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RISK FACTORS FOR INTRAVENTRICULAR HEMORRHAGE IN VERYAND EXTREMELY LOW BIRTH WEIGHT PREMATURE NEONATES

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ABSTRACT

Background: Intraventricular hemorrhage (IVH) remains a common and severecomplication in premature infants with poor outcome, especially in severe cases. **Objective:** The aim of this study is to evaluate the risk factors that associated with occurrence of IVH. **Materials and Methods:** An observational prospective cohort study was conducted for the period two years (2020 and 2021) at Tishreen University Hospital in Lattakia-Syria. The study included two groups of premature neonates were compared: group I consisted of 31 neonates with a diagnosis ofIVH(cases), whereas group II consisted of 84 neonates without IVH(controls). **Results:** The results showed that 26.95% of the study population had IVH, including 42% 0f mild grade and 58% of severe grade. IVH occurred during 72hours after birth in 71% and after 3 days in 29%. The prevalence of IVH was increased significantly with decreasing of gestational age (p:0.006), birth weight (p:0.0001), Apgar score(p:0.0001), and non- using corticosteroid in the perinatal period (p:0.007). Post-natal factors that associated significantly with IVH were: need for mechanical ventilation, pneumothorax, hyaline membrane disease, PDA, hyperglycemia, acidosis, using of inotropic drugs, and septicemia($p<0.05$). Gestational age <28 week (RR 3.3), birth weight <1000 g (RR 4.5), presence of PDA (RR 8.2), acidosis (RR 10.7), pneumothorax (RR 7.3), hyperglycemia (RR 7.5), and mechanical ventilation (RR 3.9) were independent factors that associated with the risk of progression IVH. **Conclusion:** There is an important prevalence of IVH in our health center, and presence of extremely prematurity with acidosis, pneumothorax, hyperglycemia, PDA, and mechanical ventilation are all warning flags that maypredispose to IVH.

KEYWORDS: Intraventricular hemorrhage IVH, risk factors, premature.

INTRODUCTION

Premature birth is defined as a birth that occurs before 37 completed weeks of gestation, and there are sub-categories of prematurity based on gestational age(GA) and birth weight(BW).[1] Classification of prematurity based on GA includes: late preterm (GA between 34 weeks and 36 weeks and 6 days), very preterm (GA<32 weeks), and extremely preterm (GA <28 weeks), whereas classification according to BW includes: low birth weight (BW<2500 g), very low birth weight (BW<1500 g), and extremely low birth weight (BW<1000 g).[2]

Intraventricular hemorrhage(IVH) is defined as bleeding into the germinal matrix, in infants who are born prematurely, but a rare event in full-term newborns.[3] The incidence of IVH is inversely proportional to GA, BW, and it has been reported that incidence of IVH is as high as 50%, which declines in relatively recent years. A clear understanding of the pathophysiology is essential for appropriate diagnosis and management.[4] The pathogenesis of IVH in premature infants is multifactorial which includes: germinal matrix fragility from lack of structural support resulting from immaturity, and cerebral blood flow instability related to impaired cerebral autoregulation and hypoxia- ischemia and reperfusion.[5,6]

IVH can present as a catastrophic event, salutatory, or as a clinical silent phenomenon. A clinically silent syndrome occurs in 25 to 50 percent of cases, and detected by routine ultrasound screening.[7] Catastrophic deterioration evolves in minutes to hours, whereas salutatory presentation evolves over hourto days. Clinical manifestations of IVH are nonspecific and include:

altered level of consciousness, hypotonia, decreased spontaneous movements, bulging anterior fontanelle, decerebrate posturing, seizures, stupor, and coma.[8]

Severity of hemorrhage is based on the extent of bleeding, involvement of the white matter, and/or with presence of ventricular distension.[9] Various risk factors are known for IVH in premature infants include intrauterine infection, prolonged labor, male sex, metabolic acidosis, premature rupture of membranes, postnatal resuscitation, and respiratory distress syndrome. IVH remains a significant cause of both mortality and morbidity represented by neuro-developmental deficits and long term disability.[10] It is essential to identify risk factors for IVH in preterm neonates and develop effective prevention strategies. Therefore, the aim of this study was to investigate the risk factors for IVH in premature infants.

Patients and MethodsStudy Population

After approval by local research ethics committee, an observational prospective cohort study was conducted in premature neonates admitted at neonate intensive care unit (NICU) Tishreen University Hospital over a period of two years 2020 and 2021.

