

# Intraventricular hemorrhage in very low birth weight infants

## *Associated risk factors in Isfahan, Iran*

Zohreh Badiee, MD.

### ABSTRACT

**Objective:** Prematurely born infants with intraventricular hemorrhage (IVH) suffer significant morbidity and mortality, particularly those infants with high-grade hemorrhage. Previous studies have proposed a number of risk factors for IVH; however, lack of adequate matching for gestational age and birth weight may have confounded the results. The purpose of this study was to identify variables that affect the risk of IVH.

**Methods:** We identified 31 preterm infants with gestational age <32 weeks and birth weight <1500 g, with IVH, from November 2003 to January 2005 at Alzahra University Hospital, Isfahan, Iran. A control group of 90 infants, matched for gestational age and birth weight was selected. Maternal factors, labor and delivery characteristics and neonatal parameters were collected in both groups. Results of cranial ultrasound examinations were also collected.

**Results:** The significant risk factors for IVH were found to be: patent ductus arteriosus (PDA) [4 (13.3%) versus 3 (3.3%) ( $p=0.01$ )], longer duration of assisted ventilation [ $2.8 \pm 5.8$  days versus  $0.5 \pm 2.1$  days ( $p=0.002$ )], higher number of endotracheal suctioning [ $9.7 \pm 18.4$  versus  $3.06 \pm 13.7$  ( $p=0.004$ )], surfactant use, [7 (22.6%) versus 3 (3.4%) ( $p=0.003$ )], positive pressure ventilation at birth [(12 (38.7%) versus 12 (13.3%), ( $p=0.004$ )] and low Apgar score at 1 and 5 minutes. Whereas antenatal steroid treatments and cesarean section have a protective effect on the occurrence of IVH.

**Conclusion:** Our data emphasize the importance of obstetric and perinatal care to improve outcomes of premature infants.

*Saudi Med J 2007; Vol. 28 (9): 1362-1366*

*From the Division of Neonatology, Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran.*

*Received 26th November 2006. Accepted 13th May 2007.*

*Address correspondence and reprint request to: Dr. Zohreh Badiee, Assistant Professor, Division of Neonatology, Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran. Tel. +98 (311) 2670524. Fax. +98 (311) 6684510. E-mail: badiei@med.mui.ac.ir*

Despite improvements in the assistance and treatment of preterm infants, intraventricular hemorrhage (IVH) remains a frequent complication among these patients.<sup>1</sup> Severe abnormalities of the head ultrasound are important predictors of cerebral palsy and mental retardation.<sup>2</sup> Identifying the antecedent risk factors and underlying mechanisms for periventricular/intraventricular hemorrhage has the potential to allow the development of effective strategies for prevention of cerebral injury in preterm infants. The risk of IVH is inversely related to gestational age and birth weight.<sup>3</sup> Previous studies have proposed a number of other risk factors for IVH such as premature rupture of membranes,<sup>4</sup> maternal infection,<sup>5</sup> mode of delivery,<sup>6</sup> prolonged labor,<sup>6</sup> postnatal resuscitation and intubation,<sup>7,8</sup> development of respiratory distress syndrome<sup>4,8,9</sup> or pneumothorax,<sup>7</sup> recurrent endotracheal suctioning,<sup>5</sup> histological evidence of acute placental inflammation,<sup>9</sup> fertility treatment and especially IVF.<sup>3</sup> For reducing the incidence of IVH, several pharmacological interventions have been proposed, including antenatal steroids,<sup>6,10</sup> postnatal administration of low-dose indomethacin,<sup>11</sup> and surfactant.<sup>12</sup> However, lack of adequate matching for gestational age and birth weight may have confounded the results. We therefore performed a prospective, case-control study with a high degree of matching for birth weight and gestational age to increase the sensitivity of detection of potential risk and protective factors that could be altered by medical intervention, in the hope of reducing the incidence of IVH.

