Electronic Physician (ISSN: 2008-5842) http://www.ephysician.ir
August 2017, Volume: 9, Issue: 8, Pages: 4946-4951, DOI: http://dx.doi.org/10.19082/4946

Early predictors of neonatal intraventricular hemorrhage

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Type of article: Original

Abstract

Objective: Current study aimed toward the early prediction of neonatal intraventricular hemorrhage (IVH) for better management and prognosis.

Methods: This prospective study was conducted on forty neonates at the Neonatal Intensive Care Unit of Pediatrics and Medical Biochemistry department (Tanta University, Egypt) from July 2016 to June 2017. Cord blood erythropoietin and venous blood Activin A were assayed within the first hour of life. Neonates were divided into 2 groups: Group 1 (with IVH) included twenty neonates who developed IVH proved by transcranial ultrasonography (u/s) and Group 2 (without IVH) included twenty neonates who were admitted to the NICU but did not develop IVH, also proved by transcranial u/s. Data were analyzed using Chi Square and t-test.

Results: Group 1 had a significantly higher cord blood erythropoietin concentration than group 2 (46.75±27.98 mIU/mL vs. 18.82±8.91 mIU/mL), respectively ($p<0.05$). Group 1 had a significantly higher venous blood Activin A concentration than group 2 (3.18±2 ng/L vs. 0.42±0.25 ng/L) with ($p<0.05$).

Conclusion: Cord blood erythropoietin and venous blood Activin A were presumed to be used as early predictors of IVH in neonates with early treatment and better prognosis

Keywords: Neonate, Hemorrhage, Predictors

1. Introduction

Worldwide, intraventricular hemorrhage (IVH) is a serious problem that occurs in the neonatal period especially in premature infants. Its incidence is increased in preterm neonates who suffer from bleeding disorders and neonates exposed to birth trauma, however, it can occur in any neonate, and it may be complicated by mental retardation and/or cerebral palsy (1). Fragility of the cerebral blood vessels, or cerebral blood flow disturbance are the main causes of IVH, that may lead to bulging of the anterior fontanel of neonates, or neonatal seizures especially when the hemorrhage is severe or rapid (2). Instrumental delivery, depressed APGAR score, severe respiratory distress syndrome, air leak syndromes, anoxia, hypercapnia, convulsions, decreased platelet number, patent ductus arteriosus and infection are the main risk factors to the development of IVH (3). The majority of infants with IVH are asymptomatic, and the diagnosis is based on screening cranial ultrasound within the first 48 hours and repeating the scans early at 5 or 6-day intervals until the age of 4 weeks. Moreover, some infants manifest with minimal abnormalities in the level of consciousness, movement, tone, respiration and eye movement, and uncommonly, there is a severe deterioration presenting with disturbed consciousness, irritability, coma, seizures and quadriparesis (4). A glycoprotein hormone that controls erythropoiesis is erythropoietin (EPO). Human EPO is 34 kDa molecular weight; it is produced mainly from the kidney and liver, it also has several functions as; brain's response to the injury to the neuronal system and wound healing. It has been previously proposed as a potential marker in neonates with IVH, asphyxia and meningitis or other central nervous system affection (5). Increased EPO concentrations in cord blood have been identified as markers for fetal hypoxia and brain injury (6). The central nervous system produces Activin

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Received: June 10, 2017, Accepted: July 06, 2017, Published: August 2017
iThenticate screening: July 06, 2017, English editing: July 21, 2017, Quality control: July 23, 2017

A, which enhances the survival of midbrain and hippocampal neurons and decreases ischemic brain injury. Moreover, Activin A induction occurs early after brain injury, so its measurement may provide a potential index of the presence, location and the extent of the brain injury (7). Newborns with hypoxia and cerebral hemorrhage showed elevated Activin A (8).

