



Lack of relationship between cord blood erythropoietin and intraventricular hemorrhage in premature neonates: a controversial result

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Abstract

Purpose The aim of this study was to assess the incidence and risk factors of intraventricular hemorrhage (IVH) as well as the role of cord blood erythropoietin (EPO) level in predicting the possibility of IVH in premature neonates.

Materials and methods This prospective study included 140 preterm neonates born at hospitals affiliated to Shiraz University of Medical Sciences from May 2014 to April 2015. Complete blood count and cord blood EPO level was measured after birth. Brain ultrasonography was performed at 3 and 7–10 days after birth in these newborns.

Results Brain ultrasonography showed IVH in 8.57% (12/140) until the third day and 20% (28/140) at 7–10 days of life in premature neonates. Early gestational age, low birth weight, low Apgar score, and failure to give prenatal steroid were significant risk factors for developing IVH. The mean level of cord blood EPO was 20.95 ± 21.09 mIU/mL in premature newborns without IVH and 15.82 ± 17.11 mIU/mL with IVH. There was no correlation between the cord blood EPO and IVH in premature newborns.

Conclusion Antenatal steroids therapy should be encouraged among women at risk of premature delivery. Our results showed that the cord blood EPO was not correlated with IVH in preterm neonates and further research is required to assess this relationship.

Keywords Premature · Intraventricular hemorrhage · Erythropoietin · Risk factors

Introduction

Intraventricular hemorrhage (IVH), which occurs in the germinal matrix of the brain, is much more common in the premature infants or those with very low birth weight. The chance of developing IVH is 30% in premature infants < 1500 g [1,

2]. Although prematurity and low birth weight are the major risk factors for IVH, it has been proposed with a wide range of other risk issues, including gender, maternal smoking, multiple pregnancy, and premature rupture of membrane, mode of delivery, gender, hypercapnia, and hypotension [3–7]. The history of no consumption of corticosteroids during pregnancy, low Apgar score of the first minute, and early sepsis are also mainly related to developing IVH [8–10].

IVH occurs about 90% within the first 3 days of life and 20–40% more lengthened over the first week of life [11]. The incidence of IVH is decreasing, but it is a serious problem in developing short- and long-term sequel, such as cerebral palsy and mental retardation in premature infants [12]. Several studies introduce various interventions to reduce IVH and improve the outcomes of affected newborns like antenatal steroid usage and indomethacin in the first hours after birth [13, 14]. IVH might be associated with germinal matrix hemorrhage and hydrocephalus. Some infants with transient hydrocephalus will have spontaneous

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resolution of symptoms, but fewer infants will ultimately need serial lumbar punctures or even neurosurgical intervention, such as ventriculosubgaleal shunt [15, 16].

Recently, measurement of concentrations of some biomarkers in different compartments makes it possible to predict the risk of IVH in preterm newborn. Erythropoietin (EPO), a determinant of tissue oxygenation, has been previously established to be higher in the cerebrospinal fluid of the neonates with central nervous system injury including hypoxia, meningitis, and IVH [17]. High level of EPO in the cord blood has been identified as marker for fetal hypoxia, and a number of studies on premature neonate found elevation in the cord blood EPO can predict IVH in them [18, 19].

As far as many environmental and genetic factors are suggested to be effective in the prevalence of IVH [20], the objective of the present study was to report the incidence of IVH and the associated risk factors among premature newborns in Fars province, Southwestern Iran. We also aimed to assess the role of the cord blood EPO level in predicting the possibility of IVH in premature neonates.

Materials and methods

All preterm neonates, born at 26–34th gestational week at hospitals affiliated to Shiraz University of Medical Sciences from May 2014 to April 2015, were recruited in this prospective study using a convenient sampling method.

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1394.s332). The design and objectives of the study were explained to the neonates' parents, and written informed consent was obtained from the parents who were willing to participate in the study. Hence, they were insured that they could withdraw from the study whenever they desired, and it was explained to them that their data would be kept confidential and anonymous.

Any premature newborn with a specific genetic syndrome, malformations affecting neuronal development, anemia, or asphyxia at birth were excluded from the study. Birth asphyxia was defined as pH < 7.0 or blood base excess (BE) < -15 mmol/L in the cord blood. Newborns with TORCH (toxoplasmosis, other, rubella, cytomegalovirus, and herpes) abnormalities were excluded, as well. All the participants' information, including newborn's gestational age and birth weight, mode of delivery (vaginal or caesarian section), Apgar score of the first and fifth minutes, mother's age, twin pregnancy, as well as history of taking corticosteroids (betamethasone 12 mg intramuscularly every 24 h for one or two doses) by the mother during pregnancy were recorded. Blood coagulation disorders is defined as prolonged prothrombin time (PT) below 65% and/or prolonged partial thromboplastin time (PTT) more than 45 s in accordance with the reference values for

the local laboratory. Thrombocytopenia is considered as platelet count < 150,000/mm³ of blood.

