Original Research Article

Role of cord blood bilirubin and albumin levels as predictors of subsequent hyperbilirubinemia in newborns

Sourika P[1], Arigela V[2], Nanda kishore P[3]

[1]Dr. Sourika Polavaram, Assistant Professor, [2]Dr. Arigela Vasundhara, Professor, [3]Dr. Nanda kishore P, Senior Resident, all authors are affiliated with Department of Paediatrics, ASRAM Medical College, Eluru, Andhra Pradesh, India.

Address for Correspondence: Dr. Arigela Vasundhara, Professor, Department of Paediatrics, ASRAM Medical College, Eluru, A.P. Email:drarigelav@yahoo.com

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Abstract

Introduction: Neonatal hyperbilirubinemia is one of the most common problems in term and preterm babies. Development of hyperbilirubinemia in neonates is fretful for the parents and a concern for the pediatrician too. Healthy babies born through normal vaginal delivery who are getting discharged early are being readmitted for the treatment of hyperbilirubinemia. **Aimsand Objectives:** The present study is done to determine the correlation of cord blood bilirubin, albumin and neonatal hyperbilirubinemia in identifying newborn babies at risk of developing significant hyperbilirubinemia and to establish the cutoff values of cord blood bilirubin and cord blood albumin levels to identify such high-risk neonates. **Materials and Methods**: In present study, 303 term neonates who are delivered in ASRAM, Eluru from January 2012-January 2013, were included after parental consent. Cord blood bilirubin, Blood grouping and typing, Cord blood albumin and serum bilirubin levels were done in all babies. **Results:** The incidence of significant hyperbilirubinemia in this study was 23.7%. Cord serum unconjugated bilirubin level ≥2.0 mg/dl and total cordserum bilirubin level ≥ 2.5mg/dl as high risk indicator towards predicting neonatal hyperbilirubinemia in first week of life. 58.53% babies had cord serum albumin level < 2.8gm/dl. **Conclusion:** Cord serum unconjugated bilirubin level ≥2mg/dl and total cord serum bilirubin level ≥2.5mg/dl, cord blood albumin <2.8g/dl is a high-risk indicator towards predicting neonatal hyperbilirubinemia in the first week of life.

Key words: Hyperbilirubinemia, Cord blood bilirubin, Cord blood Albumin.

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Introduction

Neonatal hyperbilirubinemia is one of the most common problems in term and preterm babies. Though babies with ABO/Rh incompatibility are at high risk for developing subsequent hyper bilirubinemia, many times it is physiological. Physiological hyperbilirubinemia results from immature liver cell having very low Uridine Diphospho- Glucuronosyl Transferase activity compared to mature hepatocyte, low concentration of Bilirubin binding ligand Albumin, and higher volume of short life erythrocytes in the circulation. Physiological jaundice arises as a "normal" response to the baby's limited ability to excrete bilirubin in the first days of life. Every newborn develops unconjugated hyperbilirubinemia due to increased level of unconjugated Bilirubin above 1.0mg/dl [1]. Physiological Jaundice takes place in approximately 60% of newborns, though it is unimportant in most, a few (5-6%) will become deeply jaundiced requiring investigation and treatment.If inadequately managed, it may result in death survival with severe brain damage [2]. Development of hyper bilirubinemia in neonates is fretful for the parents and a concern for the pediatrician too. Early discharge of healthy term newborns after normal vaginal delivery has become a common practice, because of medical reasons like prevention of nosocomial infections, social reasons like early naming ceremony and also due to economical constrains, but many have to be readmitted for the treatment of hyperbilirubinemia[3]. Requirement of phototherapy based on cord blood Bilirubin level

