors and establish their local protocols to avoid IVH in babies born less than 1000 grams. Regarding this fact, we conducted an observational cohort to evaluate IVH incidence, maternal and neonatal characteristics and risk analysis in ELBW preterm infants at a highly-referral, tertiary neonatal intensive care unit (NICU).

Materials and Methods

The study was designed as a single-center, retrospective cohort in ELBW (<1000 grams) neonatal admissions to one of the largest, level III, university-affiliated NICU with 34 incubators around the Mediterranean region between 2010 and 2019.

The patient records were extracted from the hospital's electronic database. The inclusion criteria were neonatal intensive care unit admissions i) born in the same perinatal center where the neonatal care will be delivered, ii) birth weight <1000 grams, iii) who had a transfontanel ultrasound (TFU) in the first seven days of life. Exclusion criteria were, i) birth delivery at another facility and transferred postnatally, ii) major central nervous system (CNS) anomalies, iii) antenatal diagnosed IVH, iv) newborns who died before obtaining TFU and v) incomplete patient dataset.

Based on 2018 Volpe's ventricular hemorrhage grading classification, IVH severity was defined as, Grade-1 (bleeding in the germinal matrix), Grade-2 (bleeding <50% in the ventricle, without any expansion into the ventricular system, Grade-3 (bleeding ≥ 50% of the ventricle with expansion) and PVHI (5,11). The infants developing IVHs were categorized as mild IVH (grades-1 and 2 IVHs), severe IVH (grade-3 IVH and PVHI) and the control group (infants who did not present any hemorrhage on cranial imaging). The statistical analysis assessed the maternal factors and neonatal characteristics including maternal anticoagulant use (aspirin, low molecular weight heparin and heparin), preeclampsia (hypertension and proteinuria) (12), chorioamnionitis (clinical and/or histological), antenatal steroid administration, intrauterine growth restriction (IUGR: birth weight <10th percentile) (13). The clinical variables were examined for resuscitation at birth delivery; low-umbilical -cord blood pH, echocardiographically-confirmed and medically-intervened PDA, inotrope-required hypotension. Of note, the study center follows the recommendations of the Turkish Neonatal Society on neonatal hemodynamics and management of hypotension (the use of intravenous fluids, inotropes, vasopressors, and steroids when necessary) (14). According to the national guideline, the definition of hypotension is, i) mean blood pressure (BP) below the gestational week or at the <3rd (or 10th) percentile according to the gestational age; ii) systolic, diastolic, and mean BP <95% CI according to the gestational week; iii) mean BP of <30 mm Hg in the first 72 hours in preterm babies with gestational age of <32 weeks; iv) BP value that disrupts tissue perfusion. Other clinical variables such as RDS, invasive mechanical ventilation (MV), bronchopulmonary dysplasia (BPD: oxygen requirement in the postmenstrual 36th week) (15), early-onset sepsis (suspected or confirmed sepsis in the first 48 hours of life), necrotizing enterocolitis (NEC), duration of NICU stay and survival were extracted from the medical files.

The routine TFUs were performed by the staff radiologists using General Electric LOGIQ S6 2007 device (C3/5L/10 L MHz probs) within the first 24 hours, third day, 7th day and at least once a week in subsequent weeks until the end of the first month. Sequential TFUs were performed for follow-up once a week for four weeks and at the time of discharge in grade I-II IVH, and two times a week and until the time of discharge in grade III-IV IVHs. If the initial IVH grade progresses, the final stage of the hemorrhage was recorded and grouped accordingly. The decision of surgical intervention depended on the risk stratification of the patient defined by El-Dib et al. (red zone – high-risk patient: ventricular index >97th percentile +4 mm and anterior horn width >10 mm and/or thalamo-occipital distance >25 mm in TFU measurements in addition to clinical findings such as the growth of head circumference >2cm per week, separated sutures and bulging fontanelles) (16).

