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Original article

Prediction of Neonatal hyperbilirubinemia by The Cord Blood Alkaline Phosphatase

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ABSTRACT

Background: Owing to early discharge of neonates from the hospital, the readmission rate has been increased. Therefore, early detection of jaundice and prompt measures are important. Measurements of bilirubin and alkaline phosphatase levels in cord blood have been used for this function.

The aim of the work: To assess the cord blood alkaline phosphatase value in predicting neonatal jaundice.

Patients and Methods: This study carried out during the period from August 2019 to January 2020 in pediatric department [Al-Azher University Hospital in Damietta]. This study included a total of 101 term infants with gestational age between 37 and 42 weeks, weighing more than 2500g born to healthy mothers. We performed an assessment of the complete medical history [maternal history and neonatal history]. Cord blood samples were collected for measurement of alkaline phosphatase. Neonates were followed-up for the emergence of jaundice. Infants with clinical jaundice were recalled and serum bilirubin level was measured. Significant indirect neonatal hyperbilirubinemia was considered.

Results: The study showed that patients with neonatal jaundice had statistically significant higher reticulocyte count, alkaline phosphate level and total bilirubin than patients without neonatal jaundice. However, the study shows the best cut-off points of regarding ALP to predict neonatal jaundice in neonates. A value of 200 or more IU/L was the best cut-off point to predict occurrence with a sensitivity of 98.3%, a specificity of 97.6%.

Conclusion: Increased alkaline phosphatase level in cord blood act as an indicator to neonatal jaundice, and may be used as a marker for early diagnosis.

Keywords: Alkaline Phosphatase; Enzyme; Bilirubin; Neonate; Hyperbilirubinemia.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Neonatal jaundice [hyperbilirubinemia] is the commonest medical condition in the newborn infants. Early discharge is recommended but hospital readmission is higher and represented a problem among clinicians, as it represented a risk of delayed identification and recognition of neonatal jaundice [1].

In normal healthy conditions, a slight hyper-bilirubinemia is present as normal serum bilirubin levels range between 0.2 to 1.2 mg/dL. The human neonates could develop mild to severe jaundice with bilirubin levels of 5-15mg/dL. Mild elevation is usually physiological and resolves spontaneously with few weeks after delivery. Severe increase of serum bilirubin permits the passage of bilirubin through blood brain barrier, leading to irreversible brain destruction, known as kernicterus [2].

Higher bilirubin concentrations in neonates are mainly due to the inadequate function of bilirubin-metabolizing enzymes. To prevent kernicterus, the human neonates commonly treated by phototherapy, which removes bilirubin. Bilirubin had cytotoxicity to other different cells, besides neurotoxicity [3,4].

The reported kernicterus incidence is 1 in 50,000-100,000, and usually developed with high with total serum bilirubin levels of >30 mg/dL. To prevent kernicterus, phototherapy is recommended [5].

Acute bilirubin encephalopathy [ABE] remains an important etiology of morbidity and mortality all over the world, especially in countries of low-middle-income, as it accounts for up to 15% of neonatal deaths. ABE is a significant cause of cerebral palsy, developmental delay and hearing impairment. Kernicterus refers to the yellow staining of the basal ganglia and cerebellum [6].

Due to early hospital discharge of neonates, the readmission rate is higher. Thus, early prediction and diagnosis of neonatal hyperbilirubinemia and timely interventions are crucial. Several techniques have been used to determine the risk of neonatal jaundice as the measurement of cord bilirubin level itself have been used [7].

Alakline phosphatase [ALP] is an intracellular enzyme found in almost all cells including red blood cells. It is found in these cells abundantly and is secreted to plasma after destruction of the cells. Therefore, it had been hypothesized that it may be used as a marker of hemolysis and evaluation of significant neonatal hyperbilirubinemia [8].

