

Study of Intraventricular Hemorrhage in VLBW Neonates Admitted in Al-Zahra Hospital, Tabriz, Iran

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ABSTRACT

INTRODUCTION AND AIM: Intra-ventricular hemorrhage (IVH) is an important predictor of adverse neurodevelopmental outcome. IVH risk factor identification may conduct improvement of quality of care in Neonatal Intensive Care Units. The aim of the current study was to determine possible risk factors associated with IVH in VLBW neonates admitted in our hospital.

PATIENTS AND METHODS: All neonates with birth weight below 1500 gr admitted to NICU. Cranial ultrasonography was done for premature neonates weighed <1000 g in 3 to 5 days and in 1 month again. In premature infants weighed >1000 g, sonography was done in 7 days and 30 days of life respectively. If there is any conditions such as apnea, seizure, significant decrease in level of hemoglobin, increased head circumference, increased oxygen consumption, and other significant changes another sonography was done again. Exclusion criteria were cerebral malformations, metabolic disturbances, chromosomal anomalies, central nervous system infection, and genetic syndromes. Data was analyzed by SPSS ver 16.0 (SPSS Inc, Chicago, IL, USA)

RESULTS: In this study 64 cases with IVH and 110 without IVH were included. Mean of gestational age was 28.78 ± 2.08 . From neonates, 54.6% were boys and 45.4% were girls. Vaginal delivery and cesarean section was done in 56 (32.2%) and 118 (67.8%) cases respectively. Mean \pm SD of pH in cases with IVH and without IVH was 7.19 ± 0.22 and 7.30 ± 0.12 respectively ($p=0.001$). Mean \pm SD of pco₂ in cases with IVH and without IVH was 65.15 ± 29.89 and 49.88 ± 40.89 respectively ($p=0.001$). Mean of 5th min APGAR score in patients required CPR was 7.36 ± 1.57

and in patients without CPR was 8.68 ± 1.25 ($P=0.001$).

From cases with IVH, hydrocephaly was detected in 20 cases. From cases without IVH, hydrocephaly was detected in 6 cases. Result of chi-square showed significant correlation between IVH and prematurity ($\chi^2=21.94$, $df=1$, $P<0.001$). From cases with IVH, 18 cases (28.1%) expired. From cases without IVH, 11 cases (10%) expired ($\chi^2=9.398$, $df=1$, $P=0.002$). Results of chi-square test showed that there were a correlation between IVH and PDA, pressure support, surfactant therapy,

inotrop drug administration, vaginal delivery, neonatal resuscitation, and antenatal corticosteroid therapy ($p<0.05$). Hyaline membrane disease, history of preclampsia in mother was significantly higher in cases without IVH (Chi-square, $p<0.05$).

CONCLUSION: PDA, pressure support, surfactant therapy, inotrop drug administration, vaginal delivery, neonatal resuscitation, and antenatal corticosteroid therapy were significantly higher in cases with IVH. Hyaline membrane disease and preeclampsia in mother was significantly higher in cases without IVH.

KEYWORDS: Intraventricular hemorrhage, APGAR, low birth weight, hyaline membrane disease, corticosteroid, surfactant, inotrop, pre-eclampsia

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INTRODUCTION AND AIM: Intraventricular hemorrhage (IVH) is an important predictor of neuro-developmental disability in very preterm infants. IVH is an important cause of morbidity and mortality in very low birth weight

(VLBW) infants. More than 50% of bleeding episodes occur during the first 24 hours of life, with <5% occurring after 4-5 days. Identifying the antecedent risk factors and underlying mechanisms for P/IVH has the potential to allow the development of effective strategies for prevention of cerebral injury in preterm infants. Almost all P/IVH occurs in the first 4 days after birth, but a proportions of these P/IVH are presented with in the first few hours after birth. Although the incidence of IVH is decreasing, it remains a serious problems in the VLBW infants. A number of risk factors have been proposed for the development of IVH: low birth weight and gestational age, maternal smoking, breech presentation, gender, premature rupture of membranes⁸, intrauterine infections, mode of delivery^{10,12}, prolonged labor,² post natal resuscitation and intubation,² transfer from one unit to another, early onset of sepsis; development of respiratory distress syndrome^{11,12}, pneumothorax,³ recurrent endotracheal suctioning,^{2,15} metabolic acidosis and rapid bicarbonate infusion^{14,15}, and high frequency ventilation. The aim of the current study was to determine possible risk factors associated with IVH in VLBW neonates admitted in our hospital.