Laboratory data consisted of platelet counts obtained in the first and third days of life. Coagulation tests (prothrombin time, activated partial thromboplastin time – aPTT, the international normalized ratio - INR and levels of fibrinogen) at NICU admission were also collected from the database. We defined coagulopathy if fibrinogen was < 5th % (<71 mg/dL), prothrombin time >95th% (>21 sec), aPTT > 95th% (>4 seconds) (17), and thrombocytopenia as platelet counts <100x10^{9}/L (18). In respect to transfusion guidelines of the Turkish Neonatal Society, babies born less than 1000 grams deliver platelet transfusions in presence of severe thrombocytopenia (platelets counts <50x10^{9}/L) to avoid bleeding complications (18). The authors also recorded whether if the newborn received platelet transfusion or not.

SPSS–23 program was utilized for descriptive analysis of variables, central tendency and dispersion of quantitative variables. Kolmogorov-Smirnov test was applied for normality assumption, then we used Kruskal Wallis or One-way analysis of variance (followed by posthoc comparisons by Tamhane test) were performed for analysis within three groups. Receiver operating characteristic (ROC) assessed the area under the curve (AUC) and the cutoff values of the platelets using Medcalc statistical program (free trial version). Univariate logistic regression was performed to predict potential risk factors of developing IVH. The multivariate logistic regression determined independent risk factors of severe IVHs. All data were expressed as percentage (%), median (interquartile range - IQR) and odds ratios (OR) and 95% confidence intervals (CI). A p-value of less than 0.05 was considered significant.

The study was approved by the Institutional Review Board of Istinye University Antalya Medical Park Hospital (no: 2019/10, date: 23.10.2019). We did not perform a power analysis due to the retrospective nature of the study.

Results

Total of 455 ELBW infants out of 592 NICU admissions with birth weight <1000 grams were enrolled in the study (exclusions due to birth in another facility in 109 infants, lack of patient data in twelve infants, CNS anomaly in eight infants, death before obtaining TFU in five infants and antenatal-diagnosed IVH with CNS anomaly in three infants). One hundred and four (22.9%) ELBW infants developed IVH (Grade-1 IVH: 11.7%, Grade-2 IVH: 5.7%, Grade-3 IVH: 3.7%, PVHI: 1.8%). The majority of IVHs occurred within 72 hours of life (day-1 22.1%, day-3 61.5%, day-7 16.4%). In respect to gestational weeks, the incidence of IVHs at ≤25, 26, 27,28 and 29 weeks were 52.9% (18/34), 49% (24/49), 31.5% (23/73), 13.4% (38/284) and 6.7% (1/15) (Table 1). The neonatal seizure was the first sign of IVH in 32.7% (34/104) of the infants.

Maternal and neonatal characteristics can be observed in Table 2. The presence of chorioamnionitis, neonatal resuscitation at birth delivery, low-umbilical-cord blood pH, PDA were all associated with developing IVH (p<0.001, p=0.001, p<0.001, p<0.001); but once the bleeding started, they did not have any impact on proceeding to severe IVH (mild IVH → severe IVH; p=0.782, p=0.109, p=0.566, p=0.111) (Table 3). On the contrary, gestational age, invasive MV and inotrope-required hypotension have been identified as three variables associated with expanding severe hemorrhage (p<0.001, p=0.025, p=0.013; Table 3)

Infants developing IVH have exhibited significant thrombocytopenia at day-1 and day-3 (p=0.005, p=0.023; Table 3); but the platelet counts in the first 72-hours of life have shown low sensitivity and specificity for developing IVH (sensitivity: 74%, 45.9%; specificity: 68.3%, 52.1%; Figure 1). The predictive strength of platelets in developing severe IVH was also weak: the highest area under the curve for the severe hemorrhage was observed with platelet counts day-1 with a negative predictive value (NPV) of 97%.

Several risk factors for developing IVH can be observed in Table 4. After adjusted for birth weight, the multivariate logistic regression model has identified inotrope-required hypotension

Table 1. IVH and radiological diagnosis based on gestational weeks

	Gestational weeks					
	≤25 weeks (n=18)	**26 weeks (n=24)**	**27 weeks (n=23)**	**28 weeks (n=38)**	**29 weeks (n=1)**	**Overall IVHs (n=104)**
Grade 1 IVH*	5 (27.8%)	10 (41.7%)	8 (34.8%)	29 (76.3%)	1 (100%)	53 (51%)
Grade 2 IVH*	4 (22.2%)	7 (29.2%)	9 (39.1%)	6 (15.8%)	-	26 (25%)
Grade 3 IVH*	7 (38.9%)	4 (16.7%)	4 (17.4%)	2 (5.3%)	-	17 (16.3%)
PVHI	2 (11.1%)	3 (12.5%)	2 (8.7%)	1 (2.6%)	-	8 (7.7%)

