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ASSESMENT OF CORD BLOOD ALBUMIN AS A PREDICTOR OF HYPERBILIRUBINEMIA

By

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ABSTRACT

Background: Jaundice is one of the commonest problems that can occur in a newborn. It affects more than 60% of late preterm and term newborns, peaking at 3–5 days of life many time. It is physiological in the newborn because liver is not mature enough to handle the bilirubin and usually resolving by 2 weeks of age.

Objectives: The aim of this work was to evaluate if cord blood albumin levels are useful in predicting the development of jaundice in neonates.

Subjects and Methods: This prospective study was conducted on 60 neonates. They were classified into 2 groups, group I (30 neonates with high risk factors for neonatal jaundice) as cases group and group II (30 neonates without any risk factor for neonatal jaundice) as a control group. Cord blood was collected from the newborns for cord serum albumin level measurement. Total serum bilirubin was measured directly after birth and 4th day of life.

Results: In the present study, there was significant inverse correlation between cord albumin level and serum bilirubin level in 4th day in the case group. Also, there was asignificant inverse correlation between cord albumin level and serum bilirubin level in 4th day in control group.

Conclusion: Umbilical cord albumin levels are useful as a screening test in predicting the development of hyperbilirubinemia in neonates. It will help to detect infants at low or high risk for hyperbilirubinemia. This will minimize hospitalization and prevent readmission of infants with jaundice.

INTRODUCTION

Hyperbilirubinemia is one of the commonest problems that can occur in a newborn. Many a times it is physiological in the newborn because liver is not mature enough to handle the bilirubin and there is an increased load of bilirubin due to a higher circulating erythrocyte volume, a shorter erythrocyte life span and a larger early labeled bilirubin peak ***(Sahu et al., 2011)***.

Neonatal hyperbilirubinemia occurs in more than 60% of late preterm and term newborns, peaking at 3–5 days of life and usually resolving by 2 weeks of age ***(El-Beshbishi et al., 2009).***

Physiologic jaundice is the transient elevation of serum bilirubin during the first week of life. As the common, generally harmless, jaundice seen in many newborn babies with no underlying cause ***(Colletti et al., 2007).***

Total bilirubin levels in cord blood range from 1.4 to 1.9 mg/dl. Because of maturational limitations in bilirubin conjugation and excretion, all newborns experience a rise and then a fall of total serum bilirubin (TSB) levels after birth.

The rates of increase and decline in TSB and peak TSB level are affected by many factors, including gestational age, race, and breast feeding ***(Watson, 2009)***.

It is notable that susceptibility for bilirubin-induced neuro-toxicity is enhanced by prematurity And drugs that displace bilirubin from albumin thereby increasing free fraction of plasma bilirubin, and possibly concurrent marked conjugated bilirubinemia ***(Watchko, 2009).*** The development of kernicterus is thought to be associated with increased unbound bilirubin levels in the blood, the disruption of the blood–brain barrier or increased acidosis in the brain tissue ***(Lee et al., 2009).***

Albumin is the major binding protein in the human neonate. Albumin comprises 60% of the total serum protein and 60 to 80% of colloid osmotic pressure ***(Tabernero et al., 2002).***

Albumin synthesis in preterm infants is higher than in adults, preterm infants on day 7 had a fractional albumin synthesis rate (FSR) of albumin ≈12%/day. It could be suggested that albumin synthesis in preterm infants is higher than in adults, who were found to have a FSR of ≈7%/day and an ASR of ≈115mg/kg/day ***(Prinsen et al., 2003).***

Albumin binds to potentially toxic products like bilirubin and antibiotics. Bilirubin binds to albumin in an equimolar ratio. Free bilirubin is anticipated when the molar bilirubin to albumin (B/A) ratio is > 0.8 ***(Bunt et al., 2007).***

The aim of this work was to evaluate the role of cord blood albumin levels in predicting the development of neonatal hyperbilirubinemia.

SUBJECTS AND METHODS

The study was conducted in delivery room and NICU in Edfo General Hospital during the period from December 2015 to september 2016.

This prospective study included 60 newborn infants divided into 2 equal groups: ***The 1st group*** consisted of newborns with high risk for neonatal hyperbilirubinemia, for example, Rh incompitability, ABO incompitability, preterm infants, infants of diabetic mothers, newborn with previous family history of neonatal jaundice or glucse 6-phosphate dehydrogenase deficiency. ***The 2nd group*** consisted of full term neonates with no risk factors for neonatal jaundice as a control group.

