Original Article

Iran J Ped
June 2007, Vol 17(No 2), Pp:101-107

Risk Factors for Intraventricular Hemorrhage in Very Low Birth Weight Infants

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Received: 19/11/06; Revised: 27/12/06; Accepted: 2/02/07

Abstract

Objective: The purpose of this study was to determine the risk factors which predispose to the development of high grade IVH (grade 3 and 4) in very low birth weight infants.

Material & Methods: In a retrospective case control clinical study files of all premature infants with birth weights less than 1500 grams admitted between April 2004 and Oct 2005 to the neonatal intensive care unit of Akbar Abadi hospital in Tehran were reviewed. 39 infants with IVH grade 3 and 4 were identified. A control group of 82 VLBW infants matched for gestational age and birth weight were 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 entered to multivariate logistic regression analysis.

Findings: A total of 325 VLBW infants were evaluated. Mortality rate was 21.5%. Of the remaining the incidence of high grade IVH was 15.5%. Multivariate logistic analysis showed that following factors are associated with greater risk of high grade IVH occurrence: Low gestational age (OR: 3.72; 95% CI: 1.65-8.38), low birth weight (OR: 3.42; 95% CI: 1.65-8.38), low Apgar score at 5 minute (OR:1.58; 95% CI:1.59-6.32), hyaline membrane disease (HMD, OR: 3.16; 95% CI: 1.42-7.45) and maternal tocolytic therapy with magnesium sulfate (OR: 4.40; 95% CI: 1.10-24.5).

Conclusion: Our results showed that maternal tocolytic therapy, mechanical ventilation, low gestational age, low birth weight, apnea, and low 5 minute Apgar score increased the risk of major IVH.

Key Words: Intraventricular hemorrhage, Very low birth weight, Cranial ultrasonography, Tocolytic therapy, Hyaline membrane disease

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Introduction

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 infant 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%-50% in 1980s to 20%-25% in 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 less than 1500 grams[3].

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

The purpose of this study was to determine the risk factors which predispose to the development of high grade IVH (grade 3 and 4) in very low birth weight infants.

Material & Methods

The present study was conducted at the neonatal intensive care unit of Akbar Abadi Hospital, Tehran, Iran. Included in the study were all VLBW infants (birth weight<1500 g) admitted to the newborn intensive care unit of Akbar Abadi Hospital (Tehran) between April 2004 and September 2005. Exclusion criteria were death within 48 hours after birth and/or lack of cranial ultrasound up to 10 days of life. Data was obtained by review of medical records. 325 VLBW infants were born over the study period. 21 deaths occurred during the first 48 hours of life; these were excluded from the study.

All the cranial sonograms were performed and interpreted by the same sonologist experienced in neonatal cranial sonograms using Siemens ultrasound. The IVH diagnosis was based on ultrasonographic examination performed during the 10 postnatal days. Based on the criteria of Papile et al[16], ultrasound was performed routinely on the 3rd and 10th day of life. If the initial scans were normal a repeat scan was done at the age of one month. 39 patients of our study group developed high grade IVH. A group of 82 VLBW infants were selected as control group. Case records were reviewed. Maternal data, labor and delivery as well as postnatal factors were collected. Maternal data consisted of maternal age, maternal hypertension or preeclampsia, premature contraction, placenta abruption/ previa, maternal tocolytic therapy (magnesium sulfate), fertility treatment, antenatal steroids, and PROM.

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

Neonatal course parameters were as follow: hyaline membrane disease (presence of respiratory distress and radiographic evidence), apnea (breathing pauses>20 seconds, followed by bradycardia and/or cyanosis and/or oxygen saturation drop), mechanical ventilation, blood pH≤7.2 in the first 24 hours of life, first 24 hour-hemoglobin and hematocrit.

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

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variables that has achieved significance (p<.05) on univariate analysis were identified and entered into a stepwise logistic regression analysis.

Findings

Three hundred twenty-five VLBW infants were admitted to our neonatal intensive care unit over the study period. The neonatal mortality rate was 21.5%. 21 deaths occurred during the first 48 hours of life; these were excluded from the study. Thirty-nine infants developed high grade IVH that represent an incidence of 15.2%. The mortality rate of IVH group was 46%. The results of univariate analysis are shown in tables 1-3. As it can be seen from table 1 the results indicate that IVH occurs with low birth weight (p=0.02), low gestational age (p=0.03), delivery room resuscitation (0.03), and low 5 minutes Apgar score (p=0.01). The incidence of multiple pregnancies and mode of delivery (vaginal versus C-section) was almost similar between the two groups.

Results of univariate analysis for the relationship between prenatal data and occurence of high grade IVH are demonstrated in table 2. Maternal tocolytic therapy with magnesium sulfate was significantly associated with higher incidence of major IVH (p=0.02). There was no significant difference between following factors and IVH: maternal fertility treatment, premature contractions, preeclampsia, PROM, and maternal steroid therapy.

Neonatal course data are shown in table 3. Significant association on univariate analysis was found to be linked with IVH and following parameters: presence of hyaline membrane disease, apnea, mechanical ventilation and low hematocrit during the first 24 hours of life. Multivariate logistic regression analysis was performed to assess those factors that achieved significance (p<0.05) in univariate analysis including Apgar score at 5 minutes, delivery room resuscitation, birth weight, gestational age, maternal tocolytic therapy with magnesium sulfate, apnea in the first 24 hours, 24-hour hematocrit and HMD.