**Methods.** The study population comprised preterm infants (gestational age [GA] <32 weeks) admitted to the Neonatal Intensive Care Unit of the Alzahra Hospital, Isfahan, Iran,

between November 2003 and January 2005 in whom it was possible to perform cranial ultrasound studies. We prospectively identified all 31 premature infants with IVH, which composed of our study group. A control group composed of 3 infants for each case, matched for gestational age ( $\pm 2$  week) and birth weight ( $\pm 250$  g), was selected on the basis of the first compatible live-born infant before and after each study infant. In 3 cases, only a single control infant could be matched according to our criteria; hence, the control group consists of 90 infants. The local ethics committee approved the study design. Criteria for exclusion were death within 24 hour after birth and/or lack of cranial ultrasound examination up to 7 days of life. Obstetrical data were collected from the patient charts, and neonatal data were collected prospectively. Diagnosis and grading of IVH was performed as follows. Infants were scanned with a mechanical sector scanner with a multi-frequency transducer (5-, 7.5-, and 10- MHz crystals). The 7.5-MHz scan was used whenever possible to ensure the best possible resolution. Scans were performed within 7 days after birth and then weekly until discharge or more frequently, if necessary, by attending radiologist who was unaware of the study results. Intraventricular hemorrhage was graded as reported previously as follows: grade I = small germinal layer hemorrhage; grade II = intraventricular hemorrhage without ventricular dilatation; grade III = intraventricular hemorrhage with ventricular dilatation; grade IV IVH = associated ventricular with parenchymal involvement.<sup>13</sup> The need for recurrent lumbar punctures, ventriculoperitoneal shunt insertion or ventriculomegaly was recorded. Labor, delivery, and newborn characteristics were: gender; mode of delivery (vaginal, cesarean-section); singleton

or twin or triplet, gestational age (determined according to last menstrual period and first prenatal ultrasound); birth weight; Apgar score at one and 5 minutes; and delivery room resuscitation (use of oxygen, bag and mask or mechanical ventilation, intubation, cardiac massage, and epinephrine). Other parameters included, first hematocrit, lowest platelet count, treatment with bicarbonate, and number of suction procedures during mechanical ventilation. For the neonatal course, the presence of any of the following neonatal diagnoses was recorded: respiratory distress syndrome (RDS); diagnosed in infants who required either supplemental O<sub>2</sub> more than 50% or mechanical ventilation; together with radiographic evidence of RDS, use of surfactant therapy, pneumothorax, patent ductus arteriosus (PDA), necrotizing enterocolitis, and presence of sepsis. Maternal attributes included maternal age, mode of delivery, fertility treatment (including clomiphene, IVF), the presence of preeclampsia and maternal steroids therapy.

**Statistical analysis.** Data were stored in a computer database and analyzed by SPSS software version 11.5 (Chicago, Inc, USA). Univariate analysis was performed to identify differences between the study and control groups, using the *t* test, Pearson  $\chi^2$  test, and Mann-Whitney non-parametric test, as appropriate. Statistical significance was defined as  $p \leq 0.05$ .

**Results.** During the study period, 31 infants developed IVH, an incidence of 19.52%, including 9 cases with grade I, 12 with grade II, 9 with grade III and 1 with grade IV. Three of these (0.97%) developed posthemorrhagic hydrocephalus, no infant requiring ventriculoperitoneal shunt insertion. In

**Table 1** - Demographic data and delivery characteristics.

Parameter	IVH Group n=31	Control group n=90	P value
Maternal age (years)	26.1 $\pm$ 6.1	28.1 $\pm$ 5.5	0.46
<b>Gender</b>			0.31
Male	12 (40.0)	39 (47.6)	
Female	18 (6.0)	43 (52.4)	
Gestational age (week)	29.19 $\pm$ 2.10	30.02 $\pm$ 2.08	0.8
<b>Mode of delivery</b>			0.04
Vaginal	15 (50.0)	65 (72.2)	
C-Section	15 (50.0)	25 (28.7)	
Birth weight (g)	1196 $\pm$ 247	1250 $\pm$ 248	0.15
Apgar score at 1 min	4.8	6.2	0.004
Apgar score at 5 min	6.9	7.9	0.003
Delivery room intubation	5 (5.6)	4 (12.9)	0.14
Positive pressure ventilation	12 (38.7)	12 (13.3)	0.004
Multiple pregnancy	9 (29.0)	27 (31.0)	0.8
5 minute Apgar score <7	11 (37.9)	8 (9.6)	0.001

