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Leukocytosis in Preterm Infants with Intraventricular Hemorrhage

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Abstract

Background: Intraventricular hemorrhage is the most common intracranial hemorrhage in premature infants. The objective of this study was to investigate the relationship between intraventricular hemorrhage and blood leukocyte count.

Materials and Methods: This was a cross-sectional simple sampling study conducted from the beginning of 2006 to 2010 in Ali-Asghar Children's Hospital. Inclusion criteria were birth weight less than 1500 grams, and at least one cranial ultrasound performed in the first 7 days. The CBC was taken one hour after first entering the NICU. WBC count greater than 25000 cell/ml was considered as leukocytosis and ANC greater than 15000 as neutrophilia.

Results: Two hundred neonates were included in the study. Intraventricular hemorrhage was reported in 59 patients (29.5%). There was significant correlation between Intraventricular hemorrhage and mechanical ventilation (P=0.003). Significant correlation was observed between gestational age and WBC count in the first and second days (P=0.001), and between birth weight and WBC count in the first and second days (P = 0.03). There was also a correlation between WBC count in the first and second days and the first minutes Apgar score (P = 0.03), and between the fifth minute Apgar score and the first day WBC count (P=0.005).

Conclusion: Intraventricular hemorrhage incidence was associated with mechanical ventilation and pneumothorax, but no significant correlation was found with the total peripheral leukocyte count and neutrophil count during the first 72 hours after the birth. Further studies are needed to confirm the probable role of leukocytosis in the pathophysiology of intraventricular hemorrhage.

Key Words: Leukocyte, intraventricular, hemorrhage, infant, preterm, complications

Introduction

Intraventricular hemorrhage (IVH) is a common cause of brain damage in very low weight infants [1-4]. About 30% of infants less than 1500g will experience the symptoms of cerebral hemorrhage [2-4]. The complex etiology of IVH in preterm infants includes many causes [3-7]. IVH is a very important cause of mortality and morbidity in very low birth weight infants [4] and most intracerebral hemorrhages occur in the first 3 days after birth. Many cases with small hemorrhages (grade 1 and 2) are without symptoms [2-9], but larger hemorrhages often show disastrous manifestations that can quickly lead to shock and anemia [5]. In most cases the cause of IVH is unknown [1-6], but a relationship between IVH and leukocytosis has been indicated in some studies and the role of neutrophils has been known to be essential in reperfusion of the injury after hypoxemia [1-10]. This complication is induced by the production of oxygen free radicals [9-12]. Neutrophils accumulate in certain brain damaged areas and the protective role of neutropenia can be predicted in IVH [10-14].

The aim of the present study was to evaluate the role of leukocytosis and absolute neutrophils count in the incidence of IVH, in the first three days after birth, among very low birth weight preterm infants.

Materials and Methods

This was a cross-sectional simple sampling study conducted from the beginning of 2006 to 2010 in Ali-Asghar Children's Hospital. Inclusion criteria for infants entering the study were birth weight less

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than 1500 grams, and at least one cranial ultrasound performed in the first 7 days. The was CBC taken one hour after first entering the NICU. WBC count greater than 25000 cell/ml was considered as leukocytosis and ANC greater than 15000 as neutrophilia. A consent form was received from the parents of all newborns entering the study.

Demographic and clinical data, including sex, gestational age, birth weight, and Apgar score in the first and fifth minutes were recorded. The risk factors associated with maternal conditions including pre-eclampsia, diabetes, receiving corticosteroids by the mother before delivery, chorioamnionitis, premature rupture of amniotic membranes (PROM) for more than 18 hours, and the type of delivery were also recorded. Data were analyzed using SPSS software version 16. Data were analyzed using ANOVA Chi-Square, and T-test for quantitative variables.