PATIENTS AND METHODS

All neonates <1500gr who admitted in NICU (Neonatal Intensive Care Unit) were included. Exclusion criteria were cerebral malformations, metabolic disturbances, chromosomal anomalies, central nervous system infection, and genetic syndromes. Sonography was done for premature neonates weighed <1000 g in 3 to 5 days and in 1 month again. In premature infants weighed >1000 and <1500 g, sonography was done in 7 and 30 days of life respectively. Sonography was repeated again if there is conditions such as apnea, seizure, decreased level of hemoglobin, increased head circumference, increased oxygen consumption, and other significant changes were occurred another sonography was done again. Exclusion criteria were cerebral malformations, metabolic disturbances, chromosomal anomalies, central nervous system infection, and genetic syndromes. ROP(Reinopathy of prematurity)

was evaluate by ophthalmologist. PDA(Patent ductus arteriosus) was detected by physical examination and echocardiography. Pneumothorax was detected by physical examination and chest radiography. Hyaline membrane disease was confirmed by radiography, physical examination, and arterial blood gas. NEC(Necrotizing enterocolitis) was detected by physical examination, radiologic assessment, and stool examination. Data was analyzed by SPSS ver 16.0 (Chicago, IL, USA).

This study was supported by research affairs of Tabriz university of medical sciences. This study was approved by medical ethics committee of university. Consents form signed by parents was obtained by each case.

RESULTS

In the current study, 64 cases (M=38, F=25) with IVH and 110 without IVH(M=57, F= 53) were included. Mean of GA among IVH and Normal groups were 1.51 ± 0.53 and 2.03 ± 0.61 respectively ($P=0.0001$). Sex distribution was shown in table-1. There was no significant preponderance sex for IVH.

The most frequent age of IVH occurrence were 28 wks ($n=39, 22.4\%$), 27 wks($n=30, 17.24\%$), 29 wks($n=23, 13.21\%$), and 30wks($n=23, 13.21\%$) respectively. Mean of 5th min APGAR score in patients underwent CPR was 7.36 ± 1.57 and without CPR was 8.68 ± 1.25 ($p=0.001$).

From 55 cases born with NVD, 28 underwent resuscitation and from 118 cases born with cesarean section, 46 underwent resuscitation ($X^2=2.180, df=1, P=0.095$). Of 64 cases with IVH, 62.5% underwent resuscitation. Of 110 neonates without IVH, 34(30.90%) underwent resuscitation. Result of chi-square test showed there was significant correlation between IVH and history of neonatal resuscitation($p<0.0001, x^2=16.520$).

From all cases, 22 cases (12.6%) oxygen supplied with hood, 57 cases(32.6%) with ventilator and 92 cases(52.6%) with NCPAP. Mean of Hct was 44.23 ± 30.97 ranged from 13.1 to 44.2. Mean of Hb was 13.78 ± 1.95 ranged from 7.8 to 19.4. Mean of Plt count was 164259.04 ± 78602.716 range from 60000 to

Table1: GA, IVH, and sex distribution among cases

IVH	GA	Male	Female	Total
Yes	≤27	21(65.62%)	11(34.38%)	32
	28-31	17(54.84%)	14(45.16%)	31
	>=32	0	1(100%)	1
	Total	38(59.38%)	26(40.62%)	64
No	≤27	11(57.90%)	8(42.10%)	19
	28-31	31(45.59%)	37(54.41%)	68
	>=32	15(65.22%)	8(34.78%)	23
	Total	57(51.82%)	53(48.18%)	110

Table-2: Comparison of arterial blood gas and hematologic parameters between.