2. Material and Methods

This study was conducted at the Neonatal Intensive Care Unit of Pediatrics and Medical Biochemistry departments, Faculty of Medicine, Tanta University, Egypt, during the period from July 01, 2016 to June 01, 2017. The study included forty neonates. Written informed consent was obtained from the parents of all subjects of the study. The study was approved by the ethics committee of the Faculty of Medicine, Tanta University. Cranial ultra sound was performed within the first 48 hours and at the age of one week, searching for IVH. Examined neonates were divided into group 1 and group 2 according to whether they developed IVH or not. Group1 (with IVH) included twenty neonates who developed IVH proved by transcranial ultrasonography (u/s). Group 2 (without IVH) included twenty neonates who were admitted to the NICU but did not develop IVH, also proved by transcranial u/s. Inclusion criteria were neonates admitted to the NICU exposed to transcranial u/s, and exclusion criteria were major congenital anomalies, chromosomal abnormalities, infant of diabetic mother, inborn error of metabolism, sepsis and multiple births. All patients were subjected to the following: 1) Full history taking, including mode of delivery, APGAR score at 1 and 5 minutes, gestational age and birth weight, 2) Complete physical examination which included estimation of gestational age using modified Ballard score (9), 3) Cranial u/s was performed within the first 48 hours and at the age of one week to determine the incidence of IVH and its grading (grading based on Volpe's grading system) (10). Blood samples were aseptically collected from the umbilical vein by needle puncture on sterile plain tubes and venous blood samples on sterile EDTA tubes within the first hour after delivery, then immediately centrifuged at 3000×g for 10 minutes at 4 °C to obtain serum and plasma respectively. They were then stored at -20 °C for EPO and Activin A assay, respectively. Activin A and EPO levels were assayed using commercial kits supplied by RayBio® Human DRG International Inc. (11-13), and Human Activin A AbD Serotec – a division of MorphoSys, UK(7, 8) respectively, in accordance with the manufacturer's instructions. B-mode scanning of the neonatal cranial was performed by a radiologist with over ten years of experience in the field of pediatric imaging. Standard coronal and sagittal views of the neonatal brain were acquired through the anterior fontanel with views from the posterior fontanel and through the temporal bone. The scans were done using a 7.5 MHz sector probe using a Siemens X300 ultrasound machine (Siemens Healthcare GmbH, Erlangen, Germany), installed at the NICU in our institution (Figure 1). Regarding the research ethics, we should say that written informed consent from all parents was obtained and the study was approved by the ethics committee of the Faculty of Medicine of Tanta University.

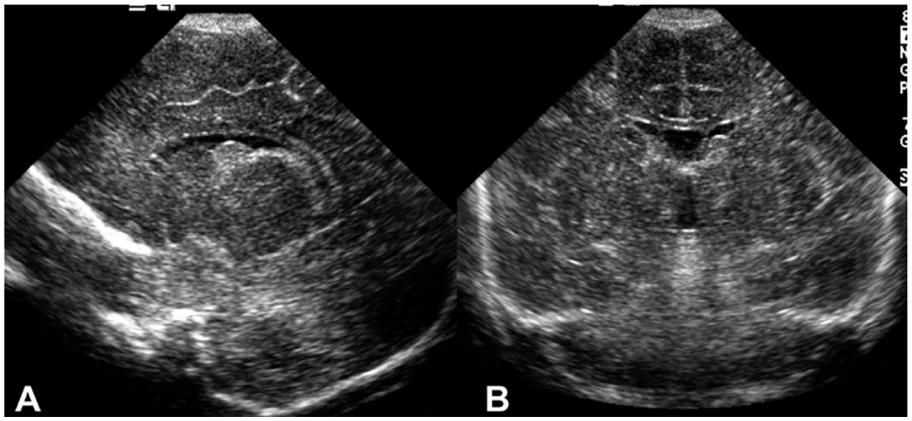

Figure 1. (A) left parasagittal view of the brain of a neonate aged 7 days showing an echogenic area obliterating the caudothalamic groove representing a Grade I intracranial hemorrhage, (B) Coronal view in the same patient showing the previous finding causing indentation of the left lateral ventricle.