Inclusion Criteria were as follows: premature neonates of both sexes with BW lower than 1500 g and GA≤32 weeks. **Exclusion Criteria:** neonates with presence of anatomical malformations in the central nervous system(CNS), or neonates who died before performing cranial ultrasound. Complete history, review of systems, physical examination, laboratory and radiology investigations including cranial ultrasonography were performed. Patients were assigned to group I(cases) with a diagnosis of IVH (31 neonate), and group II(controls) which included neonates who don't have IVH (84 neonate). IVH was graded based on Papile et al criteria into: grade I: hemorrhage into germinal matrix only, grade II: IVH without ventricular dilation, grade III: IVH with ventricular dilation, grade IV: IVH with parenchymal hemorrhage. Mild grade of IVH includes: grade I and II, whereas severe grade includes grade III and grade IV.

Statistical Analysis

Statistical analysis was performed by using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations (SD), median, Frequency and percentages. To examine the relationships and comparisons between the two group, chi-square test or Fisher's test was used. Independent t student test wasused to compare 2 independent groups. Multivariate logistic regression analysis was performed to estimate independent risk factors. This model included risk factors first identified through univariate analysis. All the tests were considered significant at a 5% type I error rate ($p<0.05$), β:20%, and power of the study:80%.

RESULTS

During the study period, 31(26.95%) premature neonates had IVH. The baseline characteristics of IVH were as shown in Table (1). Findings of IVH were graded as follow: grade I in 3 cases (9.7%), grade II in 10 cases (32.3%), grade III in 11 cases (35.4%), and grade IV in 7 cases (22.6%). According to that, 13 cases (42%) had mild IVH and 18 cases (58%) had severe IVH. IVH developed within 72 hours after birth in 22 cases (71%) and after 3 days in 9 cases (29%).

Table 1: Distribution of the study population according to thecharacteristics of IVH.

Variable	Result
IVH Grade	
I	3(9.7%)
II	10(32.3%)
III	11(35.4%)
IV	7(22.6%)
Hemorrhage intensity	
Mild	13(42%)
Severe	18(58%)
Hemorrhage initiation(day)	
≤3	22(71%)
>3	9(29%)

Males represented 48.4% of cases and 61.9% of controls, whereas females represented 51.6% of cases and 38.1% of controls, p:0.1. Gestational age was < 28 week in 25.8% of cases and 6% of controls, whereas 74.2% of cases and 94% of controls were with a gestational age 28-32 week, p:0.006. Birth weight was≤1000g in 38.7% of cases and 9.5% of controls, and >1000 g in 61.3% of cases and 90.5% of controls, p:0.0001. Cesarean section represented the method of delivery in 67.6% of cases versus 72.6% of controls, p:0.6. Among cases, 12(38.7%) were with Apgar score≤7, versus 9(10.7%) in controls, p:0.0001. A history of premature rupture of membrane was present in 11(35.5%) of cases versus 39(46.4%) in controls, p:0.2. Use of corticosteroid in the perinatal period was present in 51.6% of cases versus 77.4% of controls, p:0.007.

Table 2: The relationship between IVH and demographic variables of thestudy population.

Variable	IVH		RR with CI95%	P value
	Group I Cases (31)	Group II Controls (84)		
Gender				
Male	15(48.4%)	52(61.9%)	0.5[0.2-1.3]	0.1
Female	16(51.6%)	32(38.1%)		
Gestational age(week)				
<28	8(25.8%)	5(6%)	5.4[2.2-12.9]	0.006
28-32	23(74.2%)	79(94%)		
Birth weight(g)				
≤1000	12(38.7%)	8(9.5%)	6[2.1-16.7]	0.0001
>1000	19(61.3%)	76(90.5%)		
Mode of delivery				
Vaginal delivery	10(32.3%)	23(27.4%)	1.2[0.5-3.08]	0.6
Cesarean section	21(67.7%)	61(72.6%)		
Apgar score				
≤7	12(38.7%)	9(10.7%)	5.2[1.9-14.3]	0.0001
>7	19(61.3%)	75(89.3%)		
Premature rupture of membranes				
Present	11(35.5%)	39(46.4%)	0.6[0.2-1.4]	0.2
Absent	20(64.5%)	45(53.6%)		
Antenatal corticosteroid administration				
Present	16(51.6%)	65(77.4%)	0.3[0.1-0.7]	0.007
Absent	15(48.4%)	19(22.6%)		

There was a significant difference between cases and controls regarding the need for mechanical ventilation (67.7% vs 22.6%, p:0.0001), presence of pneumothorax (19.4% vs 2.4%, p: p0.001), hyaline membrane disease (74.2% vs 29.8%, p:0.0001), PDA (87.1% vs 20.2%, p:0.0001), hyperglycemia (41.9% vs 7.1%, p:0.0001), acidosis (71% vs 17.9%, p:0.0001), using of inotropic drugs (51.6% vs 11.9%, p:0.0001), and septicemia (93.5% vs 66.7%, p: 0.004)

Table 3: The relationship between IVH and postnatal factors of the studypopulation.