*IVH refers to intraventricular hemorrhage, PVHI: periventricular hemorrhagic infarction

Table 2. Perinatal and demographic data of the study population

n (%)	Control	Mild IVH (Grade 1-2 IVH)	Severe IVH (Grade 3 IVH-PHVI)	p	p1	p2	p3
Maternal characteristics							
Maternal age	31 (26-34)	28 (24-34)	29.5 (25-35.25)	0.359	0.154	0.878	0.480
Antikoagulants use *	33 (9.4%)	13 (16.7%)	3 (12.0%)	0.165	0.061	0.721	0.755
Preeclampsia	50 (14.2%)	6 (7.7%)	7 (26.9%)	**0.044**	0.120	0.091	**0.017**
Chorioamnioitis	14 (4.0%)	16 (20.5%)	4 (15.4%)	**< 0.001**	**0.001**	**0.028**	0.566
Gestational diabetes	32 (9.1%)	8 (10.3%)	5 (19.2%)	0.255	0.754	0.160	0.303
Antenatal steroids	206 (58.7%)	43 (55.1%)	14 (53.8%%)	0.775	0.564	0.629	0.909
In vitro fertilization	111 (31.6%)	26 (33.3%)	8 (30.8%)	0.951	0.770	0.928	0.809
Neonatal characteristics							
Birth weight(grams) †	900 (750-961)	720 (673.75-882.5)	685 (606-846.25)	**0.001**	**< 0.001**	**< 0.001**	0.403
Gestational weeks†	28 (27-28)	27 (26-28)	26 (24.75-27)	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
IUGR	36 (10.3%)	8 (10.3%)	2 (7.7%)	0.961	0.999	0.999	0.999
Gender – Males	164 (47.1%)	46 (59.0%)	14 (53.8%)	0.155	0.059	0.508	0.647
Multiple birth	54 (15.4%)	17 (21.8%)	4 (15.4%)	0.382	0.168	0.999	0.481
CS delivery	305 (86.9%)	67 (85.9%)	22 (84.6%)	0.903	0.814	0.763	0.999
Resuscitation	24 (7.4%)	16 (20.5%)	6 (23.1%)	**0.001**	**< 0.001**	**0.016**	0.782
Umbilical cord blood pH <7.2	12 (3.4%)	8 (10.3%)	6 (23.1%)	**< 0.001**	**0.016**	**0.001**	0.109
n=455	n= 351	n=78	n=26				

IUGR: intrauterin growth restriction, CS: Cesarean section*Anticoagulants refer to aspiririn, low molcular weight heparin and heparin delivery at pregnancy; † median (interquartile range: 25%-75%). Statistics for numerical variables were obtained by Kruskall Wallis and pairwise comparisons by Tamhane test; P1: control – mild IVH, P2: control – severe IVH, p3: mild-severe IVH.