	With IVH	Without IVH	P-value
pH	7.19±0.22	7.30±0.12	0.001
HCO3	29.34±35.40	26.06±20.44	0.504
Po2	58.92±23.20	56.10±30.9	0.531
Pco2	65.15±29.84	49.88±20.89	0.001
BE	-2.64±8.39	-2.48±5.42	0.891
Hb	13.27±1.70	14.07±2.03	0.009
Hct	40.12±6.18	42.99±6.10	0.003
Plt	169655±62102	161123±86892	0.502

Table - 3: Comparison of associated condition between IVH and Non - IVH group.

Condition	Status	IVH		P - value
		With IVH	Without IVH	
PDA	Yes	18(28.13%)	15(13.51%)	P=0.016, X2=5.664
	No	46(71.87%)	96(86.49%)	
Pressure support	Yes	62(96.87%)	88(80.00%)	P=0.001, X2=9.69
	No	2(3.13%)	22(20.00%)	
HMD	Yes	56(88.88%)	59(96.72%)	P<0.001, X2=23.6
	No	7(11.11%)	2(3.28%)	
NEC	Yes	7(10.93%)	4(3.61%)	P=0.057, X2=3.707
	No	57(89.06%)	107(96.39%)	
ROP	Yes	5(7.81%)	4(3.61%)	P=0.194, X2=1.474
	No	59(92.19%)	107(96.39%)	
Surfactant	Yes	50(78.13%)	35(31.53%)	P=0.001, X2=35.28
	No	14(21.88%)	76(68.46%)	
Inotropes prescription	Yes	16(25.00%)	9(8.19%)	P=0.003, X2=9.302
	No	48(75.00%)	101(98.1%)	
Pneumothorax	Yes	2(3.12%)	2(1.80%)	P=0.465, X2=0.318
	No	62(96.88%)	109(98.20%)	
Pre-eclampsia in mother	Yes	16(25.39%)	46(41.44%)	P=0.024, X2=4.511
	No	47(74.61%)	65(58.56%)	
Sex	Male	38(59.38%)	57(51.81%)	P=0.348, X2=0.032
	Female	26(40.62%)	53(48.19%)	
Delivery	Vaginal	30(47.61%)	26(23.42%)	P=0.001, X2=10.780
	C/S	33(52.38%)	85(76.58%)	
Resuscitation	Yes	40(62.5%)	34(30.90%)	P<0.0001, X2=16.520
	No	24(37.5%)	76(69.10%)	
Neonatal Death	Yes	18(28.13%)	11(10.11%)	P = 0.003, X2= 9.39
	No	46(71.87%)	98 (89.89%)	
Antenatal Corticosteroid	Yes	28(51.85%)	38(34.86%)	P=0.002, X2=9.717
	No	26(48.15%)	71(65.14%)	

PDA: Patent Ductus Arteriosus, HMD: Hyaline Membrane Disease, NEC: Necrotizing Enterocolitis; ROP: Retinopathy of Prematurity

880000. There were significant differences between cases with IVH and without IVH in terms of pH, pCo₂, HCT, and Hb(P<0.05)(Table-2).

From cases, 47 cases (27%) underwent HCO₃ therapy and 127 cases did n't require HCO₃. History of preeclampsia was found in 62(35.6%) cases and in 113 cases (64.4%), no history of preeclampsia were found. Of neonates with IVH, 25.39% had history of preclampsia in mother. Of newborn without IVH, 41.44% had history of preclampsia in mother. There was significant difference between two group(P=0.024,X²=4.511).