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was predicted [4]. So, it is possible to predict hyperbilirubinemia on day one. There are a few references which predict postnatal hyper-bilirubinemia by estimating cord blood bilirubin levels but vary in opinions. Robinson et al reported cord bilirubin levels above 3mg/dl were suggestive of significant jaundice [5]. Simpson et al believed cord bilirubin greater than 2.5mg/dl was associated with development of significant jaundice**,** whereas Rosenfeld in their study states cord blood bilirubin level more than 2.0mg/dl have more than 95% chances of developing hyperbilirubinemia [6,7]. Thus, different authors have used different cutoff values for predicting significant jaundice. Early detection of risk factors is the first step towards prevention of hyperbilirubinemia and a step ahead in protecting newborns from complication at later age. Usually, albumin binds with unconjugated bilirubin and protects against Kernicterus [8]. Blood albumin in neonates is mostly derived from maternal circulation till baby's liver starts synthesis. There is paucity of reports on cord blood albumin level as predictor of hyperbilirubinemia.

Aims and Objectives

1. To determine the correlation of cord blood bilirubin, albumin and neonatal hyper-bilirubinemia in identifying newborn babies at risk of developing significant hyperbilirubinemia.

2. To establish the cutoff values of the cord blood bilirubin and cord blood albumin levels to identify such high risk neonates.

Materials and Methods

Place of study: The study was carried out at ASRAM Hospital, Eluru, Andhra Pradesh.

Period of study: 12 months (January 2012 – 2013).

Study design: It is a prospective clinical study done on all neonates born in ASRAM Hospital, Eluru. For feasibility, only those babies whose families were residents of Eluru and surrounding areas who could be followed up till the end of the study were included in the study.

Study population: The study was conducted on 303 newborns with the following criteria:

Inclusion criteria

- Term babies both genders
- Mode of delivery (normal and Cesarean section)
- Birth weight >2.5kg.
- APGAR ≥ 7/10 at 1 min.

Exclusion criteria

- Preterm
- Rh incompatibility.
- Neonatal sepsis.
- Instrumental delivery (forceps and vacuum)
- Birth asphyxia.
- Respiratory distress.
- Meconium stained amniotic fluid.
- Neonatal jaundice within 24 Hours of life.
- ABO Incompatibility
- Neonatal Hypothyroidism

Sampling methods: Cord blood bilirubin was analysed by spectrophotometry by spectral method. Blood grouping and typing was done. Cord blood albumin collected at birth was analyzed by auto analyzer method. Total serum bilirubin level was analysed via the colorimetric Diazo method.

Sampling collection: Three milliliters of cord blood was collected by a sterile syringe, put in clean capped tube and then sent immediately to the laboratory of the hospital for Cord bilirubin and albumin levels. All enrolled babies are followed up for 5 days and clinical assessment for jaundice is done according to Kramer dermal scale. Under aseptic precautions,1ml of venous blood is drawn from all the babies enrolled in study on or after72 hours and on day 5 of life for estimation of serum total bilirubin after informed parental consent.

Statistical analysis: The analysis was carried out using the statistical package for the social sciences (SPSS) program and *p* values with significance of less than 0.05 were considered statistically significant.

Results

The study was done on 303 newborns recruited based on above inclusion and exclusion criteria during the period of January 2012 to January 2013 to know the correlation between Cord blood Bilirubin, Albumin and neonatal hyperbilirubinemia.

Table-1: Demographic parameters of studypopulation.

Parameter	N	Mean	Std Deviation	Std error mean
Birth wt (kg)	303	2.58	0.23	0.242
Time of TSB* (hrs)	303	25.18	1.7%	0.186
Mean TSB*(mg/dl)	303	6.028	1.156	0.1587

*TSB –Total serum bilirubin

The mean birth weight of babies was 2.58 ± 0.23 kg and range were 1.92 kg to 4.14 kg. Mean time of 24th serum bilirubin estimation was 25.18hrs ± 1.71 hours ranging from 20hrs – 30hrs. Mean 24th hour serum bilirubin levels were 6.028 ± 1.156 mg/dl ranging from 2.8 mg/dl to 13 mg/dl.

Table-2: Demographic parameters of jaundiced babies.

