Utility of Cord Blood Alkaline Phosphatase Enzyme as a Predictor of Significant Neonatal Jaundice in Well Term Infants

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Abstract: Background: Early diagnosis and appropriate management of neonatal hyperbilirubinemia are very important in order to prevent bilirubin encephalopathy and kernicterus. Several diagnostic tests may be used for this purpose, including bilirubin level itself.

The aim: of the present study was to investigate whether serum alkaline phosphatase (ALP), which is an intracellular enzyme found abundantly in red blood cells, could be used for the early prediction of hyperbilirubinemia in newborns.

Methods: A total of 200 healthy full term babies with apparently healthy mothers were evaluated and investigated for ALP assay and follow up the level of serum billirubin.

Results: ALP levels were significantly higher in babies requiring therapy such as phototherapy or exchange transfusion which The best cut off point for serum ALP to predict neonates needed treatment of NJ was found > 315 with sensitivity 84.2% and specificity of 84.48% and area under curve 88.8 %.

Conclusion: cord ALP levels may be a significant predictor of developing hyperbilirubinemia requiring treatment.

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1. Introduction

Jaundice is the yellow discoloration of skin or the eyes due to an increase in the bile pigment bilirubin in the blood. Neonatal jaundice is such a common problem in newborns that 60% of term newborns and 80% of preterm infants succumb to the condition, which is caused by an increase in bilirubin level [1]. Neonatal jaundice or hyperbilirubin is mostly cured (20% cases) though it can still prove hazardous and need medical intervention [4]. Appropriate treatment with phototherapy and/or exchange transfusion are effective in controlling excessive bilirubin levels in the affected infants [5]. Otherwise, Bilirubin may be entered the brain as free (unbound) bilirubin or as bilirubin bound to albumin in the presence of a disrupted blood-brain barrier in conditions like severe metabolic acidosis, asphyxia and prematurity [6]. The objective tests for estimating and monitoring the degree of jaundice are transcutaneous bilirubin (TCB) and/or serum bilirubin levels. TCB is a non-invasive, portable screening tool ideally used to determine the need for the more accurate serum bilirubin which requires a venous or capillary blood sample [7]. American Academic of Pediatrics (2004) recommends that newborn discharged within 48 hours should have a follow-up visit within 48 to 72 hours for any significant jaundice and other problems [9]. Several methods have been used to determine risk of neonatal hyperbilirubinemia. The measurement of bilirubin level [10] and alpha fetoprotein [11] in cord blood have been used for this purpose. For the first time Aysin Nalbantoglu et al (2011). used alkaline phosphatase (ALP) level 6 hours after birth as a marker for determining hemolysis and hyperbilirubinemia [12] Alkaline phosphatase is a hydrolase enzyme and responsible for removing phosphate from many types of molecules [13]. Alkaline phosphatase is found in almost all body cells, including red blood cells, bones, intestines, and kidneys. In pregnant women, ALP is made in the placenta [12].

Aim of the work

Due to early discharge of infants from the hospital, readmission has been increased. Therefore, early diagnosis of jaundice and timely actions are necessary.

Therefore this study will evaluate the serum alkaline phosphatase (ALP) level as a marker for early detection of neonatal jaundice.

Study site

Study will be carried out at Al-Hussein University hospital, Kafr El Sheikh general hospital

and Baltim central hospital (delivery rooms and neonatal intensive care units).

2. Patients and Methods

A prospective study will be performed on 200 sequentially born healthy term (gestational age ≥ 37 weeks) of either gender, delivered vaginally or cesarean section, with Apgar score ≥7, to apparently healthy mothers.

All infants will be subjected to the following after taking the informed consent of their parents.

I. Complete history taking.

II. Complete clinical examination.

III. Laboratory investigations as serum alkaline phosphatase.

Inclusion criteria

1- Full term (gestational age ≥37 weeks).

2- Appropriate for gestational age (AGA).

3- Apparently healthy mothers.

4- Apgar score of more than 7 at first and fifth minute of life.

Exclusion criteria

1- Infants of gestational age less than 37 weeks.

2- Low Apgar score of less than 7 at first and fifth minute after birth.

3- Infants of maternal diseased such as; eclampsia –diabetes – bone, kidney and liver diseases.

4- Infants with apparent significant congenital malformations.

5- Infants with perinatal asphyxia.

6- Infants with cephalhematoma or contusions.

Five mL umbilical cord blood will be taken after birth for determination of alkaline phosphatase (ALP) level for all infants In the study.

After history and clinical examination, all the study population will be followed up daily up to seven days after birth.

So 200 infants will be monitored for the emergence of clinical jaundice based on clinical observation by parents or physicians.

Infants with clinical jaundice will be subjected to measure serum bilirubin level and will receive the proper treatment based on American Academic of Pediatrics protocols (2004).