We obtained consents from the parents of the neonates to make invistigations after we told them full information about the study.

All patients included in the study were subjected to :

1. Adequate history taking laying stress on history of previous sibling with hyperbilirubinemia, maternal blood group and Rh, history of G6PD deficiency in the family, and maternal illness especially gestational diabetes.
2. Clinical examination laying stress on gestational age using new Ballard score, birth weight measurement, presence of any signs of birth trauma like cephalhematoma or other cutaneous bruises.
3. Investigations were done as guided by the case including: blood group and Rh for the mother and the baby**,** complete blood picture (CBC)**,** serum C- reactive

protein (CRP) by using Latex serology test**,** serum cord bilirubin (total and direct) at birth by using automated (Cobas C 111) (Roche)**,** serum bilirubin level (total & direct)**,** *and* serum cord albumin level at birth by using bromcresol green method (BCG).

Statistical analysis: The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 16.0. quantitative data were analyzed using mean and standard deviation, while frequency and percentage were used with qualitative data. Two tailed Student's t- test was used to compare means of different groups, while chi square to compare frequencies of the different groups. Pearson correlation was used to find relationship between variables. Comparisons were significant if p value < 0.05. Receiver operating characteristics (ROC) curve was used to define the best cut off value of total cord bilirubin which was ≥1.9. and cord albumin which was ≤ 3.1.

RESULTS

- **GROUP 1 (Control):** Neonates without any risk factor for neonatal jaundice (n=30).
- **GROUP 2 (cases):** Neonates with high risk factors for neonatal jaundice (n= 30).

Both study groups were divided according to level of cord albumin:

- **Group (a):** Neonates with albumin level less than 2.8 g/dl.
- **Group (b):** Neonates with albumin level 2.8-3.3 g/dl.
- **Group (c):** Neonates with albumin level more than 3.3 g/dl

There were a highly significant difference between group 1(cases) and group 2 (control) as regard gestational age, weight and Apgar score at 1 min and no significant difference as regard other demographic data (Table 1).

Table (1): Comparison between group I (cases) and group II (control) as regards demographic data.

Parameters \ Groups		Control group	Case group	p-value
Sex	Male	14 (46.7%)	15 (50%)	0.796
	Female	16 (53.3%)	15 (50%)	
Mode of delivery	Cesarean section	18 (60%)	19 (63.3%)	0.791
	Normal vaginal delivery	12 (40%)	11 (36.7%)	
History of oxytocic drug	Yes	6 (20%)	7 (23.3%)	0.754
	No	24 (80%)	23 (76.7%)	
Gestational age (weeks)		38.7 (±0.8)	35.3 (±2.9)	<0.001 (HS)
Weight (kg)		3.3 (±0.4)	2.5 (±0.8)	<0.001 (HS)
Apgar score	1 min.	8 (±1)	7 (±1)	<0.001 (HS)
	5 min.	9 (±1)	9 (±1)	1

There were significant higher levels of total cord bilirubin, total serum bilirubin and retics in group 1 than group 2 and no significant difference as regard other laboratory data (Table 2).

Table (2): Comparison between group I and group II as regards laboratory data.

Parameters \ Groups		Control group	Case group	p-value
Cord ablumin (g/dl)		3.6 (±0.7)	3.2 (±0.7)	0.031
Total cord bilirubin (mg/dl)		1.5 (±0.3)	2.0 (±0.8)	**0.002**
Direct cord bilirubin (mg/dl)		0.2 (±0.1)	0.3 (±0.2)	0.017
Total serum bilirubin (mg/dl) in 4th dy		9.9 (±5.0)	13.4 (±6.6)	**0.024**
Direct serum biliurbin (mg/dl)		0.4 (±0.3)	0.7 (±0.5)	0.007
CBC	TLC (x103/mm3)	9.4 (±3.0)	8.5 (±3.7)	0.305
	Hb (g/dL)	15.8 (±2.2)	15.0 (±2.0)	0.146
	PLT (x103/mm3)	314.7 (±125.6)	319.2 (±99.1)	0.878
	HCT %	44.3 (±8.9)	39.9 (±6.8)	0.036
	Retics %	2.2 (±2.1)	3.8 (±3.3)	**0.029**
CRP	Negative (less than 10mg/l)	30 (100.0%)	28 (93.3%)	0.150
	Positive (more than 10mg/l)	0 (0.0%)	2 (6.7%)	

There were negative correlations which were statistically significant between cord albumin level and total serum bilirubin in 4th day in control group and case group (Table 3).