Parameter	N	Mean	Std deviation	Range
Birth wt (kg)	72	2.21	0.215	1.9 – 4.1
Time of TSB*(hrs)	72	25.56	1.539	22 – 30
Mean TSB*(mg/dl)24th hr	72	7.519	1.6683	6 – 13
Mean day 5 TSB*(mg/dl)	72	17.03	1.560	16 – 24

*TSB – Total serum bilirubin

The demographic parameters of babies with jaundice were as follows:

1. Out of 303 babies, 72 developed significant jaundice by day 5.
2. Jaundice was seen in 23.7% of cases.
3. Mean birth weight of these babies with jaundice was 2.21 ± 0.215kg, ranging from 1.9 to 4.1 kg.
4. Mean time of TSB estimation was 25.56hrs ± 1.539 hr, ranging from 22 to 30hrs.
5. Mean 24th hour TSB levels were 7.5191 mg/dl ± 1.668 mg/dl, ranging from 6mg/dl to 13mg/dl.
6. Mean D5 (TSB5) serum bilirubin levels were 17.03 ± 1.5mg/dl from 16- 24mg/dl.
7. There was a moderate degree of correlation between 24th hour TSB and day 5 serum bilirubin, r = 0.486 (n-72), P = 0.003.

Table-3: Correlation table.

Parameter	r correlation coefficient	N	P value
Cord bilirubin with TSB*	0.655	72	0.004
Cord bilirubin with 24th hr TSB*	0.905	303	0.000
24th hour TSB* with TSB*	0.486	72	0.003

*TSB – Total serum bilirubin

In our attempt to correlate Cord blood bilirubin and 24th hour serum bilirubin levels, ROC curve plotted for 24th hour TSB has shown a cut off value of ≥ 6mg/dl with a sensitivity of 100%, specificity of 96.3%, 78.3% PPV and 100% NPV with a false positive rate of 3.7%[n=10]. Area under the curve was 0.997 with a P value of 0.000. Cut off ≥ 6.1 mg/dl had 88.9 sensitivity, specificity of 99.6%, PPV 97% and NPV 98.5% with a false negative rate of ll.l%[n=4]. We would like to consider the cut off values for cord bilirubin and 24th hour serum bilirubin has ≥ 2.3mg/dl and ≥ 6mg/dl respectively.

ROC curve for cord bilirubin established a cut off value of 2mg/dl with 100% sensitivity, 98.1% specificity, 85% PPV and 100% NPV with a false positive rate of 2%[n=3]. Whereas cut off value of ≥ 2.3mg/dl had 94.1% sensitivity, 100% specificity, 100% PPV and 99.4% NPV with a false negative rate of 5.9%[n=l]. Area under the curve was 0.999, with a P value of 0.000.

Table-4: Cord Bilirubinand Albumin levels in newborns with hyperbilirubinemia.

Cord blood albumin & bilirubin levels	No of cases
Cord bilirubin >2.3 mg/dl	41
Cord albumin <3.5 g/dl	31

Out of 72 newborns who developed jaundice, 41 babies had Cord blood bilirubin >2.3mg/dl and 31 babies had Cord Albumin <3.5g/dl.

Distribution of Cord Blood Albumin in newborns with hyperbilirubinemia: Out of the babies who developed Jaundice, 18 had Cord blood Albumin levels<2.8g/dl, 9 had levels between 2.8-3.5g/dl and 4 had levels >3.5g/dl.

Table-5: Cord serum bilirubin and albumin Levels.

	Hyperbilirubinemia Yes	Hyperbilirubinemia No	P value
CST*Bilirubin mg/dl Interval	3.83 ± 1.72 2.23 – 7.10	2.11 ± 0.58 0.82 – 3.29	<0.001
CSU†Bilirubin mg/dl Interval	3.76 ± 1.28 1.27 – 5.91	1.91 ± 0.59 0.64 – 2.89	<0.001
CSC‡ Bilirubin mg/dl Interval	0.27 ± 0.14 0.18- 0.28	0.30 ± 0.141 0.21 – 0.52	
CS§ Albumin gm/dl Interval	2.15 ± 0.81 1.8 – 2.7	3.64 ± 0.30 3.1 – 3.9	<0.05
CS§ Albumin/CSC‡ Bilirubin ratio	3.13 ± 1.09	2.03 ± 0.14	
Baby serum Total Bilirubin level on 4th day mg/dl	14.88 ± 2.91 11.92 – 18.21	0.9 ± 0.2 1.2 – 1.5	<0.001