Previous trials confirmed the involvement of ALPs in different cellular events [e.g., regulation of cell growth, protein phosphorylation, apoptosis and cellular migration during intrauterine development] [9].

ALP is distinguished for four isozymes according to the site of tissue expression [e.g., intestinal, placental, germ cell and tissue nonspecific] [10-12].

Cord blood ALP level six hours after delivery could be used as a marker for determining hemolysis and neonatal jaundice [13].

THE AIM OF THE WORK

This study aimed to examine the value of the cord blood alkaline phosphatase levels for predicting neonatal jaundice.

PATIENTS AND METHODS

This was a prospective research carried out from August 2019 to January 2020 in the pediatric department of Al-Azhar University Hospital [New Damietta]. This study included 101 neonates with gestational age between 37 and 42 weeks [45 males, 56 females], weighing more than 2500g born to healthy mothers admitted. The thesis was accepted by the Faculty of Medicine's ethical review committee at Al Azhar University. The work was carried out for human studies in agreement with the World Medical Association's Code of Ethics [Helsinki Declaration].

Inclusion criteria: Healthy newborn infants born to healthy mothers. **Exclusion criteria**: Infants who were born to mothers diagnosed with eclampsia, diabetes, bone, kidney and liver diseases. Preterm infants. Full-term infants with congenital anomalies or any other diseases.

All patients included were subjected to taking complete medical history [maternal history and neonatal history], clinical examination including [Anthropometric measurements. Assessment of

gestational age by Ballard. Apgar score. Detailed chest, cardiovascular, abdominal and neurological examination. Phototherapy or exchange transfusion were recorded.

Analytic method: Two milliliter of cord venous blood was taken after birth and sent for determination of ALP level, Serum ALP was measured by using kinetic, photometric, optimized DCGK method. We measured direct bilirubin by colorimetric method. Cord reticulocytic count examined manually after staining with brilliant-cresyl blue under oil emersion lens. Blood groups [ABO, Rh] were determined for newborns and mothers. Follow up was done by monitoring the emergence of clinical observation by parents or physicians up to 10 days after birth. Infants with clinical jaundice were be recalled and serum bilirubin level was measured. Significant indirect neonatal hyper-bilirubinemia was considered according to American Academy of Pediatrics Clinical Practice Guidelines in neonates who developed neonatal hyperbilirubinemia needing intervention in the form of phototherapy and/or exchange transfusion.

Statistical Analysis: The statistical analysis was performed using IBM SPSS Statistics® 22 for Windows 8 operating system. Student T-test was used to analyze the continuous variables between the two studied groups and Chi-test for categorical and dichotomous variables. One-way analysis of variance [ANOVA] with repeated measures were used to analyze the continuous variables among the follow-up points within the same group. The level of statistical significance was significant when p value <0.05.

RESULTS

This study showed that baseline characteristics of the studied sample. It was found that the mean gestational age of patients was 37.8 ± 0.78 weeks with mean birth weight 3.2 ± 0.38 kg. More than half of the patients had positive consanguinity and history of previous siblings with jaundice [53.5%] [Table 1].

Moreover, patients with neonatal jaundice were found to have a significantly higher Apgar score than patients without neonatal jaundice [p=0.008]. Finally, about 57% of the participants had developed neonatal jaundice.

This study showed that blood group B+, AB+ and A+ were the most prevalent blood groups among maternal blood grouping with frequencies 39.6%, 23.8%, and 19.8%, respectively. Regarding fetal blood grouping, blood group B+, A+ and O+ were the most prevalent blood groups among maternal blood grouping with frequencies 36.6 %, 28.7 %, and 21.8%, respectively [Table 2].

There was no statistically significant association between Neonatal jaundice and blood groups of mothers or neonates.

This study showed laboratory measures in both groups. It was found that patients with neonatal jaundice had statistically significant higher reticulocyte count, alkaline phosphate level and total bilirubin than patients without neonatal jaundice [p<0.001] [Table 3].