Table (1): Correlation between cord albumin and other variables in control group and case group

Cord albumin level / Parameters	Control group		Case group	
	R	p-value	r	p-value
Gestational age	0.021	0.912	-0.002	0.992
Weight (kg)	0.033	0.862	0.045	0.813
1min.	0.360	0.150	-0.408	0.25
5 min.	0.214	0.255	-0.450	0.13
Cord bilirubin (total)	-0.192	0.310	-0.309	0.096
Cord bilirubin (direct)	-0.136	0.474	0.153	0.420
Serum bilirubin level (total)	-0.413	**0.029 (S)**	-0.350	**0.050**
Serum bilirubin level (direct)	0.078	0.682	0.103	0.589
TLC (x103/mm3)	-0.162	0.392	0.024	0.899
Hb.(g/dL)	-0.084	0.658	0.227	0.228
Plt (x103/mm3)	0.071	0.709	0.067	0.725
HCT %	0.244	0.193	0.356	0.054
Retics %	-0.225	0.232	-0.103	0.587

Control group has **75%** of neonates in group A **(albumin < 2.8)** developed clinical hyper-bilirubinemia, **50%** of neonates in group B **(albumin 2.8-3.3)** developed clinical hyperbilirubinemia, while **5%** of neonates in group C (albumin > 3.3) developed clinical hyperbilirubinemia.and case group have 85.7% of neonates in group a (albumin < 2.8) developed clinical hyperbilirubinemia, 76.9% of neonates in group b (albumin 2.8-3.3) developed clinical hyperbilirubinemia while 30% of neonates in group C (albumin > 3.3) developed clinical hyperbilirubinemia (Table 4).

Table (4): General characters of control group and case group according to cord albumin level.

Groups / Parameters	Control group				Case group			
	Cord albumin level			Chi-Square test	Cord albumin level			Chi-Square test
	Group IIa	Group IIb	Group IIc		Group Ia	Group Ib	Group Ic	
	(n=4)	(n=6)	(n=20)	P	(n=7)	(n=13)	(n=10)	P
No. of neonates developed clinical hyperbilirubinemia	3(75.0%)	3(50.0%)	1(5.0%)	0.002	**6 (85.7%)**	**10 (76.9%)**	**3 (30.0%)**	0.026
No. of neonates didn't develop clinical hyperbilirubinemia	1(25.0%)	3(50.0%)	19(95.0%)		**1 (14.3%)**	**3 (23.1%)**	**7 (70.0%)**	

There were a diagnostic Performance of total cord bilirubin and cord albumin in predicting significant hyper-bilirubinemia in 4th day of life (Table 5).

Parameters / Cord bilirubin &albumin	Cut-off	Sen.	Spe.	PPV	NPV	Accuracy
Total cord bilirubin	≥ 1.9	35.11%	83.91%	81.9%	40.6%	56.6%
Cord albumin	≤ 3.1	78.95%	72.73%	83.3%	66.7%	77.8%

Receiver operating characteristics (ROC) curve **(Figure 1)** was used to define the best cut off value of:

- Total cord bilirubin which was ≥1.9, with sensitivity of 35.11% specificity of 83.91% positive predictive value of 81.9%, negative predictive value of 40.6% with diagnostic accuracy of 56.6%.
- Cord albumin which was ≤ 3.1, with sensitivity of 78.95% specificity of 72.73% positive predictive value of 83.3%, negative predictive value of 66.7% with diagnostic accuracy of 77.8%.

