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Cerebral Intraventricular Hemorrhage and Interleukin-6 in Preterm Neonates

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ABSTRACT

Background: Intraventricular hemorrhage (IVH) in preterm neonates is a serious problem in neonatal intensive care units (NICU) worldwide. IVH is reported in approximately 60-70% of very-low-birth-weight (VLBW) neonates. The present study aimed to assess the association of IVH with neonatal characteristics and serum markers, such as serum Interleukin-6 (IL-6) level, in preterm neonates in an academic hospital in the Northeast of Iran.

Methods: In this cross-sectional study, a number of 71 VLBW preterm neonates (≤34 weeks of gestational age (GA), birth weight (BW) ≤1500g) were examined regarding the evidence of IVH up to the 40th week of GA in Gorgan, Northeast of Iran. The serum interleukin-6 (IL-6) level was measured within the first 12 hours of lifebirth. The association among the variables was analyzed in SPSS software (version 16) using the chi-square test.

Results: Out of 56 preterm neonates who survived until the 40th week, 15 (26.8%) cases demonstrated evidence of IVH at discharge, they had a significantly lower GA (29.04±2 weeks vs. 30.44±1.7 weeks; P=0.003) and BW (1075.43±208 kg vs. 1251.6±199.4 kg; P=0.001), as compared to 41(73.2%) newborns with no IVH. Preterm neonates with IVH had a significantly higher IL-6 serum level, as compared to those without IVH (224±210 pg/ml vs. 91.93±138 pg/ml; P=0.035).

Conclusion: As evidenced by the obtained result, low birth weight and premature birth could be serious risk factors for the development of IVH. Furthermore, IL-6 concentration may play a pivotal role in the occurrence of IVH.

Keywords: Cerebral intraventricular hemorrhage, Interleukin-6, Premature birth

Introduction

Birth trauma and asphyxia could result in intraventricular hemorrhage (IVH) in newborns with a higher risk among low-birth-weight and more pre-mature neonates. It rarely occurs as a result of primary coagulative disorders or vascular anomalies (1-5).

IVH could be detected in approximately 60-70% of very-low-birth-weight neonates (i.e., under 1500 g). Moreover, the incidence of IVH is reported to be inversely associated with the gestational age (GA) and birth weight (BW) (6).

Approximately 12,000 preterm neonates develop IVH each year just in the United States which poses a serious challenge to preterm neonates. However, the occurrence rate of IVH has remained intact during the last two decades (7, 8).

IVH commonly initiates in the periventricular germinal matrix which is vulnerable to hemorrhage in premature newborns, especially in the first 48 hours of life (9). Severe deficiency in coagulation system has been considered a major risk factor for the occurrence of IVH in preterm neonates. High-grade IVH has been indicated to be accompanied by the severe derangement of coagulation profile in newborns with low BW (10).

Previous studies have revealed an association between IVH development in preterm neonates and an increased level of interleukin-6 (IL-6) in the cord blood (11-13); nonetheless, controversy still exists surrounding this issue. The assessment of

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coagulation parameters in full- and preterm neonates revealed a direct association among coagulation factors, platelet count, and the down-regulation of physiological anticoagulation mechanisms in IVH (14).

The present study aimed to assess the relationship between IVH development and serum IL-6 level in preterm neonates.

Methods

Ethical considerations

The study protocol was confirmed by the Local Ethical Committee of Golestan University of Medical Sciences in Gorgan, Iran, and informed consent was obtained from the subject's parents. All the neonates who were diagnosed with IVH received treatment, according to the standard guidelines.

Among preterm neonates who were born in our academic Hospital, 71 cases were selected with gestational age (GA) ≤ 34 weeks and birth weight (BW) ≤ 1500 grams and were followed up until the end of the 40th week of GA.