The most common conditions associated with IVH were HMD and surfactant therapy(Table-3). Sixty-four cases(36.6%) in this study had IVH. Thirty-eight cases was male and 26 were females(X²=0.932, df=1, P=0.210). IVH grades 0,1,2,3, and 4 were found in 64.43%, 20.57%, 3.43%, 10.29%, and 2.29% of cases respectively.

From 64 cases with IVH, hydrocephaly were detected in 20 cases. From 111 cases without IVH, hydrocephaly was detected in 6 cases. Chi-square test showed significant correlation between IVH and hydrocephaly(X²=21.94, df=1, P<0.001).

Of cases, 4 (2.3%) had seizure and 2 of them had IVH. There was no significant correlation between IVH and seizure(x²=0.318, df=1, P=0.465).

Of 64 neonates with IVH, shunt was placed for one case. Of 111 cases without IVH, no shunt was placed. There was no significant correlation between shunt placement and IVH(Chi-square=1.744, p=0.366).

From 64 cases with IVH, 18 cases (28.1%) expired. From 111 cases without IVH, 11 cases(10%) expired. There was significant relationship among IVH and death rate in VLBW neonates(X²=9.398, df=1, P=0.002).From these cases, 30 cases had grade I, 6 cases grade 2, 16 cases grade 3, and 4 cases grade 4.

From 64 cases with IVH, 62 (96.8%) had pressure support. In these cases, 35 cases had IVH grade I, 6 cases had grade 2, 17 cases

grade 3, and 4 cases grade 4. Chi-square analysis showed significant correlation between IVH and PS(P=0.001,df=1,X²=9.69). Preeclampsia, PDA, pressure support, surfactant administration, and inotrop drug administration are risk factors correlated with IVH(Table-3).(See page 94)

DISCUSSION

In the current study, there was a positive correlation between PDA, pressure support, surfactant therapy, vaginal delivery, neonatal resuscitation, antenatal corticosteroid therapy, and inotropic drug administration with IVH occurrence.

There was no significant difference between two group regarding to ROP, pneumothorax, and sex. Mohamed and Aly, showed that male newborns are at greater risk to develop IVH and severe IVH.

In our study, GA of newborn with IVH was significantly lower than newborns without IVH. in contrast to our study, Ajay and Nzeh, found that there was no association between birth weight and gestational age with IVH.

In another study, uni-variate analyses identified maternal, intrapartum, and early postnatal hemodynamic risk factors; multivariate regressions indicated that emergent caesarian section, patent ductus arteriosus, and lower 5-day minimum pH independently increased the odds of cerebellar hemorrhage.

Surfactant therapy identified as a risk factor in this study which is not consistent with Limperopoulos et al. and Linder et al. study.²¹ In the study by Badiie on 31 preterm infants with birth weight <1500 g, surfactant use was a risk factor for IVH.

In our study, vaginal delivery was significantly higher in cases with IVH than neonates without IVH. In Linder et al., study, no significant difference was found.²² In another study, vaginal delivery was reported as a risk factor of IVH. However, general anesthesia using during cesarean section was found to be a risk factor for IVH.

Pco₂ in arterial blood gas was significantly higher in VLBW neonates with IVH compared

to neonates without IVH. In Kaiser et al study, they showed that Paco₂ is a dose dependent predictor of severe IVH during permissive hypercapnia era. In other study, an association between low Paco₂ and IVH was found.⁸

In our study, hydrocephaly was significantly higher in cases with IVH. This finding was similar to Mancini et al study.

We found a negative correlation between IVH and PDA. In Limperopoulos et al study, rate of PDA significantly was higher than control group.²¹

In this study, IVH was significantly higher in cases underwent resuscitation compared to other cases. This finding was similar to other studies.^{2,11,15}

In our study, there is no significant difference between IVH and Non- IVH group regarding occurrence of pneumothorax. In Linder et al study, they found pneumothorax in 42% of cases with IVH and 20% of control groups.²² There were some reports that mentioned pneumothorax as risk factor of IVH.³

In the current study, use of inotropes was significantly higher among IVH cases and may be the risk factor of IVH. In Linder et al study, there was no significant difference for inotrop administration among IVH and control cases.²² In study by Köksal et al, use of vasopressor was suggested as risk factor for IVH.²⁴ Use of inotropes also was reported as risk factor of IVH in the study by Lee et al. The result of this study was similar to our findings.