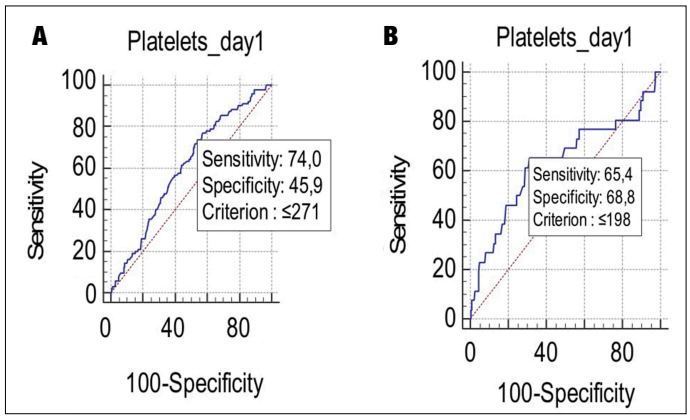


Figure 1A-B. The predictive strength of platelets in ventricular hemorrhage

Platelet counts and IVH Development (**Platelets day1:** AUC: 0.605[0.546-0.664], sensitivity: 74.0% [64.5% - 82.1%)], specificity: 45.9% [40.6% - 51.2%], LH+: 1.37 [1.2 - 1.6], PPV: 28.8% [23.5% - 34.7%], NPV: 85.6% [79.8% - 90.3%]; **Platelets day3:** AUC: 0.619 [0.559 - 0,679], sensitivity: 68.3% [58.4% - 77.1%], specificity: 52.1% [46.8% - 57.5%], LH+: 1.43 [1.2 - 1.7], PPV: 29.7% [24% - 35.9%], NPV: 84.7% [79.2% -89.2%])
Statistics were obtained by ROC analysis. PPV: positive predictive value, NPV: negative predictive value, LH: likelihood ratio.

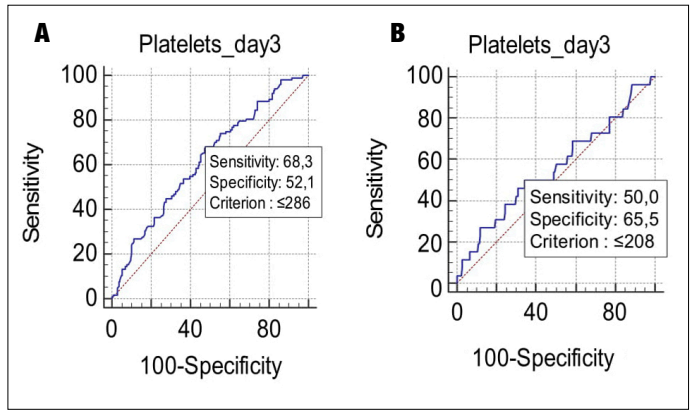


Figure 2A-B. The predictive strength of platelets in severe ventricular hemorrhage

Platelet counts and Severe IVH Development (**Platelets day1:** AUC: 0.635[0.503 - 0.766], sensitivity: 65.4 [44.3% - 82.8%], specificity: 68.8% [64.1%) - 73.1%], LH+: 2.1 [1.5 - 2.9], PPV: 11.3% [6.7% -17.4%] f NPV: 97.0% [94.5% - 98.6%]; **Platelets day3:** AUC: 0.558 [0.434 - 0,683], sensitivity: 50.0% [29.9% - 70.1%], specificity: 65.5% [60.8%) - 70.0%)], LH+: 1.45 [1.0 - 2.2], PPV: 8.1% [4.4% -13.4%], NPV: 95.6% [92.6% - 97.6%]).
Statistics were obtained by ROC analysis. PPV: positive predictive value, NPV: negative predictive value, LH: likelihood ratio.

Table 3. The clinical features of the study population

n (%)	Control	Mild IVH (Grade 1-2 IVH)	Severe IVH (Grade 3 IVH–PVHI)	p	p1	p2	p3
RDS	125 (35.6%)	36 (46.2%)	13 (50.0%)	0.098	0.082	0.142	0.734
Invasive MV	91 (25.9%)	23 (29.5%)	14 (53.8%)	**0.008**	0.520	**0.002**	**0.025**
BPD	35 (10.0%)	25 (32.1%)	8 (30.8%)	**< 0.001**	**< 0.001**	< 0.001	0.257
PDA	84 (23.9%)	31 (39.7%)	15 (57.7%)	**< 0.001**	**0.004**	< 0.001	0.111
Hypotension	19 (5.4%)	12 (15.4%)	10 (38.5%)	**< 0.001**	**0.002**	< 0.001	**0.013**
Early onset sepsis	31 (8.8%)	16 (20.5%)	3 (11.5%)	**0.013**	**0.003**	0.719	0.390
NEC	27 (7.7%)	18 (23.1%)	5 (19.2%)	**< 0.001**	**< 0.001**	0.058	0.682
Thrombocytopenia $_{day1}$	19 (5.4%)	3 (3.8%)	6 (23.1%)	**0.005**	0.778	**0.004**	**0.007**
Thrombocytopenia $_{day3}$	53 (15.1%)	21 (26.9%)	7 (26.9%)	**0.023**	**0.012**	0.158	0.999
Platelets infusion	14 (4.0%)	9 (11.5%)	4 (15.4%)	**0.004**	**0.021**	**0.028**	0.733
Coagulopathy	13 (3.7%)	5 (6.4%)	3 (11.5%)	0.091	0.344	0.089	0.409
NICU stay (days)*	47 (39-63)	58.5 (43-81.5)	62.5 (39.5-83.75)	**< 0.001**	**< 0.001**	**0.040**	**0.894**
Mortality	39 (11.1%)	13 (16.7%)	11 (42.3%)	**< 0.001**	**0.174**	**< 0.001**	0.007
n=455	n= 351	n=78	n=26				