There was found that patients with neonatal jaundice who received IVIG had statistically significant higher alkaline phosphate level than patients who did not receive IVIG [p<0.001]. Moreover, patients with neonatal jaundice who had exchange transfusion had statistically significant higher alkaline phosphate level than patients who did not have exchange transfusion [p=0.014] [Table 4].

There was receiver operating characteristic curves for alkaline phosphate [ALP] [Table 5].

ALP showed a good discriminative ability where the area under the curve for ALP was 0.966 [95% CI: 0.917 – 1.0] [p<0.001].

This study showed the best cut-off points of regarding ALP to predict neonatal jaundice in neonates. A value of 200 or more IU/L was the best cut-off point to predict occurrence with a sensitivity of 98.3%, a specificity of 97.6% [Table 6].

Logistic regression analysis was used to assess predictors of neonatal jaundice among term infants [Table 7].

Table [1]: Baseline characteristics of the studied sample [n=101]

Variables		All patients [n=101]	Neonatal jaundice		p-value
			Absent [n=43]	Present [n=58]	
Gestational age [weeks]	mean ± SD	37.8 ± 0.78	37.84 ± 0.72	37.79 ± 0.83	0.69[b]
	median [range]	38 [36 – 40]	38 [37 – 39]	38 [36 – 40]	
Gender, n [%]	Male	45 [44.6]	22 [51.2]	23 [39.7]	0.25±
	Female	56 [55.4]	21 [48.8]	35 [60.3]	
Birth weight [kg]	mean ± SD	3.2 ± 0.38	3.28 ± 0.32	3.17 ± 0.42	0.16[a]
	median [range]	3.2 [2 – 4]	3.2 [2.5 – 3.9]	3.1 [2 – 4]	
Consanguinity, n [%]	Negative	47 [46.5]	19 [44.2]	28 [48.3]	0.68±
	Positive	54 [53.5]	24 [55.8]	30 [51.7]	
Mode of delivery, n [%]	Vaginal	49 [48.5]	21 [48.8]	28 [48.3]	0.95±
	CS	52 [51.5]	22 [51.2]	30 [51.7]	
Apgar score	mean ± SD	7.71 ±0.91	8.07 ±0.91	7.45 ±1.3	**0.008***
	Median [range]	8 [4 – 10]	8 [6 – 10]	7 [4 – 10]	
History of previous siblings with jaundice, n [%]	Absent	47 [46.5]	20 [46.5]	27 [46.6]	0.99±
	Present	54 [53.5]	23 [53.5]	31 [53.4]	
Antenatal care, n [%]	Absent	48 [47.5]	23 [53.5]	25 [43.1]	0.30±
	Present	53 [52.5]	20 [46.5]	33 [56.9]	

[a] values are based on Independent t-test. Statistical significance at P <0.05; [b] values are based on Man-Whitney test. Statistical significance at P <0.05; ± values are based on chi-square test. Statistical significance at P <0.05

Table [2]: Comparison of maternal and neonatal blood grouping between participants with and without neonatal jaundice

Variables		All patients [n=101]	Neonatal jaundice		p-value
			Absent [n=43]	Present [n=58]	
Maternal blood grouping	A+	20 [19.8]	11 [25.6%]	9 [15.5%]	0.37
	B+	40 [39.6]	19 [44.2%]	21 [36.2%]	
	AB+	24 [23.8]	10 [23.3]	14 [24.1%]	
	O+	11 [10.9]	3 [7]	8 [13.8%]	
	A^-	1 [1]	0 [0]	1 [1.7%]	
	B^-	2 [2]	0 [0]	2 [3.4%]	
	O^-	3 [3]	0 [0]	3 [5.2%]	
Fetal blood grouping	A+	29 [28.7]	11 [25.6%]	9 [15.5%]	0.30
	B+	37 [36.6]	15 [34.9]	22 [37.9]	
	AB+	10 [9.9]	3 [7]	7 [12.1]	
	O+	22 [21.8]	13 [30.2]	9 [15.5]	
	A^-	1 [1]	1 [2.3]	0 [0]	
	B^-	2 [2]	0 [0]	2	