Methods

A checklist including demographic and some gestational variables (e.g., gender, GA, BW) was completed for each neonate. In addition, blood samples (3 cc) were obtained from all neonates within the first 12 hours of life to measure complete blood count (CBC), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and serum IL-6 level. Serum was separated from the blood clot and maintained frozen at -70°C, and an enzyme-linked immunosorbent assay (ELISA) test was performed using the interleukin kit (Platinum ELISA, Ready-to-Use Sandwich Human, EBioscience Company). Moreover, all neonates underwent brain ultrasound as follows: 3-7 and 10-14 days after birth, 28 days after birth, at discharge, and in the 40th weeks of GA by the same radiologist in the radiology department of the hospital using a portable ultrasound device (Hyundai 2000). The grade of IVH and the associated complications were also recorded if present. If patients died before the 40th week of birth, brain ultrasound was performed on the exact day of their deaths.

Data analysis

The data were analyzed in SPSS software (version 16) using descriptive statistics and Chi-square test. A p-value less than 0.05 was considered statistically significant.

Results

In the present study, out of 71 preterm newborns who were examined, 15 (21.13%) cases died before the 40th week. It is noteworthy that evidence of IVH was detected in the sonographic study on the exact day of their deaths in all these subjects (i.e., 10 newborns: IVH grade 4, two cases: grade 3, one neonate: grade 2, one case: grade 1, and one newborn was without evidences of IVH). Out of 56 neonates who survived until the 40th week, 15 cases (26.8%) demonstrated evidence of IVH at discharge, while 41 neonates (73.2%) were not diagnosed with IVH. Neonates with IVH had a significantly lower GA (29.04±2 weeks vs. 30.44±1.7 weeks; P=0.003) and BW (1075.43±208 kg vs. 1251.6±199.4; P=0.001), as compared to their counterpart who were not affected by IVH.

No significant difference was observed in coagulation factors between the neonates with IVH and those without IVH, except for IL-6 level (P<0.05) (Table1).

Table 1. Mean (SD) of Interleukin -6, platelet count, international normalized ratio, prothrombin time, and partial thromboplastin time in preterm neonates with and without intraventricular hemorrhage

	Neonates without intraventricular hemorrhage	Neonates with intraventricular hemorrhage IVH	P-value
IL-6 (pg/ml), Mean (SD)	91.93 (138)	224 (210)	0.035
PTT (sec), Mean (SD)	61.4 (39)	70.4 (29)	0.4
PT (sec), Mean (SD)	17 (5.1)	29 (29.2)	0.13
PLt (per microliter), Mean (SD)	181320 (59120.4)	178630 (59737.3)	0.9
INR, Mean (SD)	1.82 (1)	2.14 (0.83)	0.23

PTT: Partial thromboplastin time, PT: Prothrombin time, IL-6: Interleukin 6, INR: International normalized ratio, PLt: platelets

Discussion

In the current study, preterm neonates with lower BW were found to be at a higher risk of IVH, and the serum level of IL-6 was observed to be significantly higher in cases with IVH. The possible role of high levels of IL-6 in the occurrence of IVH has been highlighted in some previous studies (11, 15, 16). Nonetheless, it has not been clearly illustrated if the higher level of IL-6 is a

complication of IVH or occurs as a consequence; therefore, further studies are needed in this regard.

In the present study, no significant association was detected between IVH and other coagulation factors. There has been controversy surrounding the role of platelet count in the morbidity of preterm neonates. In a study conducted by Cekmez et al. (2013) on neonates with GA<34 weeks and BW<1500 g, the mean platelet volume was recognized as a major risk factor for the development of IVH in preterm infants (17). In another study, Dani et al. (2011) reported that the mean platelet volume was not associated with the development of IVH (18). In another cohort study, Von Lindern et al. (2011) assessed thrombocytopenia and the risk of IVH in neonates and observed no significant correlation between the incidence of thrombocytopenia and IVH (19).

Lower birth weight is also a critical factor in the short- and long-term prognosis of preterm neonates. In a cohort study, Deulofeut et al. (2007) indicated that newborns with the BW of <1250g were at a higher risk of mortality, greater short- and long-term morbidity, and severe IVH (20). These findings are consistent with the results of the current study. Furthermore, neonates who were diagnosed with IVH had a lower BW in the present study indicating the critical role of prematurity in the development of IVH and its complications.

Conclusion

As evidenced by the obtained results, the altered serum level of IL-6 may be detected in low-birth-weight preterm neonates with IVH. Nonetheless, further studies are needed to investigate the cause or effect of this relationship.

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Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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