Results

Two hundred neonates entered the study. One hundred and seven patients (53.5%) were male and 93 (46.5%) were female (Table-1). Thirty nine mothers (19.5%) had pre-eclampsia and 14 mothers (7%) had gestational diabetes. Premature rupture of amniotic membranes (PROM) for more than 18 hours was found in 42 patients (21%), but none suffered chorioamnionitis. Thirty nine mothers (19.5%) gave a history of corticosteroids usage. Sixty mothers (30%) had a vaginal delivery and 140 (70%) had caesarean section (Table-2).

IVH was reported in 59 patients (29.5%) with 29 cases (49.1%) being grade I, 16 cases (27.1%) being grade 2, 11 cases (18.7%) being grade 3 and 3 cases (5%) being grade 4.

One hundred infants (50%) received mechanical ventilation and 23 (11.5%) had pneumothorax.

There was not any significant correlation between IVH and maternal diabetes; steroid usage by the mother, PROM and the type of delivery.

There was significant correlation between IVH and mechanical ventilation (P=0.003). IVH developed in 42 mechanically ventilated neonates (42%) versus 17 patients (17%), who were not mechanically ventilated. There was no significant correlation between IVH and leukocytosis in the first, second and third day, and the average number of white blood cells was not significantly correlated with different grades of IVH. The mean WBC count did not show any difference in infants of mothers with diabetes, preeclampsia or receiving corticosteroids compared to healthy mothers. There was a significant correlation between leukocytosis in the first and third days, and the sex (P= 0.01), as the female infants with IVH had a higher WBC count on the first and third days (Table-3).

Significant correlation between gestational age and WBC count was seen in the first and second days (P=0.001). Also significant correlation was observed between the birth weight and the WBC count in the first and second days (P = 0.03), between the first and second days' WBC count and the first minute's Apgar (P = 0.03), and between the fifth minute's Apgar and the first day's WBC count (P=0.005).

Also we did not find an association between cystic preventricular leukomalacia (PVL) and the early neonatal peripheral leukocyte counts.

Discussion

IVH has complex multi factorial causation in low birth weight infants [1-7]. Our results indicated no significant correlation between WBC count

Table1: Demographic data as shown as mean ± S.D.

	IVH* (n=59)	Control (n=141)	P-Value
Gestational age (wk)	29.4±0.3	29.9±0.16	NS**
Birth weight (gm)	1202±34	1222±21	NS
Male (%)	30 (55.5%)	77 (54.6%)	NS
1th minute Apgar score	6±0.3	6.2±0.1	NS
5th minute Apgar score	7.6±0.2	8±0.1	NS

* No Significant

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and IVH. The subependymal germinal matrix in preterm infants is highly vascularized and prone to bleeding [2-9], and the hemorrhage can progress to the other parts of the brain [10-16]. IVH can be a silent phenomenon or show disastrous clinical signs and symptoms [1-5].

The reports from other studies have indicated an association between IVH and elevated nucleated erythrocyte count [6-12, 14]. Nucleated erythrocytes are present in hypoxic ischemic encephalopathies and tissue hypoxia [13-16]. This process causes free radical production and progression of hemorrhages in ventricular system, and also leukocytosis [11-18]. The present data in contrast to other studies did not show an association between IVH and leukocytosis in low birth weight infants.

IVH with and without ventricular dilatation have also been associated with a higher frequency of cystic PVL in some studies [8-19]. We did not find a relation between cystic PVL and leukocyte count during early days of infancy. According to other studies, in contrast to IVH, cystic PVL is usually diagnosed after neonatal period, during the follow-up [19-23]. Therefore our study could not have been able to detect cystic PVLs during the 3 days after the birth, which describes the difference in our findings and other studies' findings.