3. Results

Table 1 shows that group 1 had significantly lower gestational age than group 2 (p=0.039). It shows that group 1 had significantly lower APGAR scores at 1 and 5 minutes than group 2 (p<0.001). There were no significant differences between either group as regard to birth weight, sex and mode of delivery. Our findings showed that group 1 had a significantly higher cord blood EPO concentration (46.75±27.98 mIU/mL) than group 2 (18.82±8.91 mIU/mL), respectively (p=0.001) and showed that group 1 had a significantly higher plasma Activin A concentration (3.18±2

ng/L) than group 2 (0.42±0.25 ng/L) respectively (p<0.001) (Table 2). Also, there was a positive relation between cord blood EPO concentration and IVH grading (p=0.001) and there was a positive relation between plasma Activin A (ng/l) and IVH grading. The higher IVH grade, the higher plasma Activin A concentration (p=0.002) (Table 3). Cord blood EPO cut-off value of IVH was ≤26.8mIU/mL; the sensitivity of cord blood EPO as a diagnostic predictor of IVH was 81.8%, and specificity was 87.5%. Positive predictive value, negative predictive value, and accuracy were 94.7%, 63.6%, and 83% respectively and in the other hand it showed that plasma Activin A cutoff value was ≤0.8 ng/L; the sensitivity of plasma Activin A as a diagnostic predictor of IVH was 89.3%, specificity was 100%, positive predictive value was 100%, negative predictive value was 80.0% and accuracy was 88.5% (Table 4). Finally, there was significant positive correlation between cord blood EPO and plasma Activin-A as predictors of IVH (p=0.001) (Table 5, Figure 2).

Table 1. Demographic data of group 1 and group 2

Variables		Group 1	Group 2	p-value
Sex, n (%)	Male	8 (40)	10 (50)	0.752
	Female	12 (60)	10 (50)	
Mode of delivery, n (%)	CS	6 (30)	11 (55)	0.151
	NVD	14 (70)	9 (45)	
Gestational age (weeks)	Range	28.0-37.0	30.0-39.0	0.039*
	Mean ± SD	33.13±3.14	35.32±3.32	
Birth weight (Kg)	Range	0.9 -2.6	1.2 -2.9	0.136
	Mean ± SD	1.81±0.68	2.14±0.69	
APGAR 1	Range	3.0-7.0	5.0-8.0	<0.001*
	Mean ± SD	4.75±1.12	7.55±0.76	
APGAR 5	Range	4.0-8.0	7.0-8.0	<0.001*
	Mean ± SD	6.45±1.05	8.50±0.51	

*Significant (p≤0.05); NVD: Normal vaginal delivery, APGAR 1: Appearance pulse grimace activity respiration at one minute, APGAR 5: Appearance pulse grimace activity respiration at five minutes.

Table 2. Cord blood erythropoietin (mIU/mL) and plasma Activin A (ng/L) in group I and group II

Variable		Group I (n=20)	Group II (n=20)	t-value	p-value
Cord blood erythropoietin (mIU/mL)	Range	18.8 - 104.6	9.0 - 39.4	4.253	0.001*
	Mean ± SD	46.75 ± 27.98	18.82 ± 8.91		
Plasma Activin A (ng/L)	Range	0.76 – 5.18	0.13- 0.77	7.582	<0.001*
	Mean ± SD	3.18 ± 2	0.42 ± 0.25		

*Significant (P≤0.05)

Table 3. Relation between cord blood erythropoietin and plasma Activin A with the grading of IVH

IVH grade		Grade I (n=12)	Grade III (n=8)	t-value	p-value
Cord blood erythropoietin (mIU/mL)	Range	18.8-29.4	27-104.6	4.612	0.001*
.	Mean ± SD	25.1±7.5	64.5±37.5	.	
Plasma Activin A (ng/L)	Range	0.76-2.76	2.36-5.18	3.713	0.002*
	Mean ± SD	1.76±1	3.70±1.34		

*Significant (p≤0.05), IVH:intraventricular hemorrhage

Table 4. ROC curve between group I and group II as regard to cord blood erythropoietin (mIU/mL) and plasma Activin A (ng/L)

Variable	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
Cord blood erythropoietin (mIU/mL)	≤ 26.8	81.8%	87.5%	94.7%	63.6%	83%
Plasma Activin A (ng/L)	≤ 0.8	89.3%	100%	100%	80%	88.5%

Table 5. Correlation between erythropoietin and activin-A as predictors of IVH

Variable	Cord blood erythropoietin (mIU/mL)	
	r.	p
Plasma Activin A (ng/L)	0.754	0.001*

*Significant (p≤0.05)