±values are based on chi-square test. Statistical significance at P <0.05
*values are based on fisher exact test. Statistical significance at P <0.05

Table [3]: Comparison of maternal and neonatal blood grouping between participants with and without neonatal jaundice

Variables		All patients [n=101]	Neonatal jaundice		p-value
			Absent [n=43]	Present [n=58]	
Reticular count	mean±SD	6.47 ± 6.1	1.91± 0.94	9.84± 6.05	**<0.001***
	median [range]	4 [0 – 24]	2 [0 – 4]	8.5 [2 – 24]	
ALP [u/l]	mean±SD	308.5 ± 182.1	176.19 ± 171.2	406.6 ± 116.3	**<0.001***
	median [range]	290 [107 – 1258]	145 [107 – 1258]	401 [130 – 590]	
Total bilirubin [mg/ dl]	mean±SD	7.42 ± 4.66	3.16 ± 0.89	10.57± 3.7	**<0.001***
	median [range]	6 [1 – 20]	3 [1 – 5]	10 [4 – 20]	
Direct bilirubin [mg/ dl]	mean±SD	0.55 ± 0.35	0.479 ± 0.28	0.602 ± 0.39	0.11
	median [range]	0.55 [0.1 – 2]	0.4 [0.1 – 1]	0.5 [0.1 – 2]	

Values are based on Man-Whitney test. Statistical significance at P <0.05

Table [4]: Relationship between ALP level and different management strategies [n=58]

	Variables	n [%]	ALP	test	p-value
Phototherapy	Present	58 [100]	406.6 ± 116.3	-	-
	Absent	0 [0]	-		
IVIG	Absent	16 [27.6]	374.9 ± 110.2	141.5	<0.001*
	Present	42 [72.4]	489.6 ± 89.5		
Exchange transfusion	Absent	4 [6.9]	396.7 ± 114.2	31.5	0.014*
	Present	54 [93.1]	539.2 ± 45.5		

[a] values are based on Independent *t*-test. Statistical significance at P <0.05

[b] values are based on Man-Whitney test. Statistical significance at P <0.05

Table [5]. Area under the curve for alkaline phosphatase as a predictor of neonatal jaundice

Variable	Area	Stand. error	p-value	95% CI
ALP	0.966	0.025	<0.001*	0.917 – 1.0

Table [6]: Sensitivity, and specificity at different cut-off levels of alkaline phosphatase

Cut-off points	Sensitivity	Specificity
197.5	98.3%	95.3%
200	**98.3%**	**97.6%**
203	96.6%	97.6%

* PPV, positive predictive value; NPV, negative predictive value.

Table [7]: Logistic regression analysis of neonatal jaundice among term infant

Variables	*β* [SE]		OR [95% CI]	p-value
Constant	-2.368	4.390	-	0.59
Total bilirubin	2.365	1.175	4.321 [0.715 – 26.093]	**0.044***
ALP	0.007	0.002	1.007 [1.003 – 1.011]	**0.001***
Reticulocytes	1.66	0.462	5.259 [2.127 – 13.002]	**<0.001***
APGAR	-0.625	0.512	0.535 [0.196 – 1.459]	0.222

* Statistical significance < 0.05.

DISCUSSION

Hyperbilirubinemia and its potential complications among newborn [e.g., encephalopathy, kernicterus and subsequent permanent disability] has grabbed attention of many neonatologists as the most common etiology of the hospital readmissions in the neonatal period [14]. Such complications have been missed due to early discharge of potentially healthy term infants [14].

Accordingly, several measurements were investigated to predict neonatal jaundice among term infants, such as bilirubin level Sgro *et al*. [14] and alpha fetoprotein in cord blood [15].

