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Intraventricular hemorrhage in preterm infants: evaluation of risk factors and short-term complications

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ABSTRACT

Background and Objective: Intraventricular hemorrhage (IVH) is a major cause of brain injury in preterm infants. Considering the high prevalence of IVH in preterm infants and the importance of determining the risk factors, this study was done to evaluate the prevalence of various grades of IVH and identify the different associated factors and short-term complications.

Methods: In this retrospective study, the medical records of 54 preterm infants (26-37 weeks gestational age) admitted to the neonatal intensive care unit (NICU) of Bahrami Hospital, Tehran, Iran (2015-2018) were examined. Cranial ultrasonography was performed in all patients, and IVH was classified into 4 grades. A checklist was prepared and filled them out, and then the data were analyzed using SPSS-21.

Findings: Out of all subjects, IVH was found in 11 infants (20.4%). The most frequent IVH grades were 1 and 2. The most common Apgar scores in the fifth minute was 6. The mean weight of infants and Apgar score in patients with IVH was significantly lower than that of those without IVH. In multivariate logistic regression analysis of factors affecting IVH, Apgar score was the only significant independent predictor of IVH, such that with each number increase in Apgar score, the risk of IVH decreased (up to 100%).

Conclusion: Based on the results of this study, birth weight, gestational age and fifth-minute Apgar score were associated with IVH. Prevention of preterm birth and other preventive measures can reduce the complications of this disease.

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Introduction

Intraventricular hemorrhage (IVH) is considered an important cause of brain injury in premature infants. It is also regarded as the most frequent intracranial incident as it has a prevalence of 15% in infants with a gestational age <32 weeks or a birth weight <1500 grams [1]. The source of IVH is thought to be the germinal matrix vasculature of the lateral ventricles in the brain which is a heavily vascularized area prone to hemorrhage [2]. Factors such as a change in cerebral blood pressure, infection, coagulopathies and lack of protection mechanisms in cerebral vasculature contribute to the occurrence of IVH [3-5]. Most preterm infants who develop IVH remain asymptomatic, necessitating thorough screening of all preterm infants for this problem [3].

As mentioned earlier, the prevalence of IVH is greatly increased in low birth weight preterm infants, reaching up to 45% in extremely low birth weight (ELBW) infants <1000 grams [6]. Severe IVH is one of the causes of severe mental and neurological disorders in low birth weight infants and has a high mortality rate in these patients [7]. It is also noteworthy that more than 50% of all surviving infants develop hydrocephalus [8]. Most hemorrhage occurs in the first 72 hours, with more than 90% of cases occurring before the end of the first week.

Determining the risk factors for the occurrence of IVH plays an important role in the treatment approach and disease prevention. Overall, the risk factors can be divided into two broad categories:

1. Prenatal factors:

Asphyxia, chorioamnionitis, lack of prenatal steroid administration [9, 10].

2. Neonatal and birth-related factors:

Coagulopathies, respiratory distress, hypotension, hypoxia, hypercapnia, breech presentation [11-14].

Apart from the need to investigate risk factors, the severity of possible complications necessitates thorough screening. Brain ultrasonography is considered an ideal method to be performed in all preterm infants with a gestational age <30 weeks between 3-7 days after birth [15]. Screening should be considered in all preterm infants, especially when clinically justified [16].

The presence of hyperechoic regions on sonography is suggestive of IVH [8]. Based on the severity of the sonographic findings, IVH can be divided into 4 different grades [17]:

1. Hemorrhage is limited to the germinal matrix or involves less than 10% of the ventricles. It is without any signs or symptoms.
2. Hemorrhage affects between 10-50% of the ventricles. Signs and symptoms include nonspecific irritability and lethargy without ventricular dilatation.
3. Hemorrhage involves more than 50% of the ventricles. The lateral ventricles are usually dilated asymptomatically.
4. Parenchymal hemorrhage, regardless of severity and extent. It is accompanied by signs and symptoms such as apnea, bradycardia, opisthotonos, strabismus and nonreactive pupils to light.

First- and second-grade IVH usually does not have debilitating effects on the infant, but third- and fourth-grade IVH may cause spastic hemiplegia or learning disabilities [18]. Regardless of severity and grade, IVH can be unilateral or bilateral and may present symmetrically or asymmetrically [16].

