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Intraventricular hemorrhage: morbidity and risk factors in 3rd level centers in South-East Poland

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ABSTRACT

Introduction: We describe the incidence of intraventricular hemorrhage (IVH) in preterm infants in all 3rd level centers in Podkarpackie province, Poland. We identify the frequency of risk factors present in this population known to increase the occurrence of IVH, which if changed could result in better treatment outcomes.

Material and methods: The retrospective, observational, multicenter study included 340 preterm infants who were born at ≤ 28 weeks of gestation. Patients hospitalized at 3rd level centers between 2016 and 2020 were enrolled in the analysis.

Results: The incidence of IVH in the study population was 51%, and severe grades of IVH (sIVH) occurred in 24% of all infants. Patients diagnosed with sIVH had significantly more often lower gestational age ($p = 0.0005$), lower birth weight ($p = 0.01$), lack of antenatal steroid therapy ($p = 0.0004$), a partial course of antenatal steroid therapy ($p = 0.0009$), a lower Apgar score at 1 minute ($p < 0.0001$), invasive mechanical ventilation use ($p < 0.0001$) and a lower hematocrit (Hct) level at the first measurement after birth ($p = 0.002$). After multivariate analysis, the significant risk factors that increased risk of sIVH were: lack of or only a partial course of antenatal steroid therapy (OR: 2.85; 95% CI: 1.18–6.83, $p = 0.02$, OR: 3.16; 95% CI: 1.49–6.67, $p = 0.003$ respectively), invasive mechanical ventilation use (OR: 4.75; 95% CI: 2.18–10.34, $p < 0.001$) and the Hct level < 45% at first measurement (OR: 2.62; 95% CI: 1.28–5.37, $p = 0.008$).

Conclusions: The occurrence of any grade, but especially a severe grade of IVH is still a very common problem in premature infants. Administering a full course of antenatal steroid therapy, applying interventions to prevent anemia in preterm infants and optimizing ventilation methods may help reduce the incidence of IVH, which will improve patient outcomes.

KEY WORDS:

prematurity, brain injury, epidemiology, intraventricular hemorrhage.

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INTRODUCTION

Intraventricular hemorrhage (IVH) is one of the main factors increasing mortality of preterm infants [1]. Analyses reporting the incidence of IVH show widely different etiologies depending on the gestational age (GA) of the population included in the study and the country of publication [2].

The pathophysiology of IVH is complex and multifactorial. There are many predictors that can increase the risk of IVH, including antenatal care, GA at delivery, time of umbilical cord clamping, infections, and various factors of care during hospitalization in the neonatal intensive care units (NICU) [1, 3]. We can distinguish between four degrees of severity, which are characterized by different prognoses in later development. Low grade or "mild bleeding" is most commonly reported as grade I and II in both the Papile and Volpe classifications [4, 5]. Low grades of IVH are often not considered clinically significant, but it should not be forgotten that there is evidence of an increased risk of neurodevelopmental impairment in preterm infants as a result of these hemorrhages [6]. High grades of IVH or severe IVH (classified according to Papile as grade III and IV or according to Volpe: grade 3 or any grade of IVH complicated by periventricular hemorrhagic infarction (PVHI) and/or posthemorrhagic ventricular dilatation (PHVD)) can lead more often to ventricular dilatation, posthemorrhagic hydrocephalus and to long-term neurologic and neurodevelopmental disability, including seizures, cognitive and executive function impairment, and cerebral palsy [4, 5]. The mortality rate among preterm infants with grade I or II is 20%, but for severe grades of IVH (sIVH) it is more than twice as high (40–45%) [7].

Europe had lower rates of both any IVH and sIVH across multiple GA subgroups compared to most reports from the rest of the world [8]. The only available study from Poland on this subject reports that among preterm infants diagnosed with any IVH, 21% of patients were identified with severe IVH [9]. The above-mentioned study was published in 2016 and its conclusions suggested conducting expanded evaluations on this subject.