Fernandez *et al*. found that alkaline phosphatase [ALP] is a good marker for survival in a neonatal intensive care unit [NICU], where ALP was significantly higher in survivors compared with non-survivors [P < 0.05]. Furthermore, the logistic regression model that included ALP was able to correctly predict mortality in 84 % of cases [16].

Nevertheless, a very limited number of studies had examined ALP in cord blood to identify early neonatal hyperbilirubinemia.

ALP was firstly examined in cord serum of neonates by Hilderbrand *et al*. they compared ALP level in term, preterm, and physiologically jaundiced neonates. It was found that there is no statistically significant difference in alkaline phosphatase levels between the term and preterm cord blood [17].

It was not until 2011 when Nalbantoglu *et al*. had a different assumption about ALP in neonates. They presumed that ALP can be used as an earlier indicator to RBCs hemolysis in newborn depending on the fact that ALP is present in RBCs and is secreted to plasma upon their hemolysis. Interestingly, Nalbantoglu *et al*. noticed that serum ALP levels rose significantly with total bilirubin level, that can suggest its use as an early diagnosis and prediction of neonatal jaundice [18]. Accordingly, these latter findings derived us to further investigate correlation between cord blood ALP and early onset neonatal hyperbilirubinemia [18].

In the present study we had 101 full-term infants

with gestational age ranging between 37 and 40 weeks [mean 37.8±0.78 weeks] and mean birth weight 3.2± 0.38 kg born to healthy mothers.

About 57% of the participants had developed neonatal jaundice which is comparable to what Brits *et al.* reported [55.2% [n=96]] [19] and slightly higher than that reported by Ahmadpour-Kacho, et al. [20] [47% [n=102]]. This percentage can increase up to 84% in term newborns according to Bhutani et al [19].

In our study, we first aimed at comparing the level of cord blood ALP in both term infants with neonatal jaundice and their normal counterparts. We found that patients with neonatal jaundice had statistically significant higher ALP [406.6 ± 116.3 IU/L] than patients without neonatal jaundice [176.19 ± 171.2 IU/L] [p<0.001], a finding that is consistent with the previous articles.

For example, Nalbantoglu *et al*. [18] reported that ALP levels were significantly higher in babies requiring therapy [247.01± 1 67.44 IU/L] compared to those who do not [154.25± 56.07 IU/L] [p<0.001].

A similar report was reached by Ahmad pour-Kacho *et al*. [20] who examined the validity of cord blood alkaline phosphatase level for predicting neonatal hyperbilirubinemia, found that the mean ALP level was 367.80±73.82 IU/L in the severely jaundiced group and 309.09±82.51 IU/L in the non-jaundiced group [P = 0.040].

Additionally, when comparing ALP levels within hyperbilirubinemia subgroups, it was found that patients with neonatal jaundice who received IVIG and exchange transfusion had statistically significant higher alkaline phosphate level than patients who did not received treatment [p<0.001 and 0.014], respectively. This finding is consistent with Nalbantoglu *et al*. [18] who found that ALP levels were specifically higher in patients requiring treatment, either with phototherapy or exchange transfusion, and those who received IVIG [P <0.0001].

On the other hand, we found that there was no statistically significant association between neonatal jaundice and the types of blood groups of mothers or neonates [p=0.37] and [p=0.30]. A similar finding was reached by Nalbantoglu *et al*. that found no significant difference between the groups in terms of the Rh incompatibility [p=0.220] [18].