*median (IQR); statistics for numerical variables were obtained by Kruskall Wallis and pairwise comparisons by Tamhane test; P1: control – mild IVH, P2: control – severe IVH, p3: mild-severe IVH. Abbreviations: RDS: respiratory distress syndrome, MV: mechanical ventilation, BPD: broncho pulmonary dysplasia, PDA:patent ductus arteriozus NEC: necrotizing enterocolitis, Thrombocytopenia: platelet counts <100 x 109 /L, Coagulopathy: fibrinogen < %5th %: < 71 mg/dL, prothrombin time > 95th % >21 seconds and aPTT >95th % >4 seconds.

Table 4. Risk factors associated with developing IVH*

	OR (95% CI)	p
Birth weight	0.993 (0.991 - 0.995)	**< 0.001**
Gestational weeks	0.505 (0.414 - 0.616)	**< 0.001**
Resuscitation	3.354 (1.809 - 6.217)	**< 0.001**
Umbilical cord pH <7.2	4.394 (1.964 - 9.832)	**< 0.001**
Invasive mechanical ventilation	1.578 (0.989 - 2.517)	0.056
Medical PDA	2.521 (1.594 – 3.986)	**< 0.001**
Hypotension	4.688 (2.424 – 9.068)	**< 0.001**
Chorioamnionitis	5.731 (2.780 – 11.817)	**< 0.001**
Early onset sepsis	2.307 (1.242 - 4.285)	**0.0086**
Thrombocytopenia$_{day1}$	1.655 (0.725 – 3.778)	0.231
Thrombocytopenia$_{day3}$	2.071 (1.228 - 3.493)	**0.006**
Platelets infusion	3.439 (1.561 – 7.574)	**0.002**
Coagulopathy	2.167 (0.873 – 5.380)	0.096

*IVH includes all grades of intraventricular hemorrhage. Statistics were obtained by univariate logistic regression.
Medical PDA: Patent ductus arteriozus that requires medical intervention using ibuprofen or indomethacin

Table 5. Multivariate Logistic Regression for Severe IVH

		95% C.I. for EXP(B)		
	Exp (B)	Lower limit	Upper limit	p
Hypotension	6.678	2.557	17.443	**<0.001**
Umbilical cord pH <7.2	3.554	1.089	11.602	**0.036**
Chorioamnionitis	1.156	0.294	4.545	0.835
Platelet infusion	1.351	0.345	5.286	0.666
Invasive MV	2.352	0.971	5.695	0.058

MV: mechanical ventilation

and low-umbilical-cord blood pH as independent risk factors of severe hemorrhage (OR: 6.678, 95% CI: 2.557-17.443 and OR: 3.554, 95% CI: 1.089–11.602; Table-5).

Four infants developed progressive post-hemorrhagic ventricular dilatation (PHVD) necessitating a cerebrospinal fluid (CSF) diverting procedure (ventriculo-peritoneal shunt – VP shunt). Twenty-two convulsive infants (22/104, 21.2%) received anti-seizure medications at hospital discharge. All patients developing any IVH grade were taken into neurological follow-up after hospital discharge, but the long-term morbidity was not included because the study period was limited to neonatal intensive care unit. Overall mortality in babies born less than 1000 grams was 13.9% due to miscellaneous prematurity-related causes (nosocomial sepsis and NEC). The mortality rate has increased to 23.1% in the infants developing any hemorrhage IVH (16.7% in patients with mild IVH, 42.3% in severe IVH)