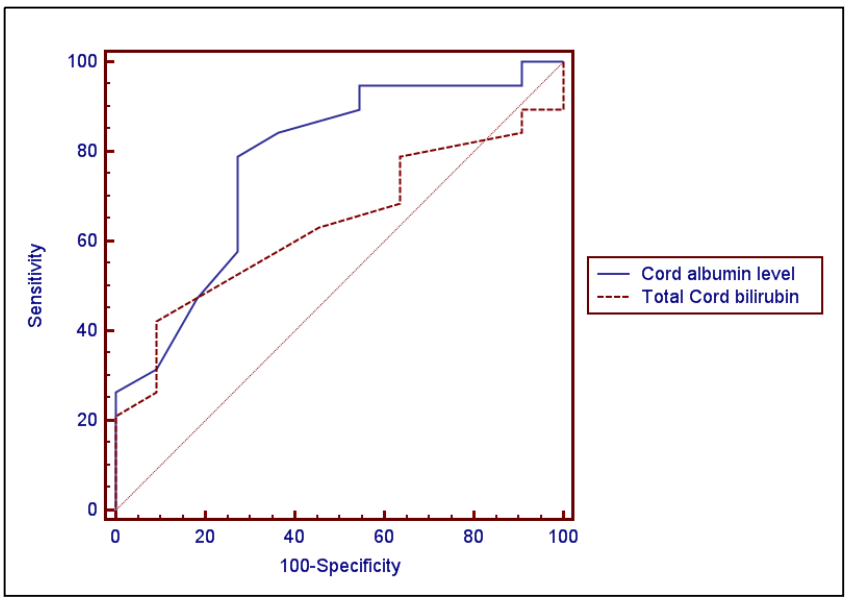

Figure (1): Receiver operating characteristics (ROC) curve.

DISCUSSION

Neonatal hyperbilirubinemia continues to be a leading cause of morbidity and mortality in resource-limited countries ***(Satrom et al., 2014).***

In Egypt, it is common that infants are discharged at less than one day of age with little or no evaluation for the risk of developing jaundice or any instructions for follow-up. A study by ***Iskander et al. (2012***)showed that clinical or laboratory assessment of hyperbilirubinaemia was almost nonexistent even among those who were discharged after the second day of life.

The need for early detection of hyperbilirubinemia in newborns discharged early from the hospital is therefore important ***(Rostami and Mehrabi, 2005).***

This study was conducted on 60 neonates in delivery room and NICU in Edfo General Hospital. They were classified into 2 groups, group I (neonates with high risk factors for neonatal jaundice) as cases group which included 30 neonates and group

II (neonates without any risk factor for neonatal jaundice) as a control group which included also 30 neonates.

The current study showed that the mean gestational age in the case group was 35.3±2.9**,** while in the control group were 38.7±0.8.This difference was statistically significant. The mean weight in the case group was 2.5±0.8 kg**,** while in the control group was 3.3±0.4 kg. This difference was statistically significant.

Cashmore (2000) and ***Watchko &* Maisels *(2003)*** stated that neonatal jaundice and hyperbilirubinemia occur more commonly and more prolonged among late preterm infants than full term infants due to higher bilirubin load, shorter erythrocyte survival time, increased erythrocyte volume, reduced excretion uptake of bilirubin by hepatocytes, less efficient conjugation of bilirubin by hepatocytes, less efficient conjugation of bilirubin and reduced bile flow .

In the present study, the mean total cord bilirubin in patients was 2.0±0.8 mg/dl while in the control group was 1.5±0.3 mg/dl**,** and this difference was statistically significant. Also, the mean total serum bilirubin in patients was 13.4±6.6 mg/dl in the 4^{th} day of life, while in the control group was 9.9±5.0 mg/dl. This difference was statistically significant, and can be explained as our patients have risk factor for hyperbilirubinemia.

In our study, the risk factors in group 1 were prematurity in 50%, ABO incompatibility in 16.7%, Rh incompatibility in 13.3%, infants of diabetic mothers in 6.7%, history of neonatal jaundice in previous babies in (3.3%), cephalehematoma in a newly born 3.3%, history of G6PD in a newly born 3.3%**,** and presence of neonatal sepsis in 3.3%.

The current study revealed that there was a significant inverse correlation between cord albumin level and total serum bilirubin level at 4th day in the patients Also**,** there was a significant inverse correlation between cord albumin and total serum bilirubin in 4th day in the control group.

In the present study, ROC curve analysis showed that critical cord albumin ≤ 3.1 as a cut-off value in predicting significant hyperbilirubinemia had sensitivity of 78.95%, specificity of 72.73%, positive predictive value of 83.3%, negative predictive value of 66.7% and accuracy of 77.8%. So, cord blood albumin was considered more accurate in predicting neonatal hyperbilirubinemia. Also, ROC curve analysis showed that critical cord bilirubin level of ≥ 1.9 mg/dl as a cut -off value in predicting significant hyperbilirubinemia had a sensitivity of 35.11%, specificity of 83.91, positive predictive value of 81.9%, negative predictive value of 40.6%, and accuracy of 56.6%. This agreed with ***Carbonell et al. (2001)***. Cord blood was tested for

bilirubin, blood group, Rh factor and direct Coomb's test, while TSB was measured at 60–96 h of life.

In our study**,** there was no significant correlation between cord bilirubin level and serum bilirubin level in the 4th day in control group**,** but there was significant inverse correlation between cord albumin level and serum bilirubin level in 4th day in patients group. So, we can depend on cord albumin level in newborns with no risk factors for neonatal jaundice in predicting incidence of neonatal jaundice even if the cord bilirubin level is within normal values.