At the time of delivery, 5 cm³ of the cord blood sample was taken through aseptic method from the clamped umbilical vein, about 2–3 cm³ of which were collected in polypropylene plastic tubes and kept at 4 °C for 2–4 h for the serum to be separated. Then, the samples were centrifuged for 5 min at 3000 rpm, and the obtained serum was kept in the freezer at -20 °C to be transferred to Shahid Dastgheib Hospital for measuring the erythropoietin level. The EPO level was measured with an enzyme-linked immunosorbent assay (IBL International, Hamburg, Germany) according to the manufacturers' instructions. The calculated sensitivity for detecting the umbilical EPO was 1.1 mIU/mL. The rest of the cord blood was used for calculation of complete blood count (CBC) to diagnose anemia and analysis of the arterial blood gas for asphyxia risk assessment. Newborns underwent brain ultrasonography once at the third day of life and repeated at the 7–10th day of life. Brain ultrasonography was performed in the neonate's intensive care unit (NICU) by the same radiologist. The stages of hemorrhage were categorized according to Papile classification of IVH [21]: hemorrhage to the periventricular germinal matrix as grade 1, hemorrhage to the ventricular system without dilatation of the ventricles as grade 2, hemorrhage to the ventricular system with dilatation of the ventricles as grade 3, and intraparenchymal echodensity and periventricular hemorrhagic infarction as grade 4.

Continuous variables are presented as mean (SD) and qualitative variables are reported through frequencies (percentage). Chi-square test was used to compare different variables between the two groups with and without IVH. Independent samples *t* test was used for comparing the variables. Logistic regression was used to determine the correlation between the variables and outcomes. Statistical analysis was performed using the SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). *P* values less than 0.05 were considered statistically significant.

Results

Parents of 144 out of 159 eligible newborn with prematurity agreed to participate in this study. Of these, four patients were excluded due to birth asphyxia. This study was prospectively completed with 140 preterm neonates (65 girls, 75 boys). The mean of the gestational age of premature newborns was 31 weeks with a range in age of 26 to 34 weeks. The demographics and clinical characteristics of the maternal and neonatal study population are shown in Table 1.

The prevalence of IVH in our population was 8.57% (8.57%) until the third day and 20% (28/140) on the 7–10th day. The neonates' birth weight, gestational age, Apgar score of the fifth minute, thrombocytopenia, and prolonged

Table 1 Frequency of different variables categorized by the presence of IVH in premature neonates

Variable	Category	Total prevalence	IVH on 3rd day N = 12	P value	IVH on 7–10th day N = 28	P value
Gender	Girl	65	3	0.12	10	0.20
	Boy	75	9		18	
Neonates' birth weight, grams	< 1500	48	8	0.01*	17	0.001*
	≥ 1500	92	4		11	
Mother's age, year	Under 20	7	1	0.81	1	0.65
	20–35	117	10		25	
	over 35	16	1		2	
Type of delivery	Vaginal delivery	1	0	0.75	1	0.61
	Cesarean section	139	12		27	
Multiple pregnancy	Single	87	10	0.62	20	0.29
	Twin	38	2		7	
	Multiple	15	0		1	
Gestational age at birth, weeks	< 30	24	9	< 0.001*	11	0.002*
	30–32	44	2		8	
	> 32–34	72	1		9	
Apgar score of the first minute	< 7	30	5	0.07	12	< 0.001*
	7–10	110	7		16	
Apgar score of the fifth minute	< 6	5	0	< 0.001*	2	< 0.001*
	6–8	38	6		14	
	9–10	97	6		12	
Corticosteroid use during pregnancy	Positive	85	12	0.28	20	0.03*
	Negative	55	0		8	
Doses of corticosteroid during pregnancy	One	18	0	0.56	8	0.02*
	Two	67	12		12	
Thrombocytopenia < 150,000/mm ³	Yes	19	3	< 0.001*	6	< 0.001*
	No	121	9		22	
Prolonged PT&PTT	Yes	7	1	< 0.001*	3	< 0.001*
	No	133	11		25	

IVH intraventricular hemorrhage, PT prothrombin time, PTT partial thromboplastin time

* $P < 0.05$

PT&PTT were significant factors in occurrence of IVH on the third day. However, Apgar score of the first minute and antenatal corticosteroid consumption were additional factors in predicting IVH on the 5–7th day of life. Single dose of the antenatal steroid treatment (odds ratio [OR]: 0.4; 95% confidence interval [CI]: 0.17–0.84) and two doses (OR = 1.4; 95% CI = 0.97–2.04) had a lower risk of developing IVH, respectively. The rest of other variables were insignificant; all the parameters are demonstrated in Table 1.