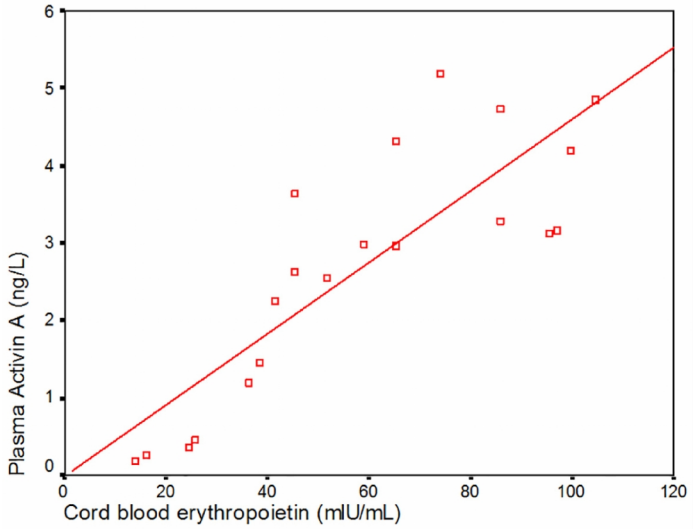

Figure 2. Correlation between erythropoietin and activin-A as predictors of IVH

4. Discussion

IVH is a main cause of brain affection in neonates. Its incidence increases with decreasing gestational age and birth weight (14). Maternal EPO does not cross the placenta in pregnancy meanwhile, its elevations in cord blood levels are related to fetal production and by primary production sites; the kidney and fetal liver (15). The results of the present study showed that group 1 had significantly lower APGAR scores at 1 and 5 minutes than group 2, and this comes in agreement with the study of Riskin A., et al. (16) and Badiee Z. (17). The results of the present study showed that there is no statistical significant difference between group 1 and group 2 as regard to birth weight. This comes in agreement with Sarkar S. et al. (3) and Badiee Z., (17) who reported that there was no association between IVH and low birth weight preterm neonates, while this contradicts the results of Vura lM et al. (18) and Kim KR et al., (19) who reported that birth weight was a statistically meaningful risk factor for IVH. In the present study, group 1 had a significantly higher cord blood erythropoietin concentration than group 2, which is in agreement with the study of Bhandari V et al., (20) who analyzed levels of umbilical cord EPO in 116 newborns and stated that elevated EPO levels could be a predictor of IVH. Previously, EPO had been used as a potential marker for central nervous system affection in neonates with asphyxia and IVH (5). The present study showed positive relation between cord blood erythropoietin concentration and IVH grading, which is in agreement with the study of Bhandari V. et al. (20). Moreover, Korzeniewski SJ. et al. (21) found that neonates with increased EPO had significantly increased risks of ventriculomegaly, cerebral palsy and microcephaly, and decreased the mental and psychomotor development. Elmahdy. et al. (22) used a human recombinant EPO with neonates with HIE of which the disease IVH is one of its complications. In the present study, plasma Activin A concentration in the 1st day of life was significantly higher in group 1 when compared to group 2. This comes in agreement with the study of Florio et al., (23) who also found that the plasma Activin A concentration is significantly higher in the group of neonates who developed intraventricular hemorrhage compared to those who did not develop IVH ($p < 0.001$). Florio et al. (23) demonstrated that Activin A at the cutoff of 0.8 µg/L, achieved the best accuracy for prediction of IVH in preterm newborns, showing sensitivity of 83.3% and specificity of 100%. In conclusion, cord blood EPO and venous blood Activin A levels increase significantly in newborns with IVH and so they could be early predictors of neonatal IVH.

Acknowledgments:

The authors acknowledge Elshahawy AZ who is a lecturer in Radiology department for her assistance in this research. The source of funding for the study was the personal fund from authors.

Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

Elfarargy MS participated in the idea of the study and the sequence alignment, and drafted the manuscript and participated in the design of the study. Soliman NA participated in the sequence alignment, drafted the manuscript,

participated in the design of the study and performed the statistical analysis. Eltomy MA did the cranial sonar for neonates, participated in the sequence alignment, drafted the manuscript and participated in the design of the study. All authors read and approved the final manuscript.

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