The aim of this study is to determine the incidence of any grade IVH and severe IVH in premature infants born in 3rd level hospitals in Podkarpackie province. In addition, we aimed to evaluate the risk factors present in this population known to increase the incidence of IVH, which if changed could result in better treatment outcomes.

MATERIAL AND METHODS

SETTING

A retrospective cohort study was conducted in preterm infants $\leq 28^{+0}$ weeks GA admitted to four 3rd level NICU in South-East Poland: (1) the Neonatology Department of the PRO-FAMILIA Specialistic Hospital in Rzeszów, (2) Clinical Department of Neonatology and NICU, Frederick Chopin Clinical Provincial Hospital No. 1 in Rzeszów, (3) Clinical Department of Neonatology and NICU, Saint Jadwiga the Queen Clinical Provincial Hospital No. 2 in Rzeszów, and (4) Department of Neonatology and NICU, John Paul II Municipal Hospital in Rzeszów. Infants who died within the first 24 hours of life were excluded (Figure 1).

Data were collected retrospectively from the records of first admissions after delivery available at each center. Patients hospitalized in 2016–2020 were included. Demographic data, antenatal and neonatal treatment were collected. Approval with a waiver of informed consent was granted by the Bioethics Committee of the University of Rzeszow (Decision No. 2022/039, dated 04/05/2022).

DATA COLLECTION AND DEFINITIONS

Data were extracted from hospital medical records covering the period from birth until hospital discharge. In order to characterize the population, the following baseline neonatal characteristics were collected for all study
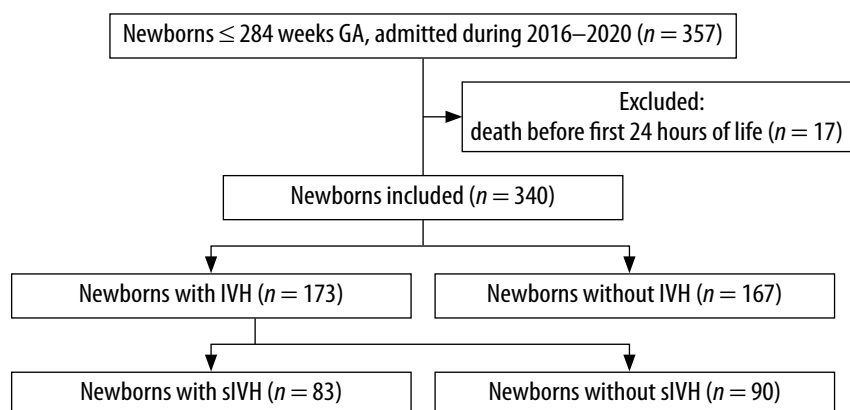
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┌─────────────────────────────────────────────────────┐
│ Newborns ≤ 28⁴ weeks GA, admitted during 2016–2020 (n = 357) │
└─────────────────────────────────────────────────────┘
                         │
                         │      ┌──────────────────────────────────────┐
                         ├─────▶│ Excluded:                            │
                         │      │ death before first 24 hours of life  │
                         │      │ (n = 17)                             │
                         │      └──────────────────────────────────────┘
                         │
            ┌────────────────────────────────┐
            │ Newborns included (n = 340)     │
            └────────────────────────────────┘
                 │                      │
    ┌────────────────────────┐   ┌────────────────────────────┐
    │ Newborns with IVH      │   │ Newborns without IVH       │
    │ (n = 173)              │   │ (n = 167)                  │
    └────────────────────────┘   └────────────────────────────┘
                 │                      │
    ┌────────────────────────┐   ┌────────────────────────────┐
    │ Newborns with sIVH     │   │ Newborns without sIVH      │
    │ (n = 83)               │   │ (n = 90)                   │
    └────────────────────────┘   └────────────────────────────┘
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FIGURE 1. Study population

GA – gestational age, IVH – intraventricular hemorrhage, sIVH – severe grades of IVH