All the study population will be **classified into three groups**:

A- Infants without emergence of jaundice.

B- Infants with emergence of jaundice but without need for treatment.

C- Infants with emergence of jaundice with indication for treatment according to American Academic of Pediatrics protocols (2004).

The last group (group C) will be subjected to further clinical evaluation and laboratory investigations, to know the underlying causes of hyperbilirubinemia including:-

–CBC (complete blood count).

– Reticulocyte count.

–Maternal and infants blood grouping and RH (Rhesus factor).

–Blood film.

–G6BD (Glucose-6-phosphate dehydrogenase) assay.

– Combs test.

–CRP (C-reactive protein).

Result

Table 1. Comparison between three groups as regards sex

Sex	**Group 1 No. = 64**	**Group 2 No. = 117**	**Group 3 No. = 19**	**Chi-square test**	
				X^2	**P-value**
Female	28 (43.8%)	55 (47.0%)	6 (31.6%)	1.597	0.450
Male	36 (56.3%)	62 (53.0%)	13 (68.4%)		

Table 2. Comparison between three groups as regards mode of delivery

Type of delivery	**Group 1 No. = 64**	**Group 2 No. = 117**	**Group 3 No. = 19**	**Chi-square test**	
				X^2	**P-value**
CS	63 (98.4%)	112 (95.7%)	19 (100.0%)	1.718	0.424
NVD	1 (1.6%)	5 (4.3%)	0 (0.0%)		

Table 3. Comparison between three groups as regards weight.

		Group 1 No. = 64	**Group 2 No. = 117**	**Group 3 No. = 19**	**One Way ANOVA**	
					F	**P-value**
Weight	Mean±SD	3.05 ± 0.47	3.15 ± 0.48	3.13 ± 0.42	0.982	0.376
	Range	2.1 – 4.3	2.3 – 4.3	2.2 – 4.0		

A total of 200 cases were followed-up consisted of 111 (55.5%) males and 89 (44.5%) females (table 1). seventy eight (97%) infants were born by cesarean section and (3%) only by vaginal delivery (table 2). Apgar scores were normal (9 - 10) at birth in all cases. The mean gestational age was 38.7 weeks and the mean birth weight 3100 grams (table 3).

Neonates classified into 3 groups according to total serum bilirubin, In group I bilirubin level ranged between 2 and 5 (with mean ± SD 3.75 ±.99), in group II bilirubin value ranged between 6 and 14 (with mean ± SD 10.22 ± 2.4), in group III bilirubin value ranged between 15 and 27 (with mean ± SD 16.84 ± 2.89) (table 4).

And In group I ALP value ranged between 108 and 383 (with mean ± SD 205.7 ± 53.49), in group II ALP value ranged between 138 and 440 (with mean ± SD 156.45 ± 62.85), in group III ALP value ranged between 210 and 420 (with mean ± SD 353.11 ± 48.48) (table 5). The best cut off point for serum alkaline phosphatase to predict neonates needed treatment of NJ was found > 315 with sensitivity 84.2% and specificity of 84.48% and area under curve 88.8% (table 6) (figure 1). 20% of all cases in the study with siblings with neonatal jaundice.

The distribution of blood groups of neonates in the third group showing that neonates with blood group A+ were 9 neonates and represent (47.4%), B + were 5 neonates and represent (26.3%), O + were 2 neonates and represent (10.5%), AB – were 1 neonate and represent (5.3%) and AB + were 2 and represent (10.2%) of all cases in the third group. But distribution of blood groups for mothers in the third group showing that mothers with blood group A+ were 9 and represent (47.4%), A - were 2 and represent (10.5%), O + were 6 and represent (31.6%), O – were 1 and represent (5.3%) and AB - were 1 and represent (5.3%).

Table 4. Comparison between three groups as regards Billirubin.

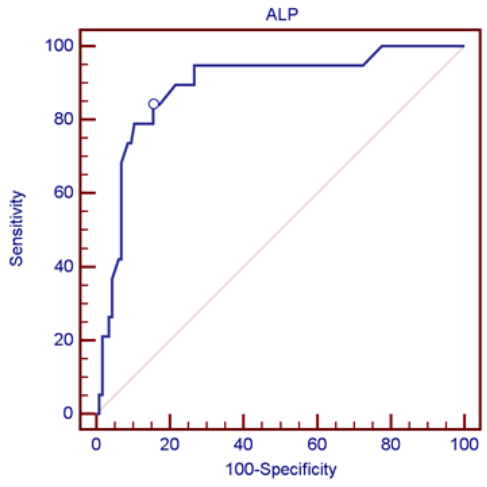
TSB	**Group 1 No. = 64**	**Group 2 No. = 117**	**Group 3 No. = 19**	**One Way ANOVA**	
				F	**P-value**
Mean±SD Range	3.75 ± 0.99 2 – 5	10.22 ± 2.40 6 – 14	16.84 ± 2.89 15 – 27	346.094	0.000

Table 5. ALP range, mean and standard deviation in the 3 studied groups.

