Risk factors for intraventricular hemorrhage in very low birth weight infants in Tehran, Iran

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Intraventricular hemorrhage (IVH) is an important cause of morbidity and mortality in very low birth weight (VLBW) infants; 80-90% of cases occur between birth and the third day of life. In a retrospective case control clinical study, files of all premature infants with birth weights <1500 grams admitted between April 2004 and October 2005 to the Neonatal Intensive Care Unit (NICU) of Akbar Abadi Hospital were reviewed. We determined risk factors that predispose to the development of high-grade IVH (grades 3 and 4) in VLBW infants. Thirty-nine infants with IVH grade 3 and 4 were identified. A control group of 82 VLBW infants were also selected. Prenatal data, delivery characteristics, neonatal course data and reports of cranial ultrasonography were carefully collected for both groups. Those variables that achieved significance ($p<0.05$) in univariate analysis were entered into multivariate logistic regression analysis. A total of 325 VLBW infants were evaluated. Mortality rate was 21.5%. Multivariate logistic analysis showed that the following factors are associated with greater risk of high-grade IVH occurrence: lower gestational age (OR: 3.72; 95% CI: 1.65-8.38), birth weight (OR: 3.42; 95% CI: 1.65-8.38), mechanical ventilation (OR: 4.14; 95% CI: 1.35-12.2), tocolytic therapy with magnesium sulfate (OR: 4.40; 95% CI: 1.10-24.5), hyaline membrane disease (HMD, OR: 3.16; 95% CI: 1.42-7.45), symptomatic hypotension (OR: 2.32; 95% CI: 1.06-5.42), hypercapnia (OR: 1.9; 95% CI: 1.1-3.4) and Apgar score at 5 minutes (OR: 1.58; 95% CI: 1.59-6.32).

Key words: intraventricular hemorrhage, very low birth weight, cranial ultrasonography.

Intraventricular hemorrhage (IVH) is a major neuropathologic lesion in premature infants. The etiology of IVH remains undefined but includes multiple factors affecting blood flow and perfusion pressure in the periventricular area. Immature blood vessels in this highly vascular area together with poor tissue vascular support predispose premature infants to IVH[1]. Improvement in perinatal and neonatal care have increased the survival of high-risk newborns, and the overall incidence of IVH decreased from 40% to 50% in the 1980s to 20% to 25% in the 1990s[2]. However, IVH is still a major cause of mortality and morbidity in premature infants, currently affecting up to 20% of those infants weighing <1500 g[3].

Several risk factors have been implicated in the pathogenesis of IVH, among them, any situation leading to an alteration in cerebral blood flow or pressure, such as postnatal resuscitation and intubation[4,5], recurrent endotracheal suctioning[4,6], and other factors including: low birth weight and gestational age[4,7], early onset sepsis[8], metabolic acidosis[9], development of hyaline membrane disease (HMD)[5,10], mode of delivery[10], pneumothorax[11], transfer from another hospital[5], and premature rupture of membranes[9,12]. Factors that are considered to reduce the risk of IVH are as follows: tocolytic therapy with indomethacin[13], pregnancy-induced hypertension, and antenatal administration of steroids[14,15].

Material and Methods

The present study was conducted at the neonatal intensive care unit of Akbar Abadi Hospital, Tehran, Iran. All very low birth weight (VLBW) infants with IVH admitted between

April 2004 and September 2005 to the newborn intensive care unit at Akbar Abadi Hospital were identified. Three hundred and twenty-five VLBW infants (birth weight <1500 g) were born over the study period. The IVH diagnosis was based on ultrasonographic examination performed up until the 10th postnatal day. All the cranial sonograms were performed and interpreted by the same sonologist experienced in neonatal cranial sonograms. Based on the criteria of Burstein et al.[16], the 39 patients who developed high-grade IVH formed our study group. A group of 82 VLBW infants were selected as the control group. Case records were reviewed. Maternal data, and labor and delivery and postnatal factors were collected. Maternal data were maternal age, maternal hypertension and preeclampsia, premature contraction, placenta abruption/previa, maternal tocolytic therapy (magnesium sulfate), fertility treatment, antenatal steroids, and premature rupture of membranes.

Labor and delivery factors included gestational age, sex, birth weight, multiple pregnancy, mode of delivery (vaginal/cesarean (C)-section), Apgar score at 5 minutes, and delivery room resuscitation.

Neonatal course parameters were as follows: HMD (presence of respiratory distress and radiographic evidence), apnea (breathing pauses >20 seconds, followed by bradycardia and/or cyanosis and/or oxygen saturation drop), use of conventional mechanical ventilation, first 24-hour hemoglobin and hematocrit levels, symptomatic hypotension during the first three days of life (neonates who received pressors in an attempt to increase blood pressure), and minimum and maximum levels of arterial pressure of carbon dioxide (PaCO2) and pH in blood gases determined over the first three days of life.