Due to the high prevalence especially in preterm infants and the importance of determining risk factors and correct classification of IVH, the aim of the current study was to determine the prevalence of IVH and its grades in our setting and its relationship with different risk factors using ultrasound imaging data and to determine the prevalence of its short-term complications.

Methods

Study design and participant

This retrospective cross-sectional descriptive study investigated the records of 54 preterm infants (inclusion criteria were all neonates with a gestational age of 26-37 weeks), hospitalized in the neonatal ward and NICU of

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Bahrami Hospital from 2015 to 2018. The total number of subjects was derived from previous studies and was based on statistical calculations.

Data collection

All these patients were examined by the same radiologist using a BK-mini focus portable ultrasound machine with a 7 MHz linear probe on days 3 to 7 through the anterior fontanelle and, if present, IVH was classified into 4 grades based on severity and symptoms (As described above).

Study variables such as gestational age, birth weight, gender, apnea, respiratory distress syndrome, Apgar score at the 5th minute, childbirth method, diagnosis of chorioamnionitis before birth, steroid prescription before birth, severe acidosis, tocolytic therapy with magnesium sulfate, and early-onset complications of IVH were extracted from the hospital records in a checklist created by us.

To determine the prevalence of each grade of IVH, and to define the correlation of each variable recorded with the grade and severity of IVH and early onset complications.

Data analysis

Data (birth weight, 5th minute Apgar score, gestational age, seizure at birth, metabolic acidosis) were analyzed using descriptive and analytical statistics including Chi-square, logistic regression and T-test for independent samples in SPSS 21.

Results

A total of 54 preterm infants admitted to the Bahrami Center were investigated for IVH (F=22, M=32), and 11 patients were found to have IVH. The patients had a mean weight of 1636.85 g (SD=568.98, Min=700 g, Max=3200 g). Moreover, 7, 23 and 24 patients had a gestational age of <28 weeks, between 28-32 weeks and >32 weeks, respectively.

The IVH was diagnosed in 20.4% of patients. The frequency of IVH grades 1, 2, 3 and 4 was 7.4%, 7.4%, 3.7% and 1.9%, respectively (table 1). The mean Apgar score was 4 in infants with IVH and 6.56 in infants without IVH.

In the current study, the frequency of several proposed risk factors was recorded (table 3). Of all studied factors, the correlation between IVH and birth weight (P=0.014), 5th minute Apgar score (P=0.001), gestational age (P=0.001), seizure at birth (P=0.025), and metabolic acidosis (P=0.012) was statistically significant (table 3). The correlation between these factors and grade of IVH was also determined. The details are illustrated in table 4. Our current analysis found that a low Apgar score at the fifth minute, low gestational age, presence of seizures at birth and presence of metabolic acidosis were all correlated with higher grades of IVH, whereas the correlation between low birth weight and higher grades of IVH was only marginally significant (p=0.053). The correlation between IVH and other factors was not statistically significant (table 5).

In multivariable logistic regression analysis of our data regarding factors correlating with IVH, Apgar score was the only statistically significant predictive factor for IVH, such that with a one-point increase in Apgar score, the risk of IVH incidence was multiplied by a factor of 0.276 (Odds ratio: 0.276, 95% confidence interval: 0.084-0.908, P=0.034), (table 6).

Table 1. Frequency and distribution of IVH and its grading

Brain ultrasonography	Frequency	Percent	Grades	Grade Frequency	Grade Percent
With IVH	11	20.4	1	4	7.4
			2	4	7.4
			3	2	3.7
			4	1	1.9
Without IVH	43	79.6	-	43	79.6

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Table 2- Frequency and distribution of risk factors for IVH

		Brain ultrasonography		Total number	P-value
		With IVH	Without IVH		
birth weight	Mean weight	1267.73	1731.28	-	0.014
	SD	409.89	568.96	-	
5th minute Apgar score	2	2 (100%)	0 (0%)	2	0.001
	3	2 (100%)	0 (0%)	2	
	4	3 (33.3%)	6 (66.6%)	9	
	5	2 (50%)	2 (50%)	4	
	6	2 (11.8%)	15 (88.2%)	17	
	7	0 (0%)	6 (100%)	6	
	8	0 (0%)	10 (100%)	10	
	9	0 (0%)	4 (100%)	4	
Gestational Age	<28 w	4 (57.1%)	3 (42.9%)	7	0.001
	28-32 w	7 (30.4%)	16 (69.6%)	23	
	>32 w	0 (0%)	24 (100%)	24	
History of seizure at delivery room	+	4 (57.1%)	3 (42.9%)	7	0.025
	-	7 (14.9%)	40 (85.1%)	47	
Metabolic Acidosis	+	4 (66.7%)	2 (33.3%)	6	0.012
	-	7 (14.6%)	41 (85.4%)	48	
Total		**11**	**43**	54	