TABLE 1. Patients' characteristics

Characteristics	Newborns with sIVH diagnosis (*N* = 83)[a]	Newborns without or with mild IVH diagnosis (*N* = 257)
Gestational age at birth, *n* (%)		
− < 25	27 (33)	48 (19)
− 25−26	36 (43)	88 (34)
− 27−28	20 (24)	121 (47)
Birth weight, *n* (%)		
− < 500	6 (7)	9 (4)
− 500−749	34 (41)	63 (25)
− 750−1000	32 (39)	108 (42)
− > 1000	11 (13)	77 (30)
Sex, *n* (%)		
− Female	42 (51)	133 (52)
− Male	41 (49)	124 (48)
Singleton, *n* (%)	61 (73)	193 (75)
Vaginal delivery, *n* (%)	24 (29)	191 (74)
Inborn, *n* (%)	68 (82)	228 (89)
Prenatal steroids, *n* (%)		
− Lack of prenatal steroids	16 (19)	22 (9)
− Part course	22 (27)	39 (24)
Apgar score at 1 min, *n* (%)		
≤ 3	44 (53)	66 (26)
Apgar score at 5 min, *n* (%)		
≤ 3	6 (7)	8 (3)
Invasive mechanical ventilation, *n* (%)	69 (83)	130 (51)
Hematocrit level < 45%, *n* (%)	59 (71)	139 (54)
Thrombocytopenia < 150 × 10^9/l of blood, *n* (%)	19 (23)	45 (18)

IVH − intraventricular hemorrhage, sIVH − severe grades of IVH
[a] sIVH

participants: birth date, birth weight, GA, sex, delivery mode (i.e., cesarean section or vaginal delivery), multiple gestation and the occurrence of IVH. The present study included 12 regressors for IVH incidence: GA at birth, birth weight, birth type, sex, mode delivery, place of birth, antenatal steroids treatment, Apgar score at 1 min and 5 min, invasive mechanical ventilation, hematocrit (Hct) level (i.e. from the first measurement taken) and thrombocytopenia (i.e. if the platelet count was < 150 × 10^9/l of blood at the first measurement) (Table 1). In all centers, IVH diagnostics are reported based on cranial ultrasound (cUS) screening. Intraventricular hemorrhage was further classified into grades 1–4 according to Papille [4]. Severe IVH was defined as IVH grade 3/4 or any grade of IVH complicated by PVHI and/or PHVD.

STATISTICAL ANALYSIS

All variables were categorical and described as absolute numbers and percentages. The χ^2 test was used to an-alyze the relationship between categorical variables. For frequencies below 5, the Yates correction was applied. The preliminary analysis of the data includes univariate logistic regression analysis and comparison of all regressors in sIVH and non- or low IVH groups. Regressors having significance at the level of $p \leq 0.05$ in univariate analysis were selected to fit a multivariate logistic regression model using a step-wise method. The best model was chosen with the Akaike information criterion (AIC). The best model is one with a minimum AIC value. The regressors contributing significantly to the prediction model were used to train a 5-fold cross-validation logistic regression model area under the receiver operating characteristic (ROC) curve; area under the curve (AUC) was calculated for both cases. The level of statistical significance was 5%. In the present logistic regression model, success was defined when the dependent variable took the value of sIVH. The statistical analysis was performed using Statistica 13.3PL software (StatSoft, Poland).

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TABLE 2. Odds ratio of various regressors with univariate and multivariate analysis for severe intraventricular hemorrhage