Variable	IVH		RR with CI95%	P value
	Cases (31)	Controls (84)		
Mechanical ventilation	21(67.7%)	19(22.6%)	7.1[2.8-17.8]	0.0001
Pneumothorax	6(19.4%)	2(2.4%)	9.8[1.8-15.8]	0.001
Hyaline membrane disease	23(74.2%)	25(29.8%)	6.7[2.6-17.2]	0.0001
Patent ductus arteriosus (PDA)	27(87.1%)	17(20.2%)	10.8[4.1-19.1]	0.0001
Hyperglycemia	13(41.9%)	6(7.1%)	9.3[3.1-18.1]	0.0001
Acidosis	22(71%)	15(17.9%)	11.2[4.3-29.2]	0.0001
Using of inotropic drugs	16(51.6%)	10(11.9%)	7.8[3.1-20.7]	0.0001
Septicemia	29(93.5%)	56(66.7%)	5.1[1.2-20.1]	0.004

In the multivariate logistic regression analysis**,** gestational age <28 week (RR 3.3,95% CI 1.1-6.8, p=0.005), birth weight <1000 g (RR 4.5,95% CI 1.9-8.2, p=0.001), presence of PDA (RR 8.2,95% CI 3.1-11.3, p=0.0001), acidosis (RR 10.7,95% CI 2.9-14.2, p=0.0001), pneumothorax (RR 7.3,95% CI 2.5-9.9, p=0.0001), hyperglycemia (RR 7.5,95% CI 2.2-10.6, p=0.0001), and mechanical ventilation (RR 3.9,95% CI 1.7-6.4, p=0.001) were factors that associated with the risk of progression IVH, Table (4).

Table 4: Risk factors for IVH of the study population.

Variable	RR [CI 95%]	P value
Gestational age <28 week	3.3[1.1-6.8]	0.005
Birth weight <1000 g	4.5[1.9-8.2]	0.001
PDA	8.2[3.1-11.3]	0.0001
Acidosis	10.7[2.9-14.2]	0.0001
Mechanical ventilation	3.9[1.7-6.4]	0.001

Pneumothorax	7.3[2.5-9.9]	0.0001
Hyperglycemia	7.5[2.2-10.6]	0.0001

DISCUSSION

IVH remains a serious complication among extremely low-gestational age neonates with an increasing evidence of abnormal neurodevelopmental outcomes. Prevention of IVH, halting its progression and reducing its complication represent the main goal of identifying risk factors for IVH. There is no detailed information about the prevalence and risk factors of IVH in Lattakia.

The result of the current study revealed that, compared with control group, IVH was associated with a significant relationship with gestational age <28 week, birth weight <1000 g, presence of PDA, acidosis, pneumothorax, hyperglycemia, and mechanical ventilation, and these factors are associated with a risk ratio of IVH. Acidosis represented the highest risk factor in the current study, without any effect of gender, method of delivery, or presence of premature rupture of membrane on incidence. These findings might be explained by the following: IVH occurs generally within the three first days of life and affects infants with higher hemodynamic and respiratory instability frequently associated with extreme prematurity which is the most consistently associated with development of IVH. In addition to that, presence of a number of risk factors that may predispose to the development of IVH. The results of current study are consistent with the previous studies.

Haroon et al (2014) showed in a study included 201 premature neonates that the incidence of IVH was 33.3 percent, and the prevalence was higher in neonates with respiratory distress syndrome, who were on mechanical ventilation, and who received surfactant.[11]

Waitz et al (2016) demonstrated in a study conducted in 279 neonates with a GA < 28 weeks during four years that prevalence of IVH was 39.1% with various grades. Low Apgar score, multiple birth, hypercapnia during the first 72 h of life and absence of antenatal corticosteroids were independent risk factors in development IVH.[12]

Larocque et al (2019) showed in a study conducted in 495 neonates, that prevalence of IVH was 24,4% and 9.7% had severe IVH. Risk factors that associated with risk for IVH were: small birth gestation and weight, lack of antenatal corticosteroids, maternal chorioamnionitis, Apgar score<5 at 5 min, respiratory distress syndrome hypercapnia, using of inotropes, and PDA.[13]

By comparison the current study with previous studies, we found various rates of prevalence and risk factors associated with IVH among extremely premature neonates which might be explained by methodology adopted in each study.

In summary, clinical circumstances around birth and during first days of life are critical for development of IVH.

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