Statistical analysis

Statistical analysis was performed with SPSS version 11.5. Univariate analysis was performed to identify differences between the study and control groups; chi-square and Fisher's exact test were used to compare categorical variables and Student's t test was used to analyze continuous variables. All variables that achieved significance ($p<0.05$) on univariate analysis were identified and entered into a stepwise logistic regression analysis.

Results

Three hundred and twenty-five VLBW infants were admitted to our neonatal intensive care unit over the study period. Twenty-one deaths occurred during the first 48 hours of life, and these infants were excluded from the study. The numbers of infants less than 28 weeks of gestational age were 10 (25.6%) in study group and 16 (19.5%) in the control group. Thirty-nine infants developed high-grade IVH. The results of univariate analysis are shown in Tables I-III.

As can be seen from Table I, the results indicate that IVH occurs with lower birth weight ($p=0.02$), lower gestational age ($p=0.03$), delivery room resuscitation ($p=0.03$) and low 5- minute Apgar score ($p=0.01$). The incidence of multiple pregnancy and mode of delivery (vaginal versus C-section) was almost similar between the two groups.

Results of univariate analysis on the relationship between prenatal data and occurrence of high-grade IVH are demonstrated in Table II.

Table I. Univariate Analysis of Delivery Characteristics

Parameter	IVH group n=39	Control group n=82	P value
Maternal age	23±5.2	24±6	0.251
Neonate sex (males)	18	38	0.632
Gestational age (mean±SD)	29±1.7	32±2.5	0.032
Mode of delivery			
Vaginal	14 (35.8%)	27 (33%)	0.925
C-section	25 (64.2%)	55 (67%)	0.932
Birth weight (mean±SD)	1010±208	1240±231	0.025
Apgar score at 5 min (mean±SD)	6.5±2.3	8.5±1.4	0.012
Delivery room resuscitation	22 (56%)	30 (36%)	0.03

Table II. Univariate Analysis of Prenatal Data

Parameter	IVH group (n=39)	Control group (n=82)	P Value
Fertility treatment	10 (25%)	18 (21%)	0.326
Premature contraction	25 (64%)	57 (69%)	0.738
Preeclampsia	5 (12.8%)	11 (13.4%)	0.973
Placenta abruption/previa	4 (10%)	8 (11%)	0.834
Tocolytic therapy	14 (35.8%)	7 (8.5%)	0.021
Antenatal steroids	12 (30.7%)	20 (24%)	0.781
Premature rupture of membranes	12 (30%)	29 (35%)	0.097

Table III. Univariate Analysis of Neonatal Course

Parameter	IVH group (n=32)	Control group (n=82)	P Value
Pneumothorax	5 (12.8%)	8 (10%)	0.630
Apnea	21 (54%)	25 (30%)	0.021
Mechanical ventilation	25 (64%)	30 (36%)	0.032
Hyaline membrane disease	23 (59%)	25 (30%)	0.031
Hematology (first 24 hrs)			
Hematocrit	44.52±8.18	51±95	0.023
Hemoglobin	12.64±13.23	13.8±3.12	0.072
Blood PH (first 3 days)			
Minimum	7.16±0.14	7.23±0.13	0.621
Maximum	7.40±0.11	7.41±0.09	0.314
PaCO2 (first 3 days)			
Minimum	34.41±4.75	33.82±5.23	0.261
Maximum	58.72±12.83	51.82±10.78	0.032
Symptomatic hypotension (first 3 days)	11 (28.20%)	16 (19.51%)	0.012

Tocolytic therapy with magnesium sulfate was significantly associated with higher incidence of major IVH (p=0.02). There was no significant difference between the following factors and IVH: maternal fertility treatment, premature contractions, preeclampsia, premature rupture of membranes and maternal steroid therapy.

Neonatal course data are shown in Table III. Significant association on univariate analysis was found between IVH and the following parameters: presence of HMD (p=0.031), apnea (p=0.021), mechanical ventilation (p=0.032), low hematocrit during the first 24 hours of life (0.023), hypercapnia (p=0.032), and symptomatic hypotension (p=0.012).

Multivariate logistic regression analysis was performed to assess those factors that achieved significance (p<0.05) in univariate analysis. Eight factors that retained significance when entered into multivariate logistic regression analysis (Table IV) were gestational age (OR: 3.72; 95% confidence interval [CI]: 1.65-8.38), mechanical ventilation (OR: 4.14; 95% CI: 1.35-12.2), tocolytic therapy (OR: 4.40; 95% CI: 1.10-24.5), birth weight (OR: 3.42; 95% CI: 1.65-8.38), HMD (OR: 3.16; 95% CI: 1.42-7.45), Apgar score at 5 minutes (OR: 1.58; 95% CI: 1.5-6.32), symptomatic hypotension (OR: 2.32; CI: 1.06-5.19), and hypercapnia (OR: 1.93; 95% CI: 1.52-3.46).