Data shown as number of cases (%) or mean  $\pm$  standard deviation.

80% of cases, the hemorrhage occurred during the first week of life. **Table 1** displays the demographic and obstetric characteristics of the study population. No significant differences were present between the 2 groups in terms of gestational age, birth weight, gender and maternal age. The percentage of twins and triplets was found to be similar in the 2 groups. The mean period of mechanical ventilation in the group with IVH was  $2.8 \pm 5.8$  days, compared to  $0.5 \pm 2.1$  days in the group without IVH ( $p=0.002$ ). The mean number of endotracheal suctioning during the first 7 days of life in IVH group and non IVH group was  $9.7 \pm 18.4$  and  $3.06 \pm 13.7$  ( $p=0.004$ ). Patent ductus arteriosus was diagnosed in 4 (13.3%) in the IVH group and 3 (3.3%) in the non-IVH group ( $p=0.01$ ). Seven (22.6%) patients in the IVH group and 3 (3.4%) in the non-IVH group received surfactant during the first day of life ( $p=0.003$ ). The other factors found to be associated with a statistically significant higher incidence of IVH were positive pressure ventilation at birth ( $p=0.004$ ), low Apgar score at 1 minutes ( $p=0.004$ ) and low Apgar score at 5 minutes ( $p=0.003$ ). Approximately 72.2% of infants without IVH were born to mothers who had received antenatal steroid therapy, compared with 50% in the IVH group ( $p=0.04$ ). Perinatal and neonatal data are shown in **Table 2**.

**Discussion.** Our main objective was to identify risk factors for the development of IVH. The risk factors associated with increased risk of IVH were: positive

pressure ventilation at birth, low 5 minute Apgar score, PDA, number of endotracheal suction during mechanical ventilation, duration of mechanical ventilation and use of surfactant therapy. Maternal antenatal treatment with steroids and cesarean section were associated with lower incidence of IVH. Significant controversy remains whether a cesarean route of delivery is beneficial for very low birth weight infants.<sup>14</sup> Our study found that cesarean section decreased incidence of IVH in very low birth infants. A large study of 1009 infants showed improved Apgar score and a decreased incidence of IVH in very low birth weight infants delivered via cesarean section.<sup>15</sup> In the study of Synnes et al, vaginal delivery was a significant risk factor for IVH.<sup>6</sup> A large multi-center randomized trial has shown that planned cesarean section is better than planned vaginal birth for the term breech fetus.<sup>16</sup> The study performed by Martinez et al, found improved survival but not decrease in the incidence of intracranial abnormalities in infants born via cesarean section.<sup>17</sup> The protective mechanism of a cesarean section remains speculative, but warrants further research. The duration of assisted ventilation showed a trend towards the development of abnormal cranial ultrasound in our patients, that is similar to founding of Vermeulen et al.<sup>18</sup> This may reflect the severity of illness in the neonates, but assisted ventilation is also associated with fluctuations of blood pressure in the neonatal brain.<sup>19,20</sup> Suctioning procedure has been reported to increase intracranial pressure and hence has been associated with increase incidence of IVH.<sup>7</sup>