Six factors that retained significance when entered into multivariate logistic regression analysis (Table 4) are mechanical ventilation, maternal tocolytic therapy, gestational age,

Table 1: Univariate analysis of delivery characteristics

Parameter	*IVH group n=39*	*Control group n=82*	*p-value*
Maternal age	23±5.2	24±6	0.2
Neonate sex (males)	18	38	0.6
Gestational age (mean±SD)	29±1.7	32±2.5	0.03
Mode of delivery			
Vaginal	14 (35.8%)	27 (33%)	0.9
C-section	25 (64.2%)	55 (67%)	0.9
Birth weight (gr) (mean±SD)	1010±208	1240±231	0.02
Apgar score at 5 min. (mean±SD)	6.5±2.3	8.5±1.4	0.01
Delivery room resuscitation	22 (56%)	30 (36%)	0.03

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Table 2: Univariate analysis of prenatal data

Parameter	*IVH group n=39*	*Control group n=82*	*p-value*
Fertility treatment	10 (25%)	18 (21%)	0.3
Premature contraction	25 (64%)	57 (69%)	0.7
Preeclampsia	5 (12.8%)	11 (13.4%)	0.9
Placenta abruption/previa	4 (10%)	8 (11%)	0.8
Tocolytic therapy	14 (35.8%)	7 (8.5%)	0.02
Antenatal stroids	12 (30.7%)	20 (24%)	0.7
PROM	12(30%)	29(35%)	0.09

birth weight, HMD and Apgar score at 5 minutes.

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[17]. There is good evidence to suggest that the casual pathway leading to IVH begins in the antenatal, intrapartum or early postnatal period [18]. 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[16,19].

The purpose of this study was to determine possible risk factors for high grade (3/4) IVH. According to the present study maternal tocolytic therapy was associated with increased risk of IVH. Recent studies confirm that high dose tocolytic magnesium sulfate administered to pregnant woman during preterm labor can be toxic, elevated circulating levels of ionized

Table 3: Univariate analysis of neonatal course

Parameter	*IVH group n=39*	*Control group N=82*	*p-value*
Pneumothorax	5 (12.8%)	8 (10%)	0.6
Apnea	21 (54%)	25 (30%)	0.02
Mechanical ventilation	25 (64%)	30 (36%)	0.03
First 24 hrs hema indexes			
Hematocrite	44.52±8.18	51±95	0.02
Hemoglobin	12.64±13.23	13.8±3.12	0.07
Hyaline Membrane disease	23 (59%)	25 (30%)	0.03
Blood PH≤ (in the first 24 hrs)	7.28±0.08	7.3±0.16	0.07
Pneumothorax	5 (12.8%)	8 (10%)	0.6

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Table 4: Multivariate analysis of neonatal course

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 min	1.58	1.59-6.32

magnesium occurring in mothers and therefore in their babies at the time of delivery are associated with subsequent neonatal intra-ventricular hemorrhage and neonatal IVH is strongly associated with lenticulostriate vasculopathy (LVS), an unusual mineralization lesion involving the thalami and basal ganglia of the neonate[13]. The protective role of antenatal corticosteroids is well recognized [20], however, our study failed to confirm this; the low rate of deliveries with antenatal corticosteroid administration (26%) can be a good explanation for this finding.

We did not find any influence on the incidence of high grade IVH and other maternal and prenatal factors including premature contraction, fertility treatment, preeclampsia, placenta abruption/previa and PROM. Although, some studies showed that infants born to hypertensive mothers have a lower risk of cerebral injuries than infants born following PROM[21,22].

The results indicate that low gestational age and low birth weight influence the risk of high grade IVH[4,7,23]. 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 minutes Apgar score retained significance in the multivariate regression analysis, a similar observation has been made previously[24]. We did not find any influence on 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 on the protective role of elective C-section[10,25].

Decreases in cerebral blood flow, occurring either prenatally or postnatally, may cause injury to the germinal matrix vessels during period of asyphyxia[26,27]. 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 asyphyxia[5,10,11]. Our study demonstrated significant relation between hyaline membrane disease and major IVH, although we did not find any association between IVH and pneumothorax. Mechanical ventilation also maintained significance as a risk factor that was compatible with similar studies[28,29].

A relation between low hematocrit during the first 24 hours of life and higher incidence of IVH has been reported. A low hematocrit may change cerebral blood flow and contribute to the hemorrhage[30]. However it is difficult to interpret whether low hematocrit level was the result of IVH itself.

We were planning to evaluate the effect of antenatal steroid administration on preventing IVH but most of the premature deliveries had happened in emergency room without having enough time to administer steroid so that we did not have enough samples to evaluate.

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Conclusion

Real time cranial sonogram continues to be the standard method of diagnosis and assessment of neonatal intraventricular hemorrhage. Our study showed that mechanical ventilation, maternal tocolytic therapy with magnesium sulfate, low gestational age and low birth weight, hyaline membrane disease, low 5 minutes Apgar score, were risk factors for developing high grade IVH.

Acknowledgment

We thank Ms Marjan Baroti, secretery of Radiology Department for her kind co-operation.

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