The lower limit of normal for serum albumin in term babies is 2.8 g/dl ***(Burtis et al., 2008),*** and its level is low in premature neonates and increase significantly with increasing gestational age ***(Watchko, 2006).*** So**,** in our study, we divided our cases and control according to their cord albumin level into 3 groups: group (A) had cord albumin level less than 2.8 g/dl, group (B) from 2.8-3.3 g/dl**,** and group (C) which had cord albumin more than 3.3 g/dl.

This agreed with the study of ***Sahu et al. (2011)*** who found in their study that 82% of neonates who had cord albumin less than 2.8 g/dl developed significant hyperbilirubinemia which required phototherapy, and about 12% of them needed exchange transfusion. In the 2nd group (with cord albumin level 2.8- 3.3 g/dl), 40% developed significant hyperbilirubinemia, and all of them required phototherapy, but no one needed exchange transfusion. In the 3rd group (with cord albumin level more than 3.3 g/dl), all neonates of this group did not need any intervention for hyperbilirubinemia.

CONCLUSION

Umbilical cord albumin levels were useful as a screening test in predicting the development of jaundice in neonates. It helped to detect infants at low or high risk for hyperbilirubinemia. This minimized hospitalization and prevented readmission of infants with jaundice.

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قياس مستوي الألبيومين في دم الحبل السري للأطفال حديثي الولادة كمؤشر للكشف المبكر عن زيادة البيليروبين فى الدم

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خلفية البحث: تعتبر زيادة البيليروبين فى الدم من أكثر المشاكل الفسيولوجية التى تصيب الأطفال حديثى الولادة حيث أنها تصيب أكثر من ٦٠% من هؤلاء الأطفال ، وتصل ذروتها فى اليوم الخامس من العمر. وتعتبر زيادة البيليروبين فى معظم الأحوال فسيولوجية لعدم مقدرة الكبد على التخلص منها لعدم نضجه بما يكفى للتخلص من الصفراء .

الهدف من البحث : التحقق من قدرة إختبار نسبة الألبيومين في دم الحبل السري عند الولادة كمؤشر للإكتشاف المبكر لزيادة البيليروبين بين حديثي الولادة حتي اليوم الرابع.

الأشخاص وطرق البحث: أجريت هذه الدراسة علي ٦٠ من الأطفال حديثي الولادة. وقسمت الدراسة إلى مجموعتين متساويتين: المجموعة الأولي (الأطفال حديثي الولادة ممن لديهم عوامل خطورة لإرتفاع نسبة البيليروبين) ، والمجموعة الثانية (الأطفال حديثي الولادة دون أي عوامل خطورة لارتفاع نسبة البيليروبين) . وقد أجريت الإختبارات عند الولادة لقياس نسبة الألبيومين والبيليروبين (المباشر وغير المباشر) في دم الحبل السري، وعند اليوم الرابع من العمر أجريت إختبارات صورة الدم الكاملة ، ونسبة تكسير كرات الدم ، ونسبة بروتين سى التفاعلى ، وعمل فصيلة الدم ، والعامل الريسيسى للمولود والأم ، كما تم قياس نسبة الإنزيم المسبب لأنيميا الفول في الأطفال من ذوى التاريخ العائلى لحدوث أنيميا الفول لدي الطفل الأكبر.

النتائج: تبين من هذه الدراسة عدم وجود علاقة قوية بين نسبة البيليروبين في دم الحبل السري عند الولادة ومستوي البيليروبين في الدم عند اليوم الرابع من العمر في المجموعتين . ووجد أن هناك علاقة عكسية قوية بين نسبة الألبيومين في دم الحبل السري عند الولادة ومستوي البيليروبين في الدم عند اليوم الرابع من العمر في المجموعتين. لذلك يمكننا الإعتماد علي إختبار مستوي الألبيومين في دم الحبل السري عند الولادة للطفل حديث الولادة كمؤشر تنبؤى علي ارتفاع نسبة الصفراء بالدم.

الإستنتاج: يمكن أن تكون مستويات الألبيومين في الحبل السري عند الولادة أدوات مفيدة لإنشاء نظام للكشف المبكر والتنبؤ بحدوث الصفراء عند الأطفال حديثي الولادة المعرضين وغير المعرضين لمخاطر الإصابة بالصفراء، مما يقلل من إرتفاع معدلات الأشغال بالمستشفيات وإعادة دخول الأطفال إلى المستشفيات بعد إرتفاع نسبة الصفراء.