Meanwhile, our patients with neonatal jaundice had a significantly higher Apgar score at first minute [8.07 ±0.91] than patients without neonatal jaundice [7.45 ±1.3] [p=0.008]. Contrary to our findings, Nalbantoglu *et al*. [18] found no statistically significant difference between the groups in terms of Apgar 1 min [p=0.89] or Apgar 5 min [p=1.00]. Therefore, ALP appears to be good potential prediction of early neonatal jaundice

A previous study had recorded cord blood alkaline phosphatase with different levels. Fenton *et al*. found that, the mean level of cord blood alkaline phosphatase 159±49 IU/L [21]. However, Iranian studies showed that, the mean levels of cord blood alkaline phosphatase were 325.24 ± 85.03 IU/L by El-Amin *et al*. [22] and 314.34 ± 122.42 IU/L by DeMauro *et al.* [23].

Our results were broadly in line with that Iranian values in which the average level of cord blood alkaline phosphatase was 308.5±182.1 IU/L. This can be explained by the fact that Middle East populations had average levels of cord blood alkaline phosphatase that is higher than other populations. Moreover, ALP can show significant increase in newborn due to early ingestion of colostrum that is very common in Middle East countries [24].

Another essential objective of our study was to validate the efficacy of cord blood alkaline phosphatase as a potential predictor for neonatal jaundice for term infants. Nalbantoglu *et al*. interestingly noticed that ALP levels rose significantly with rising total bilirubin level, for which he suggested that ALP levels could be a potential predictor for hemolysis and hyperbilirubinemia after six hours from delivery [18].

Ahmadpour-Kacho M *et al*. [20] was the first to examine the validity of cord blood alkaline phosphatase level as an indicator to predict neonatal hyperbilirubinemia using receiver operating characteristic curve. They found that a cord blood alkaline phosphatase value of 314 IU/L or more was the most appropriate cutoff value that perfectly anticipates neonatal jaundice, with 80% sensitivity and 63% specificity [19].

Contrary to the findings of the previous study, we

identified a lower cutoff point, 200 or more IU/L, with higher sensitivity and specificity, 98.3% and 97.6%, respectively.

In line with Ahmadpour-Kacho *et al*. [20] who examined the same population group, healthy term infants with gestational age between 37 and 42 weeks, weighing more than 2500 g born to healthy mothers. However, this difference in cutoff point could be explained by the different time at which the cord blood sample was drawn in each study. In our study, ALP showed an excellent discriminative ability where the area under the curve for ALP was 0.966. A value that is better than what the previous two studies have reported [less than 0.700 Nalbantoğlu *et al*. [18] and 0.73 Brits *et al*. [19]].

End-tidal carbon monoxide has been observed as a good predictive tool for neonatal non-hemolytic hyperbilirubinemia with sensitivity and specificity of 86% and 80%, respectively at the cut-off level of 1.8 microL/L [p.p.m] [25]. However, ALP analysis is more available and easy to be measured than end-tidal carbon monoxide that needs breath carbon monoxide analyzer which is expensive and less accessible test.

A further novel finding in our study is that, the value of prediction was identified by a logistic regression analysis that found that for 100 IU/l increase in the ALP, the odds of neonatal jaundice occurrence in a term infant increases by 70% [OR=1.007, 95% CI [1.003 – 1.011] [p=0.001], along with bilirubin [OR=4.321, 95% CI [0.715 – 26.093] [p=0.044]. Our method of detecting ALP levels depends on cord blood just after birth which is more convenient than drawing a venous blood sampling from newborn to obtain the first day serum bilirubin Alpay *et al*. [26] or sixth hour serum bilirubin [27]. A further novel finding is that our study provides a robust regression analysis about prediction of neonatal jaundice in term infant providing that ALP is a strong predictor of neonatal jaundice beside total bilirubin. A finding that previous articles could not confirm [18].

Conclusion: This study demonstrated the clinical usefulness of measuring cord blood ALP level along with bilirubin in full term neonates within six hours from delivery before their early discharge and that ALP level was an independent predictor of hyperbilirubinemia in potentially healthy newborn. However, a multi-centric study is highly required to obtain high level of evidence regarding routine use of ALP after any delivery as permission for either further observation or home discharge.

Financial and Non-Financial Relationships and Activities of Interest

None

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