In the current study, IVH was significantly higher in cases without HMD than neonates with HMD. This finding was inconsistent with Linder et al study. In their study, however, there is no significant difference, but the rate of IVH among HMD cases was higher than cases without HMD.²²

In the current study, pH, Hb, and Hct was significantly lower among cases with IVH than cases without IVH. In Linder et al study, only Hct was significantly lower in IVH cases.²²

In our study, there was no significant difference between two group regarding platelet count. In Lupton et al., study, reduced platelet count was

not associated significantly with intraventricular hemorrhage.

In the current study, antenatal corticosteroid therapy was significantly higher in cases with IVH. This finding was inconsistent with Köksal et al., study.²⁴ In the study by Vural et al., on 103 premature neonates, maternal corticosteroid therapy was found to be significantly protective against IVH. In the study from Iran, antenatal steroid had protective effect on the occurrence of IVH.²³

We have some limitation in this study such as low sample size and a single center study. We strongly recommended, another study to determine why inotrop and surfactant therapy rises the possibility of IVH in our hospital. We recommend a cohort multicenter study to evaluate risk factors of IVH.

CONCLUSION

PDA, pressure support, surfactant therapy, inotropic drug administration, vaginal delivery, neonatal resuscitation, and antenatal corticosteroid therapy were significantly higher in cases with IVH. Hyaline membrane disease and preeclampsia in mother was significantly higher in cases without IVH.

Conflict of interest: There are no conflict of interest

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REFERENCES

1. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, et al. Neuro developmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics* 2000;105:1216-1226.
2. Wells JT, Ment LR. Prevention of intraventricular hemorrhage in preterm infants. *Early Hum Dev* 1995;42:209-233.
3. Vohr B, Ment LR. Intraventricular hemorrhage in the preterm infant. *Early Hum Dev* 1996;44:1-16.
4. Evans N, Kluckow M. Early ductal shunting and intraventricular haemorrhage in ventilated preterm infants. *Arch Dis Child* 1996;75:F183-F186.
5. Ment LR, Oh W, Ehrenkranz RA, Philip A, Duncan C, Makuch R. Antenatal steroids, delivery mode,

- and intraventricular haemorrhage in preterm infants. *Am J Obstet Gynecol* 1995;172:795-800.
6. Heuchan AM, Evans N, Henderson Smart DJ, Simpson JM. Perinatal risk factors for major intraventricular haemorrhage in the Australian and New Zealand Neonatal Network, 1995-97. *Arch Dis Child Fetal Neonatal Ed* 2002;86:86-90.
 7. Weintraub Z, Solovechick M, Reichman B, Rotschild A, Waisman D, Davkin O, et al. Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular/haemorrhage in very low birth weight infants. *Arch Dis Child Fetal Neonatal Ed* 2001;85:F13-F17.
 8. Verma U, Tejani N, Klein S, Reale MR, Beneck D, Figueroa R, et al. Obstetric antecedents of intraventricular hemorrhage and periventricular leukomalacia in the low birthweight neonate. *Am J Obstet Gynecol*. 1997;176:275-281.
 9. Spinillo A, Ometto A, Stronati M, Piazzzi G, Lasci A, Rondini G. Epidemiologic association between maternal smoking during pregnancy and intracranial hemorrhage in preterm infants. *J Pediatr* 1995;127:472-478.
 10. Shankaran S, Bauer CR, Bain R, Wright LL, Zachary J. Prenatal and perinatal risk and protective factors for neonatal intracranial hemorrhage. *Arch Pediatr Adolesc Med* 1996;150:491-497.
 11. Gleissner M, Jorch G, Avenarius S. Risk factors for