The mean level of the cord blood EPO was 19.92 ± 20.27 mIU/mL in all premature newborns ranging from 1.1 to 109 mIU/mL. This mean level was 15.02 ± 15.48 mIU/mL in the group with IVH on the third day and 15.8 ± 17.11 mIU/mL in the group on the 7–10th days. The effect of the cord EPO level is shown on occurrence of IVH in Fig. 1; there was no correlation between the cord blood EPO and IVH.

Regarding the rate of IVH on the 7 to 10th days of life, grade 1 hemorrhage was seen in 46.2% of 28 premature

infants. Table 2 demonstrates the mean level of EPO among four grades of IVH in premature newborns.

Discussion

This study revealed that the prevalence of IVH of any grade was 20% in premature newborns. Similarly, other studies have shown the incidence of IVH in premature newborns. Macini et al. mentioned IVH occurs in 29.8% of the neonates with birth weight of less than 1500 g [22]. Lu et al. conducted a study on 292 Chinese newborns with gestational age of ≤ 34 weeks, showing the incidence of IVH to be 24.1% [6]. Patra et al. demonstrated an incidence of 28.7% of an isolated grade I–II IVH among 362 extremely low birth weight infants [12]. In contrast with our study, a work in this area by Sajjadian et al. demonstrated 57 Iranian newborns with the mean gestational age of 30 weeks; the incidence of IVH was 61.4% [23]. Our

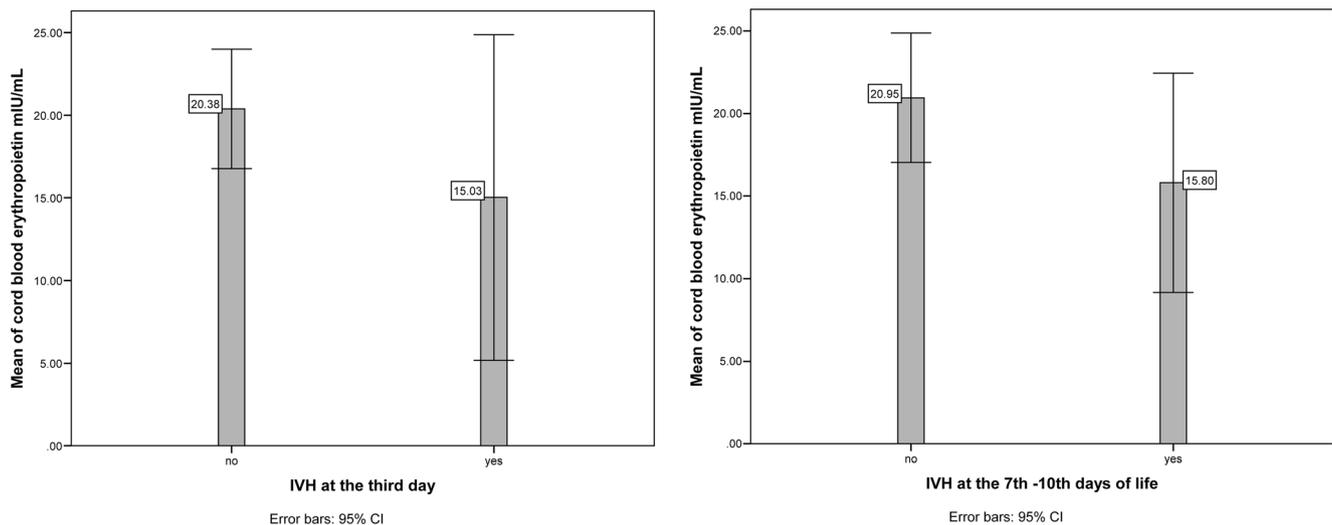


Fig. 1 Relationship between the mean level of erythropoietin in the cord blood with intraventricular hemorrhage on the third and 7–10th days of life in premature newborns

data showed lower incidence of IVH in this area; it can be explained by advances in obstetric and neonatal care of premature newborns in this decade.