The present study could not demonstrate IVH progression caused by leukocytosis and inflammatory mediator responses. Some studies have reported that premature infants with IVH have leukopenia, but other studies have not confirmed it [3-8]. Neutrophil sludging in the cerebral mirocirculation has also been illustrated after an ischemia-reperfusion injury in a baboon model [18]. Thus leukocytosis in preterm infants may increase the risk of brain injury by changing the microvascular circulation or by production of free radical oxidants and reperfusion injury, causing IVH [12-20]. Leukocytosis may have resulted from subclinical maternal or neonatal infection or may be a marker for stressed infants who are most vulnerable to developing IVH [1-4]. We did not find any significant relation between IVH and infections in PROM, maternal infection, prenatal steroid usage, diabetic mothers and preeclampsia. The leukocytosis in infants with IVH may also have resulted from shared maternal risk factors such as chorioamnionitis, which has been proved to be important in neonatal brain injury [2, 3].

Some studies have indicated no significant differences between the infants with and without IVH considering one and five minute's Apgar scores, or the need for resuscitation at birth or for

Table2: Variables in neonates with and without IVH

	IVH* (n=59)	Control (n=141)	P-Value
Preeclampsia(n)	13(6.5%)	26(13%)	NS**
Infant of diabetic mother (n)	2 (1%)	12(6%)	NS
Prenatal corticosteroid usage (n)	14(7%)	(12.5%)	NS
PROM > 18 hr (n)	12 (6%)	30(15%)	NS
Cesarean section (n)	33(16.5%)	107(53.5%)	NS
Vaginal Delivery (n)	14(7%)	46(23%)	NS
Mechanical ventilation (n)	45(22.5%)	55(27.5%)	0.003
Mechanical ventilation (days)	22.1±13.8	9.5±7.6	0.000
Pneumothorax (n)	13(6.5%)	10(5%)	0.000

* Not Significant

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Table3: Leukocyte counts at admission through day 3 in infants with and without IVH

	IVH			Without IVH			P Value
	WBC >25000/mm3	WBC <25000/mm3	Mean±SD	WBC >25000/mm3	WBC <25000/mm3	Mean±SD	
Day 1	9/59	50/59	11.8±1.2	29/141	112/141	11.6±0.5	0.8
Day 2	8/59	51/59	11.1±1.3	34/141	107/141	12.6±1.09	0.4
Day 3	11/59	49/59	12.05±2.2	32/141	109/141	9.4±0.5	0.2

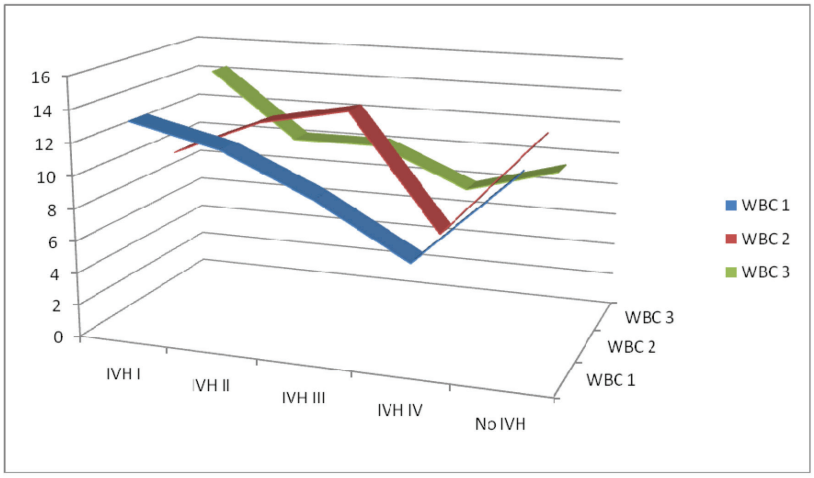


Figure1: Total peripheral leukocyte count (WBC) on day 1 to 3 in patients with IVH compared to patients without IVH

subsequent respiratory assistance [1-6]. But our study showed significant correlation between IVH and mechanical ventilation and pneumothorax.

Conclusion

The present study showed that IVH incidence is associated with mechanical ventilation and pneumothorax, but no significant correlation was found with the total peripheral leukocyte count and neutrophil count during the first 72 hours after the birth. Further studies are needed to confirm the probable role of leukocytosis in the pathophysiology of IVH.

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