**Table 2** - Univariate analysis of prenatal and neonatal data.

Parameter	IVH Group n=31	Control group n=90	P value
Pneumothorax	2 (6.5)	1 (1.1)	0.16
Respiratory distress syndrome	13 (41.9)	36 (28.9)	0.13
Surfactant	7 (22.6)	3 (3.4)	0.003
Intravenous bicarbonate	6 (19.3)	12 (13.3)	0.1
Patent ductus arteriosus	5 (16.7)	3 (3.3)	0.01
Antenatal steroid	15 (50.0)	65 (72.2)	0.04
Inotropes	3 (9.7)	5 (5.6)	0.42
First hematocrit	$41.06 \pm 5.36$	$42.07 \pm 5.69$	0.39
Necrotizing enterocolitis	1 (3.2)	6 (6.7)	0.67
Pulmonary hemorrhage	1 (3.2)	2 (2.2)	1
Fertility treatment	3 (9.7)	5 (5.7)	0.43
Preeclampsia	1 (3.2)	6 (6.7)	0.41
Duration of assisted ventilation(day)	$2.8 \pm 5.8$	$0.5 \pm 2.1$	0.002
Number of endotracheal suction	$9.7 \pm 18.4$	$3.06 \pm 13.7$	0.004
Minimum platelet count	$151000 \pm 81000$	$167000 \pm 69000$	0.30
Sepsis	18 (58.1)	37 (41.6)	0.14

Data shown as number of cases (%) or mean  $\pm$  standard deviation. IVH - intraventricular hemorrhage

Our study shows a significant relationship between the incidence of IVH and the number of suction procedure, a finding consistent with previous reports,<sup>3</sup> that support the minimal handling theory recommended for very small premature infants.<sup>21-22</sup> But the study of Linder et al, showed significant inverse relationship between the incidence of IVH and the number of suction procedures performed during the first 24 hours of life.<sup>23</sup> However, additional research is needed before proper recommendation as to airway suction procedures in very preterm infants can be made. The protective role of antenatal corticosteroids is well recognized.<sup>3,9,18</sup> Our analysis confirms their importance, with even partial treatment having a beneficial effect in reduction of IVH. The protective mechanism of corticosteroids may result from an increase in neonatal blood pressure, which prevents blood pressure fluctuations or may result from an enhanced maturation of the cardiovascular system of the neonates, in addition to the effects on the pulmonary system resulting in a decrease of the incidence of RDS.<sup>22,24-25</sup> In the present study, surfactant use was associated with increased incidence of IVH. This occurrence has been shown in a study by Martinez et al.<sup>17</sup> We attribute this finding to the use of surfactant in the sickest and smallest infants. The most reliable measure of condition of premature infants at the time of delivery is umbilical arterial PH, but this data is not routinely collected in our center. Instead we included the one and 5 minute Apgar score that retained significance in our analysis. Heuchan et al, reported that 1 minute Apgar score <4 have significant association with major IVH.<sup>26</sup> In the study of Synnes et al, low Apgar score was a significant risk factor for IVH.<sup>27</sup> Vohr and Ment<sup>21</sup> reported that intrapartum asphyxia have been associated with early onset of IVH. The anomalies of cerebral perfusion play an important role in the development of cerebral injury among preterm infants.<sup>28</sup> There is a relationship between the larger diameter of the PDA and low systemic blood flow.<sup>29</sup> Our investigations have shown that patent ductus arteriosus was associated with increased incidence of IVH. A study of 117 ventilated preterm infants showed that larger PDA diameters were significantly associated with any grade of IVH.<sup>30</sup> This study did not find any influence on the incidence of IVH by other maternal and perinatal factors such as pneumothorax, RDS, preeclampsia, number of fetus, fertility treatment, pulmonary hemorrhage, first hematocrit, sepsis and necrotizing enterocolitis. This study is limited by the small sample size. However, by reducing the confounding effects of 2 important factors including gestational age and birth weight, the sensitivity of this study to detect important risk factors for IVH was increased.

In conclusion, we have confirmed that a few perinatal factors can predict the rate of IVH in our center. This

further supports the theory that many cases of IVH have their origins around the time of delivery. These findings emphasize the importance of obstetric and neonatal care to improve outcomes of premature infants.

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