*CST – Cord Serum Total, †CSU – Cord Serum Unconjugated
‡CSC- Cord Serum Conjugated, §CS – Cord Serum

Table 5 shows levels of Cord serum bilirubin and Cord serum Albumin levels observed in subjects under study. The cutoff point taken for unconjugated bilirubin in cord blood at our hospital was 2.0 mg/dl. When Cord serum unconjugated bilirubin concentration in cord blood was ≥ 2.0mg/dl, 73.6% of babies developed jaundice in first seven days of their life. However, 26.4% babies remained normal even though their Cord serum unconjugated bilirubin concentration was ≥ 2.0mg/dl. Clear relation between Cord serum total bilirubin, Cord serum unconjugated bilirubin levels and development of jaundice was observed. Also, it was observed that mean Cord serum unconjugated bilirubin level > 2.0mg/dl at the time of birth was associated with development of hyperbilirubinemia in first 3to5 days of life.

Discussion

In this study, it is found that the incidence of significant hyperbilirubinemia to be around 23.7%. Similar findings were observed in studies done by other authors [1,9,10,11]. Males were 2.13 times more jaundiced than females in our study. Similar association was demonstrated by Friedman et al,

Maisels et al and Anand et al [10,12]. This study is aimed at prediction of significant hyper-bilirubinemia using cord bilirubin and albumin. We have established that cord bilirubin ≥ 2.3 mg/dl has good predictive value for identifying newborns at risk of hyperbilirubinemia with 94.1% sensitivity, 100% specificity, 100% positive predictive value and 99.4% negative predictive value.

In 1986, Rosenfeld J reported that infants with cord bilirubin levels less than 2.0 mg/dL have only a 4 percent chance of developing hyperbilirubinemia and 1.4 percent chance of needing phototherapy. However, if serum cord bilirubin levels are more than 2.0 mg/dL, the infant has a 25 percent chance of developing subsequent hyperbilirubinemia[13].

In 1989, Knudsen A found that if cord bilirubin was below 20 mumol/L, 2.9% became jaundiced as opposed to 85% if cord bilirubin was above 40 mumol/l. Furthermore, 57% of jaundiced infants with cord bilirubin above 40 mumol/l required phototherapy, but only 9% if cord bilirubin was 40 mumol/l or lower (p less than 0.003) [14].

It was determined that 24th hour serum bilirubin ≥ 6 mg/dl also has good predictive value for significant jaundice with 100% sensitivity, 96% specificity, 78% PPV and 100% NPV in this study. It was comparable to other studies by Alpay et al, Awasthi et al and Agarwal et al[15,16,17].

In 1994, Rataj J et al reported that if cord bilirubin was under 1 mg% the jaundice occurred in 2.4% newborns, where as 89% of the infants with cord bilirubin above 2.5mg% became jaundiced, showing cord bilirubin estimation can be used as early predictor of neonatal hyperbilirubinemia[18].

In 1996, A study done by Seidman et al found that the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was less than 5mg/dL at 24 hours of life, whereas the risk was 6.6% in cases whose bilirubin level was more than 5 mg/dL at 24 hours of life[19].