Discussion

Intraventricular hemorrhage originates in the subependymal germinal matrix layer of the developing brain with possible rupture into the ventricular system. This layer gradually decreases in size as the fetus matures and is virtually absent in full-term babies[16]. There is good evidence to suggest that the causal pathway leading to IVH begins in the antenatal, intrapartum or early postnatal period[17]. A cranial ultrasound scan in the first week of life reveals the vast majority of IVH cases, since 90% of these occur within the first 72 hours of life[18,19].

Table IV. Multivariate Analysis of Factors Influencing the Development of High-Grade IVH

Parameter	OR	95%CI
Gestational age	3.72	1.65-8.38
Mechanical ventilation	4.14	1.35-12.2
Tocolytic therapy	4.40	1.10-24.5
Birth weight	3.42	1.65-8.38
HMD*	3.16	1.42-7.45
Apgar score at 5 minutes	1.58	1.59-6.32
Symptomatic hypotension (first 3 days)	2.32	1.06-5.19
Hypercapnia (first 3 days)	1.93	1.52-3.46

P value<0.05
*HMD: Hyaline membrane disease.

The purpose of this study was to determine possible risk factors for high-grade IVH (grades 3 and 4). According to the present study, tocolytic therapy was associated with increased risk of IVH. Recent studies confirm that high-dose tocolytic magnesium sulfate administered to pregnant women during preterm labor can be toxic. Elevated circulating levels of ionized magnesium occurring in mothers and therefore in their babies at the time of delivery are associated with subsequent neonatal IVH, which is strongly associated with lenticulostriate vasculopathy (LVS), an unusual mineralization lesion involving the thalami and basal ganglia of the neonate[20].

Acidosis in our study was not associated with increased risk of IVH. The protective role of antenatal corticosteroids is well recognized[21]; however, our study failed to confirm this. The low rate of antenatal corticosteroid delivery (26%) offers a good explanation.

We did not find any relation between the incidence of high-grade IVH and other maternal and prenatal factors, including premature contraction, fertility treatment, preeclampsia, placenta abruption/previa and premature rupture of membranes, although some studies have shown that infants born to hypertensive mothers have a lower risk of cerebral injuries than infants born following premature rupture of membranes[22,23].

The results indicate that lower gestational age and birth weight influence the risk of high- grade IVH[4,7,24]. Consequently, prevention of prematurity would be the most effective means of prevention of IVH. A program for prevention of prematurity must emphasize early identification of women at risk, education concerning causes of prematurity, early diagnosis and in utero transfer to a perinatal center specializing in high-risk deliveries.

Low 5-minute Apgar score retained significance in the multivariate regression analysis, and a similar observation has been made previously[25].

We did not find any relation between the incidence of IVH and mode of delivery, although small observational studies have already suggested a relation between adverse outcomes of very immature infants and vaginal delivery and emphasized the protective role of elective C-section[10,26].

Our study demonstrated a significant relation between HMD and major IVH, although we did not find any association between IVH and pneumothorax. Mechanical ventilation also maintained significance as a risk factor, which was compatible with similar studies[27,28].

Decreases in cerebral blood flow, occurring either prenatally or postnatally, may cause injury to the germinal matrix vessels during a period of asphyxia[29,30]. On the other hand, increases in cerebral venous pressure may predispose to rupture of germinal matrix vessels. Increased venous pressure may be associated with idiopathic respiratory distress syndrome, pneumothorax, labor, delivery and asphyxia[5,10,11].

We found that symptomatic hypotension was significantly associated with the occurrence of high-grade IVH, a finding that was reported in other studies[31,33]. Analysis of arterial PaCO2 over the first three days of life in our study showed evidence of increased risk of IVH and hypercapnia, and a similar observation has been made elsewhere[32,33].

First hematocrit over the first 24 hours was significantly lower in the IVH group in univariate analysis, but it did not achieve significance in multivariate analysis. A relation between lower first hematocrit during the first 24 hours of life and higher incidence of IVH has been reported, as low hematocrit may change cerebral blood flow and contribute to the hemorrhage (34). However, it is difficult to interpret whether low hematocrit level was the result of IVH itself. Real time cranial sonogram continues to be the standard method of diagnosis and assessment of neonatal IVH. Our study showed that low gestational age and birth weight, tocolytic therapy with magnesium sulfate, mechanical ventilation, HMD, low 5-minute Apgar score, symptomatic hypotension and hypercapnia were risk factors for developing high-grade IVH.

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