Table 3- Correlation between risk factors and IVH grades

		IVH grade					Total Number	P-value
		1	2	3	4	-		
Birth Weight	mean weight	1675.00	1053.75	1015.00	1000.00	1731.28	-	0.053
	SD	395.68	206.45	190.92	0	568.95	-	
	number	4	4	2	1	43	54	
5th minute Apgar Score	2	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	2	0.003
	3	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	2	
	4	1 (11.1%)	1 (11.1%)	0 (0%)	1 (11.1%)	6 (66.7%)	9	
	5	1 (25%)	1 (25%)	0 (0%)	0 (0%)	2 (50%)	4	
	6	2 (11.8%)	0 (0%)	0 (0%)	0 (0%)	15 (88.2%)	17	
	7	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)	6	
	8	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (100%)	10	
	9	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (100%)	4	
Gestational Age	<28 w	0 (0%)	2 (28.6%)	2 (28.6%)	0 (0%)	3 (42.9%)	7	<0.001
	28-32 w	4 (17.4%)	2 (8.7%)	0 (0%)	1 (4.3%)	16 (69.6%)	23	
	>32 w	0 (0%)	0 (0%)	0 (0%)	0 (0%)	24 (100%)	24	
Seizure at Childbirth	+	3 (42.9%)	0 (0%)	0 (0%)	1 (14.3%)	3 (42.9%)	7	<0.001
	-	1 (2.1%)	4 (8.5%)	2 (4.3%)	0 (0%)	40 (85.1%)	47	
Metabolic Acidosis	+	0 (0%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	2 (33.3%)	6	<0.001
	-	4 (8.3%)	3 (6.3%)	0 (0%)	0 (0%)	41 (85.4%)	48	

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Table 4- Statistically insignificant factors for IVH

Variables		IVH		Total number	P-value
		+	-		
Sex	Male	9 (28.1%)	23 (71.9%)	32	0.167
	Female	2 (9.1%)	20 (90.9%)	22	
Fetal presentation	Cephalic	10 (20%)	40 (80%)	50	0.811
	Breech	1 (25%)	3 (75%)	4	
Mode of the delivery	Cesarean section	8 (18.2%)	36 (81.8%)	44	0.788
	NVD	2 (22.2%)	7 (77.8%)	9	
RDS	+	10 (20.4%)	39 (79.6%)	49	0.983
	-	1 (20%)	4 (80%)	5	
Apnea at the delivery room	+	7 (35%)	13 (65%)	20	0.077
	-	4 (11.8%)	30 (88.2%)	34	
Bicarbonate administration	+	2 (18.2%)	9 (81.8%)	11	0.840
	-	9 (20.9%)	34 (79.1%)	43	
Steroid administration	+	5 (27.8%)	13 (72.2%)	18	0.475
	-	6 (16.7%)	30 (83.3%)	36	
Severe acidosis	+	8 (25.8%)	23 (74.2%)	31	0.319
	-	3 (13%)	20 (87%)	23	
Tocolytic therapy	+	0 (0%)	2 (100%)	2	0.466
	-	11 (20.4%)	41 (78.8%)	52	
Magnesium sulfate administration	+	1 (12.5%)	7 (87.5%)	8	0.549
	-	10 (21.7%)	36 (78.3%)	46	
Generalized tonic seizure	+	1 (50%)	1 (50%)	2	0.232
	-	10 (19.2%)	42 (80.8%)	52	