ALP*	**Group 1 No. = 64**	**Group 2 No. = 117**	**Group 3 No. = 19**	**One Way ANOVA**	
				F	**P-value**
Mean±SD Range	205.72 ± 53.49 108 – 383	256.45 ± 62.85 138 – 440	353.11 ± 48.48 210 – 420	48.099	0.000

Table 6. figure 1: The previous ROC curve shows that the best cut off point for serum alkaline phosphatase to predict neonates needed treatment of NJ was found > 315 with sensitivity 84.2% and specificity of 84.48% and area under curve 88.8%.

Cut off point	**AUC**	**Sensitivity**	**Specificity**	**+PV**	**-PV**
>315	88.8	84.21	84.48	47.1	97.0



4. Discussion

To our knowledge this is the first clinical study that examines cord blood alkaline phosphatase level as an indicator to predict severe neonatal jaundice. The results of our study indicate that measurement of cord blood alkaline phosphatase may be a predicting marker for neonatal and necessitates treatment in the first week of life. Cord blood alkaline phosphatase level with sensitivity and specificity of 84.21% and 84.48% respectively in cutoff level > 314 IU/L predicts a need for treatment.

Ahmadpour-Kacho, et al (2015): (Cord Blood Alkaline Phosphates as an Indicator of Neonatal Jaundice) they carried out their study on 105 cases were followed-up. Three cases were lost to the study. The remaining 102 cases consisted of 50 (49%) males

and 52 (51%) females. Ninety-eight (96%) infants were born by cesarean section and 4 (4%) by vaginal delivery. Apgar scores were normal (9 - 10) at birth in all cases. The mean gestational age was 38.7 weeks and the mean birth weight 3649.59 grams. The incidence of clinical jaundice during follow-up was 47%. In 39.2%, bilirubin reached a peak of ≤ 10 mg/dL. The rate of need for treatment was 9.8% (10 cases), of which 5 cases were ABO incompatible, one case Rh incompatible, 2 cases G6PD deficient and in 2 cases the cause of jaundice remained unknown. Hct levels and reticulocyte count were in normal range and Coombs test was negative in these cases. None of the neonates needed exchange transfusion.

There was no difference between groups with regard to gestational age, birth weight and Apgar scores, but the comparison of cord blood alkaline phosphates levels revealed a significant difference between the two groups (P value = 0.041).

Comparison of cord blood alkaline phosphates levels between non-jaundiced group and jaundiced newborns in whom bilirubin level had reached ≤ 10 mg/dL, revealed a significant difference (P value = 0.016).

Comparison of the non-jaundiced group with neonates who required treatment according to AAP protocol (the treatment group) showed a significant difference in cord blood alkaline phosphates levels (P value = 0.040).

Comparison of the ROC curves of the alkaline phosphates levels between the non-jaundiced and treatment groups revealed that a cord blood alkaline phosphates level > 314 IU/L was the most suitable cutoff value for predicting severe jaundice (that needs treatment). This cut-off value was associated with 80% sensitivity and 63% specificity. [14]

Nalbantoglu et al. used blood alkaline phosphatase levels 6 hours after birth. They found that ALP levels were significantly higher in patients with hyperbilirubinemia requiring treatment, either with phototherapy or exchange transfusion (P value 0.0001) (15). In our study, there was a significant difference in the levels of cord blood alkaline phosphatase between the non-jaundiced and clinically jaundiced newborns, and it was significantly higher in patients with hyperbilirubinemia requiring treatment. Moreover, the ALP levels were significantly higher in newborns whose serum bilirubin level reached a level ≥ 10 mg/dL. These findings confirm the results of Nalbantoglu et al. (15). One of advantages in our study was the site of sample collection, which was taken from cord blood. Cord blood sample predicts hyperbilirubinemia earlier than a sample taken after birth does. In addition, the neonate may not be lost to follow-up because of early discharge.

Conclusion

Our data clearly demonstrates that the quantification of umbilical cord blood alkaline phosphates enzyme (ALP) is a useful test to predict hyperbilirubinemia in healthy full term and preterm newborns.

As a result of the study we can determine, in advanced, the healthy full term and preterm newborns that will develop neonatal jaundice by checking the alkaline phosphates levels in the umbilical cord blood and prevent problems based on early hospital discharge by closer monitoring of the babies that determined as risky for hyperbilirubinemia.

With this method, it is possible to determine the newborns with low risk for hyperbilirubinemia and prevent unnecessary monitoring and care of numerous cases.

More work and prospective wider studies should carried out with larger numbers of newborns in order to further determine the efficacy of alkaline phosphates enzyme as an early predictor of neonatal jaundice.

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