Several researches have been performed on various factors in the occurrence of IVH. The risk of IVH was mainly related to the gestational age, and a weekly decline in it is associated with more risk of developing IVH [1, 24]. Within the same line with other reports, early gestational age was proven to be a risk factor for high incidence of IVH in our premature newborns. This factor that can be controlled and changed is of a greater value, as the obstetricians will be able to change the prognosis of the neonate by these interventions.

Low birth weight was an important factor for IVH development in our study. This data is similar to those of others, Howgood et al., Partridge et al., and Mancini et al., who found

a higher incidence of IVH in newborns with lower birth weight [22, 25, 26].

A significant clinical problem, which is generally regarded as one of the risk factors of IVH, is low oxygen supply to the brain. Low Apgar score is found as an IVH risk factor in premature neonates because decreased oxygenation to the brain increase the risk of hemorrhage in the central nervous system [27, 28]. Reduction of the rate of cerebral oxygenation during immediate transition and resuscitation after birth by supplemental oxygen support is feasible for safety of IVH.

The significant association of corticosteroid consumption by mothers with fewer case of IVH has been previously established as advantages of administration of antenatal corticosteroid, especially in cases with possible preterm birth [29–31]. We also observed that this benefit was related to the number of steroid dose treatment.

A low first platelet count during the first 24 h of life and prolonged PT&PTT correlated with a higher incidence of IVH, a finding consistent with previous reports. It is explained that disturbances of the platelet and coagulation contribute to occurrence of hemorrhage [32, 33]. It is a good way to diagnose and treat the disorders of coagulation to decrease the risk of IVH.

Although IVH was significantly associated with the male sex in very low birth newborns in Cuestas et al.'s study, we found no relationship between gender and IVH [3]. Several studies have found that vaginal delivery increases the rate of IVH in premature infants [34, 35], while our study did not confirm this relationship because all modes of delivery were cesarean section except one which was delivered vaginally.

We observed no significant relationship between the levels of cord blood EPO and occurrence of IVH in

Table 2 The mean level of erythropoietin and severity of IVH

Grading of IVH	Number of cases	Mean erythropoietin level mIU/mL
Until the 3rd day of life		
Grade 1	3	16.1
Grade 2	6	6.49
Grade 3	2	19.8
Grade 4	1	13.4
At the 7–10th days of life		
Grade 1	13	9.08
Grade 2	6	31.79
Grade 3	6	22.6
Grade 4	3	10.3

IVH intraventricular hemorrhage

premature newborns; the lack of this association is not consistent with several studies in premature newborns. Bhandari et al. have measured the umbilical cord levels of EPO in 116 preterm newborns, identifying EPO as a risk factor for IVH [18]. Although both studies have measured the cord blood EPO, contradictory results may reflect the difference in demographic characteristics of the patients, like gestational age that has been proven to be an important risk factor, as more than half of the neonates in the present study were born at the 33rd–34th weeks, but the gestational age range of Bhandari's study was 25–30 weeks. Khosravi et al. recently found that the level of the cord EPO was higher in premature newborns with IVH [19]; this different result could be related to chorioamnionitis in all mothers of these 50 premature newborns.

Hypoxia and ischemia are important factors for the expression of EPO in the kidney and liver; however, experimental studies showed the expression of EPO in the human's brain. Junk et al. demonstrated that the brain-derived EPO is necessary for recovery of the neurons following acute neuronal ischemic injury [36, 37]. The large glycosylated molecule of endogenous EPO might not pass simply through the blood–brain barrier; it might be an unsatisfactory reason for lack of EPO in the cord blood.

One of the strengths of the current study was collecting a wide range of demographic data from participants in order to obtain a more precise result. Besides, this study was conducted in several referral centers and included a relatively fair number of patients for the data to be strong enough for the clinicians to be able to trust the results. Beside the strengths, this study had no result of the symptoms of intrauterine infection in the mother and the newborn.

In conclusion, gestational age, birth weight, blood clotting disorders, thrombocytopenia, Apgar score, and antenatal corticosteroid consumption were significantly different between the group with and without IVH. Awareness of these factors helps the clinicians to have a higher suspicion of IVH in neonates that have these factors and diagnose the patients in early stages for prompt treatment. The results of the present study showed that the cord blood EPO was not correlated with IVH in preterm neonates; further studies are required to open the discussion.

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Najib Fs examined the newborns and wrote the article. Each author contributed to revisions of the manuscript and approval of the final version.

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Compliance with ethical standards

Conflict of interest No conflict of interest is declared.

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