Parameters	Univariate analysis				Multivariate analysis			
	OR	95% CI		p - value	OR	95% CI		p - value
Gestational age at birth 27−28								
< 25	3.21	1.65	6.22	0.0005				
25−26	2.33	1.27	4.27	0.006				
Birth weight > 1000								
< 500	4.66	1.39	15.66	0.01				
500−749	3.77	1.77	8.05	0.0006				
750−1000	2.15	1.02	4.53	0.04				
Sex (female, male)	1.06	0.65	1.74	0.8				
Birth type (single multiple)	1.06	0.60	1.86	0.8				
Delivery mode (cesarean section, vaginal delivery)	1.25	0.72	2.18	0.4				
Inborn, outborn	1.76	0.89	3.48	0.1				
Prenatal steroids, full course								
Partial course	3.18	1.60	6.32	0.0009	3.16	1.49	6.67	0.003
No	4.11	1.88	8.98	0.0004	2.85	1.18	6.83	0.02
Apgar score at 1 min > 3								
≤ 3	3.27	1.95	5.51	< 0.0001				
Apgar score at 5 min > 3								
≤ 3	2.85	0.94	8.55	0.06				
Invasive mechanical ventilation (no, Yes)	5.52	2.857	10.70	< 0.0001	4.75	2.18	10.34	< 0.001
Pneumothorax (no, Yes)	2.23	0.82	6.07	0.1				
Hematocrit level > 45%								
< 45% first measurement	2.48	1.39	4.40	0.002	2.62	1.28	5.37	0.008
Thrombocytopenia < 150 × 109/l of blood first measurement								
> 150 × 109/l of blood	0.67	0.36	1.24	0.2				

RESULTS

Among the 340 patients included in the study, 173 (51%) newborns were diagnosed with IVH, including 83 (24%) infants who had severe grades of IVH. We compared the baseline characteristics and risk factors for IVH between infants with and without severe IVH diagnosis. In univariate analysis, factors significantly associated with sIVH diagnosis were: lower GA ($p = 0.0005$), lower birth weight ($p = 0.01$), lack of antenatal steroid therapy ($p = 0.0004$), partial course of antenatal steroid therapy ($p = 0.0009$), lower Apgar score at 1 minute ($p < 0.0001$), invasive mechanical ventilation use ($p < 0.0001$) and lower Hct level ($p = 0.002$). The multivariate analysis was performed using statistically significant variables at the level of $p < 0.05$ in univariate analysis. It was found that three regressors that contribute significantly to the prediction model are lack of or only a partial course of antenatal steroid (OR: 2.85; 95% CI: 1.18–6.83, $p = 0.02$, OR: 3.16; 95% CI: 1.49–6.67, $p = 0.003$ respectively), invasive mechanical ventilation use (OR: 4.75; 95% CI: 2.18–10.34, $p < 0.001$) and the Hct level < 45% at the first measurement after birth (OR: 2.62; 95% CI: 1.28–5.37, $p = 0.008$) (Table 2). The best model was chosen with a minimum AIC value as 231.71. These regressors and their estimates of logistic coefficients are given below:

Logit(P(Y=1) = −3.39 + 1.56 × Invasive mechanical ventilation + 0.96 × Hct level < 45% first measurement + 1.15 × part course prenatal steroids + 1.05 × no prenatal steroids

The combination of variables gave a good estimate for the ROC curve for training and 5-fold cross-validation data AUC = 0.76 and AUC = 0.71 respectively (Figure 2).

DISCUSSION

The risk of mortality is high during the first few months of life for extremely premature infants, and it is even higher for those with IVH [10]. A Netherlands study analyzed the etiology of death in infants born between 24 and 27 weeks of GA and found that the three leading causes were necrotizing enterocolitis, neonatal respiratory distress syndrome and IVH [11]. Wang and colleagues, in a study

published in 2022 involving more than 1,000 patients born < 30 weeks of GA, determined the incidence rate of sIVH to be 6.9%, with mortality rates of 20.1 and 55.2% in children without or with a diagnosis of sIVH, respectively [12]. Wang's higher mortality rates compared to our results are likely caused by the longer data collection period, which in their cases was 18–24 months of corrected age.

Comparisons of the incidence of severe IVH between studies are difficult due to the different populations included in the analyses. For this purpose, we will consider the percentage of severe IVH in infants born ≤ 28 GA, which in our study is 24% (83/340). A meta-analysis including studies published between 2010 and 2020 found the pooled incidence of sIVH in infants born < 28 GA to be 15% [8]. The highest percentage of sIVH included in the global report by Siffel and colleagues is 52% and comes from a Romanian study in 2010 involving newborns born between 25 and 28 weeks GA, but the same centers introduced a quality improvement project only a year later that brought the result down to 12% [2].