Discussion

This observational cohort in ELBW preterm infants to define neonatal characteristics and risk factors for developing IVHs has elucidated several outcomes such as, i) the rate of developing IVH was 22.9%, ii) the hemorrhage has expanded to the surrounding tissues (severe IVHs: grade-3 and PVHI) in 24% of 104 bleeding patients, iii) chorioamnionitis, neonatal resuscitation, low-umbilical-cord blood pH and PDA were associated hemorrhage with developing IVH, but once the bleeding started, they did not influence the proceeding hemorrhage from mild to severe IVH, iv) the predictive strength of platelets in the first 72-hours of life in developing hemorrhage was weak, v) hypotension necessitating the use of inotropes and low-umbilical-cord blood pH were identified as independent risk factors for severe IVH.

IVH remains to be an important issue in the vulnerable population of ELBW neonates (5,19). The incidence ranges from 15% to 40%, depending on the NICU standard care (20). Literature data suggest that approximately 22% of the ELBW neonates develop high degrees of IVH (6). A recent prospective cohort including 69 Turkish NICUs reported 8.6% overall incidence for grade >2 and higher IVHs in infants of birth weight ≤1000 grams (14.4% and 6.6% in birth weight of 501-750 grams and 751-1000 grams, respectively) (21). The present study demonstrated a 22.9% overall IVH rate including grade-1 IVHs and the hemorrhage has progressed to more severe grades in 24% of the patients. The outcome reflected the incidence of low-birth-weight infants who were born in the same birth center where intensive care would be delivered. However, the authors have concerns about the true incidence of ELBW infants delivering intensive care unit. To eliminate the risk of subjectivity in birth and/or postnatal transport data, the outborn infants (born in another birth facility and transferred to intensive care) were not included in the study data. There is evidence that birth outside the perinatal center and postnatal transports are associated with severe brain injury and adverse neonatal outcomes in infants of gestational age less than 29 weeks (22). Excluding the ones who died before obtaining cranial ultrasound might also affect the outcome by missing massive IVHs that resulted in sudden death in the present study. Both concerns raise the suspicion of increased incidence of IVH development in this vulnerable population.

The majority of IVHs occur in the first week of life and in 10% of patients, the onset of hemorrhage is within 12 hours following birth (5,8). Compared to previous ultrasound findings, the onset of diagnosis within the first day was significantly higher (22.1%) in this study, possibly due to our institutional policy. The practice is to obtain early diagnostic imaging within the first day of life once an infant with extremely lower gestation is admitted to intensive care unit. Ten out of 23 (43.5%) IVHs occurred in infants with gestational age ≤26 weeks. These infants were more likely to develop easy-to-diagnose high-grade hemorrhage.

Immature vascularity, hemodynamic instability and the consequent fluctuations in CBF, platelet abnormalities and coagulopathy contribute to IVH development (2,6-8). Several predisposing factors have been identified in the etiology and severity of IVHs. Lower gestational age and birth weight, IUGR, mode of birth (vaginal delivery), instrumental delivery, cardiopulmonary resuscitation, Apgar score, acidosis, feto-maternal infections, sepsis, RDS, PDA, air leak syndromes, hypoxemia, hypercapnia, seizures, thrombocytopenia have been shown to play a role in the pathogenesis (2,5,9,19,20,22,23). Our findings indicated inotrope-required hypotension as the most significant risk factor for developing severe IVH. CBF relies upon two cardiovascular components: cardiac output and regional vascular resistance regulated by autoregulatory mechanisms (24,25). Previous investigations demonstrated lower CBF in infants developing IVH (24,26). The limited autoregulatory capacity of the preterm and fluctuations in arterial blood pressure influence the perfusion of the brain, which lead to capillary vessel ruptures and the consequent hemorrhage (5,24-27). German Neonatal Network and Neocirculation project postulated increased risk of IVH in