Table 5- Multivariate logistic regression analysis of correlated factors of IVH

Variable	B	S.E.	Sig.	EXP(B)	95% C.I. for EXP(B)	
					Lower	Upper
Sex	0.763	1.213	0.530	2.144	0.199	23.101
Apgar score	-1.288	0.608	0.034	0.276	0.084	0.908
Gestational age	-1.533	1.186	0.196	0.216	0.021	2.207
Seizure at childbirth	-1.276	1.367	0.351	0.279	0.019	4.069
Apnea at childbirth	-0.814	1.097	0.458	0.443	0.052	3.804
Metabolic acidosis	-1.828	1.652	0.268	0.161	0.006	4.093
Birth weight	0.001	0.001	0.549	1.001	0.998	1.003

Discussion

Based on the results of the present study, out of 54 infants, 11 ones suffered from IVH (20.4%). The most common grades of IVH were 1 and 2, each present in 7.4% of the subjects. As for the Apgar score at the 5th minute, 31.5% of the infants had a score of 6 and 18.5% and 14.8% of the subjects had a score of 8 and 4, respectively.

In the current study, it was found that the mean birth weight was significantly lower in infants with IVH as compared to the other group. In a similar study by Sajadian et al., out of a total of 57 infants, all of them had a birth weight ≤1500 gram. Thirty-five of them were found to have IVH (20% of IVH patients had hydrocephalus)

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while the other 22 had no abnormal findings on their ultrasounds. They concluded that in preterm infants, low birth weight strongly correlated with the presence of IVH. These results are in agreement with those of the ongoing study [19].

It is also noteworthy that according to the results of multivariable logistic regression analysis of our data, Apgar score was the only statistically significant predictive factor for IVH, so that an increase in Apgar score caused a decrease in IVH. In a study of preterm low birth weight infants by Khodapanahande et al., 325 infants with birth weight <1500 g admitted to ICU were studied. In their study, logistic regression analysis was used to show that low gestational age, low birth weight, low 5-minute Apgar score, presence of hyaline membrane disease and tocolytic therapy with magnesium sulfate led to an increase in IVH incidence. While the 5-minute Apgar score was the only factor found to be statistically significant in the regression analysis in both studies, the two studies agree on the correlation of IVH with other factors such as low gestational age and low birth weight [20]. The differences between the two studies might be due to the difference in sample size.

Vergani et al. reached drastically different results in their study of 71 infants, in which respiratory distress syndrome and histologic findings suggestive of inflammation were the only conditions that independently correlated with IVH. These differences might be due to demographic or genetic differences between the populations studied [21].

Metabolic acidosis was another condition correlated with IVH in our study, as was the observation that metabolic acidosis was significantly more common in more severe IVH cases. Such a finding might be due to the role of hypoxic conditions as a cause of IVH [22]. Our results were also supported by another study of 39 very low birth weight infants in which respiratory distress syndrome, duration of ventilation, presence of metabolic acidosis and hypercapnia were correlated with IVH [23].

As mentioned earlier, no significant correlation was found between prenatal administration of magnesium sulfate and IVH in our study. This was in contrast to a study by Mittendorf et al., in which subjects with higher serum magnesium levels were found to be at higher risk of IVH [24]. Mittendorf found that the results remained unchanged even after matching the subjects based on birth weight, gestational age, prenatal hemorrhage, and corticosteroid therapy.

In a prospective study of 167 infants, Badeie et. al. suggested that low Apgar score, duration of ventilation, natural vaginal delivery (NVD) and low platelet count were among the risk factors, while higher gestational age, higher birth weight, and prenatal corticosteroid therapy were actually found to be protective [25]. Such an association between corticosteroids and the occurrence of IVH was not observed in the current study. This could be due to differences in patients' comorbidities or differences in sample size between studies.

In the present study, no association was observed between birth method and the occurrence of IVH. This is contrary to the results found by Osborn et al. in two cohort studies, which found a statistically significant correlation between NVD and IVH [26]. Factors such as the duration of labor or the exact techniques used during delivery might have contributed to these results.

Limitations

Shortcomings including a limited sample size, emphasize the need for further studies.

Conclusion

The results of the present study indicated that birth weight, gestational age and 5th minute Apgar score correlated with IVH. Moreover, Apgar score was found to be a risk factor for the occurrence of IVH. Also, prevention of preterm birth and other preventive and curative measures should have a positive effect on decreasing the incidence and ultimate complications of this condition.

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Ethical approval

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethical code: IR.TUMS.REC.1394.1968). The authors avoided from data fabrication and falsification.

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Conflict of interest

The authors declare that there is no conflict of interest.

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