Risk factors predominantly associated with the occurrence of sIVH in our study included lack of antenatal steroid treatment, use of conventional mechanical ventilation and Hct value at first measurement after birth. Each of the mentioned factors has been proven to be an independent risk factor for the occurrence of IVH [5, 13–15]. The first of the independent risk factors that increased the risk of sIVH in our study was found to be an incomplete course of prenatal steroid therapy. Premature infants are more likely to develop IVH due to immaturity of the choroid plexus vessels in the ventricles of the brain [1, 5]. The latest studies and a published Cochrane meta-analysis demonstrated a clear reduction in IVH when antenatal steroid treatment was given to the mother prior to preterm birth [13, 16]. The authors speculated that these results may be related to the reduced incidence of neonatal respiratory distress syndrome and the need for mechanical ventilation, which are the main effects of the steroid therapy. These two situations can cause an increase in cerebral venous pressure and fluctuations in cerebral blood flow, which are considered as factors leading to IVH [5].

Our analysis also showed a statistical relationship between a lowered Hct value and the higher occurrence of IVH, which is consistent with the results of Dekom and colleagues [15]. It should be pointed out that there are also studies proving that applying delayed cord clamping can prevent anemia in preterm infants and result in higher hemoglobin levels, lower incidence of sIVH and lower neonatal mortality [17, 18]. Moreover, decreased Hct levels at the first measurement affect the higher number of red blood cell transfusions that are performed during the first hospitalization of premature infants [19]. Regarding the ambiguous effect of transfusion on the incidence of IVH, randomized clinical trials have been conducted to determine the best values for indications of red blood cell transfusions [20, 21]. Preliminary results show that
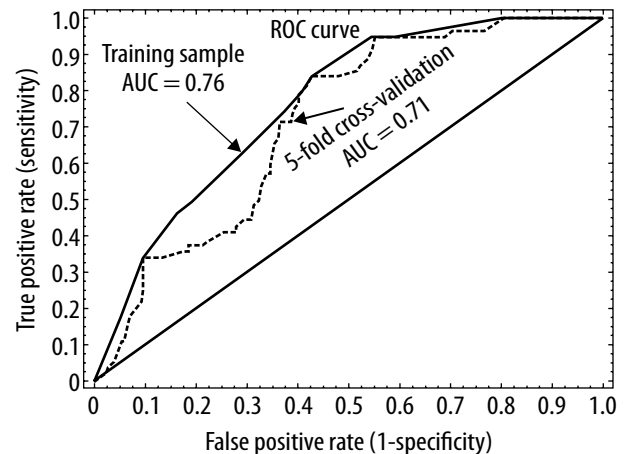

FIGURE 2. Receiver operating characteristic curve for training and 5-fold cross-validation data

AUC – area under curve, ROC – receiver operating characteristic

a strategy of liberal blood transfusions vs. restrictive transfusions did not reduce the likelihood of death or neurological disability in preterm infants, which is in contrast to previous studies on the subject claiming that transfusions increase the risk of IVH [22, 23].

We recognize that our study had limitations. First, it was observational and therefore causal inference cannot be assumed. Although we attempted to account for confounding factors, there may be potential confounding from unobserved variables. Another limitation of our study was the lack of detailed information in our dataset on timing of the onset of IVH. Some infants may not have had a cUS because they were healthy and were not assessed to have risk. Others may not have had a cUS screening due to a very severe clinical status and subsequent death prior to the ability to receive an ultrasound. Also, data for this study were started approximately 6 years ago, and since then there have been changes in recommendations in the prevention and treatment of IVH.

CONCLUSIONS

Severe IVH is still a common problem occurring in preterm infants who are born in the centers of the Podkarpackie province. Using full courses of antenatal steroid therapy, preventing anemia in preterm infants and optimizing methods of ventilation may help reduce the incidence of IVH.

DISCLOSURE

The authors declare no conflict of interest.

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