infants with gestational age less than 28 weeks in the presence of inotrope necessitating hypotension (28). However, there are controversial data on the topic of BP. Rather than measuring BP itself, monitoring the signs of perfusion should be the goal of neonatal intensive care (5,29). The selection of inotrope also influences the risk of bleeding. Vesoulis et al. reported an increase in mean blood pressure over 10 mmHg with Dopamine reduced the risk of IVH (30). On the contrary, the PROGRESS study consortium and Nationales Genomforschungsnetz Deutschland demonstrated that the use of catecholamines was more likely to develop severe IVH (31). Due to the retrospective observational design of the present study, the authors focused on risk analysis of IVH in infants born less than 1000 grams. The influence of inotrope selection in hemodynamically unstable infants was beyond the scope of this investigation. Yet, there is no doubt, future clinical research is needed to clarify whether hypotension itself or a sudden elevation in blood flood due to inotropic support is the cause of a high-grade hemorrhage. Inotrope selection and CBF monitorization should be the mainstay of clinical investigations to minimize short and long-term IVH morbidity.

Coagulopathy and thrombocytopenia are two predisposing factors related to IVH (1,6,10,23). Platelet counts less than $150x10^9$/L are very common in very low birth weight neonates that leave them vulnerable to hemorrhage (10). Lower platelet counts were frequently observed in the study population: 8.7% and 26.9% at NICU admission and 3rd day of intensive care unit. Of note, the infants were defined thrombocytopenic if the platelet counts were less than $100x10^9$/L and received platelet transfusions when the values were below $50x10^9$/L to minimize the risk of IVH. The study center's transfusion policy is compliant with the national recommendations of the Turkish Society of Neonatology to administer platelet transfusions if the platelet counts less than $50x10^9$/L in infants of birth weight less than 1000 grams (18). Approximately in 12.5% (13 out of 104) of the IVHs, the platelet counts were below $50x10^9$/L and these infants had to deliver platelet transfusions. Despite the calculated risks for lower platelet counts, ROC analysis has shown poor predictive strength in determining IVH development. The subject of platelet infusion also remains to be a matter of debate: did the increased IVH risk occur due to very low platelet counts that were already below $50x10^9$/L and leave them vulnerable to bleeding; or an immune response was catalyzed because of the transfusion itself since all transfusion product are known for their inflammatory-triggering effects (32,33). Still, controversies exist in the literature and the absence of definitive thresholds for platelet transfusion creates significant variability in clinical practice among NICUs (6,10,20,32). Coagulopathy, as another hemostatic abnormality, was not described as a potential risk factor in this study, possibly due to frequent of fresh frozen plasma as soon as an abnormality was detected. Yet, the potential benefits of all blood product transfusions need to be balanced against the risks of adverse transfusion reactions.

All IVHs delivered neurological follow-up after hospital discharge. Twenty-two convulsive infants (21.2%) received anti-seizure medication at discharge. Progressive post-hemorrhagic ventricular dilatation (PHVD) that necessitated VP-shunting was developed in four of twenty-five (16%) severe IVHs in the present study. PVHD is reported between 30% and 50% of high-grade IVHs and 25% of the infants with progressive PVHDs necessitate CSF diverting procedures (34). However, the timing of intervention is disputable; the decision of surgery is left to the attending neurosurgeon and therapeutic approaches vary greatly among NICUs (16,35). Unfortunately, the absence of post-ICU follow-ups has restrained the estimation of long-term VP-shunting rates and neurological outcome. Overall mortality in babies born less than 1000 grams was 13.9%. In the case of a developing IVH, the mortality has increased to 23.1%.

The limitations of the present study were the retrospective design leading to a potential risk of bias. Keeping the onset of ultrasound-diagnosis restricted to one week was another limitation. Even if many IVHs occur during the first week of life, there was the risk of unnoticing hemorrhage that might occur in the following weeks. The study era also consisted of intensive care unit period that limited the estimation of the long-term neurodevelopmental outcome. Despite the limitations, planning this retrospective cohort in a very specific group of newborns (birth weight < 1000 grams) and excluding the ones born in another perinatal center have created homogeneity in the study population. Hence the results have enabled us to analyze all maternal and neonatal characteristics of ELBW infants and the true incidence of IVH outcomes of this highly-referral, level III NICU.

Conclusion

Hemodynamic instability requiring inotropic support is the main predisposing factor in developing severe IVH. Monitoring cerebral blood flow and perfusion should be the focus of future investigations. Despite poor predictive strength of platelet counts, timely intervention for thrombocytopenia is essential to avoid intraventricular hemorrhage of ELBW infants.

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