In 2000, Alpay et al observed that a serum bilirubin more than 6mg/dL on the first day of life had 90% of sensitivity of predicting a subsequent Total Serum Bilirubin more than 17mg/dL between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive values were 97.9%. No cases with Total Serum bilirubin of less than 6mg/dL in the first 24 hours required phototherapy [15]. In 2005, Taksande A et al observed that cord bilirubin level of more than 2 mg/dL had the highest sensitivity (89.5%), and this critical bilirubin level had a very high (98.7%) negative predictive value and fairly low (38.6%) positive predictive value. A 98.7% negative predictive value in the present study suggest that measurement of cord serum bilirubin can help to identify those newborns who are unlikely to require further evaluation and intervention [20]. In 2007, Ge sun et al observed 523 healthy term newborns reported that there is clear correlation between umbilical cord bilirubin level and the development of hyperbilirubinnemia and minimize any unnecessary prolongation of hospitalization [21].

This study shows a significant correlation between Cord serum total bilirubin, unconjugated bilirubin levels and occurrence of neonatal jaundice. When Cord serum total bilirubin were correlated with the day of development of jaundice, it exhibited significant negative correlation ($r= -0.348$, $P<0.001$) indicating level of total bilirubin in cord blood is inversely proportional to the day of development of neonatal jaundice. Similarly, Cord Serum unconjugated and total bilirubin levels have shown positive correlation with Baby's serum unconjugated and Total bilirubinlevels on 4th day of life. This suggests, cord serum unconjugated bilirubin level ≥2.0 mg/dl and total cord serum bilirubin level ≥2.5mg/dl as high risk indicator towards predicting neonatal hyperbilirubinemia in the first week of life, and ourfinding parallels with the findings of Sun G et al & Bernaldo AJ et al [21,22].

Though Bilirubin estimation varies from laboratory to laboratory, it is important for local laboratory to use reference level to define cutoff values at one's own hospital, which can predict development of significant jaundice. Lower normal limit for cord serum albumin in term babies is 2.8gm/dl [23]. In the present study, we estimated albumin levels from the cord blood after delivery and found statistically significant difference ($P<0.05$) between mean cord serum albumin levels in babies who did not develop hyperbilirubinemia (3.64 ± 0.30gm/dl) and in the babies who developed hyperbilirubinemia (2.15 ± 0.81 gm/dl). Similar results were reported by S. Sahu et al [24].

Among babies who developed hyperbilirubinemia, 58.53% babies had cord serum albumin level < 2.8gm/dl and 28.78% babies had cord serum albumin level in the range of 2.8 – 3.5gm/dl. Where as 12.68% babiesdeveloped hyperbilirubinemia, even though cord serum albumin level was more than 3.5gm/dl.

Cord serum albumin level and cord serum conjugated bilirubin shows positive correlation (r=0.2, <0.05) whereas, Cord serum albumin levels correlated with unconjugated bilirubin shows negative correlation (r =- 0.1917). Thus, Cord serum albumin levels are high risk indicators towards predicting neonatal hyperbilirubinemia. Source of cord serum albumin is the mother's circulation, as cord serum albumin levels were estimated on delivery; it indirectly suggests the nutritional status of mother during gestational period. Thus, higher albumin levels from mothers maintaining good nutritional status resulted in lower incidence of neonatal jaundice.

Conclusion

We conclude that Cord serum bilirubin level is useful in predicting the subsequent jaundice in healthy term infants. The use of Cord serum bilirubin values may help detect infants at low or high risk for hyperbilirubinemia. Cord serum albumin gives additional clue in visualizing future hyperbilirubinemia to protect them from latter age complications.

1. Cord serum unconjugated bilirubin level ≥2.0 mg/dl and total cord serum bilirubin level ≥2.5mg/dl is a high risk indicator towards predicting neonatal hyperbilirubinemia in the first week of life.
2. Cord serum albumin <2.8 gm/dl is an indicator for developing neonatal hyperbilirubinemia in the first week of life.
3. Babies with cord serum albumin >3.5 gm/dl has low risk of developing neonatal hyperbilirubinemia and can be discharged early from hospital.

Contributions

- Dr. Sourika and Dr. Arigela V wrote the first draft of the manuscript.
- Dr. Sourika and Dr. Nanda Kishore helped in data collection, writing manuscript and did primary corrections in the manuscript.
- Dr. Sourika and Dr. Arigela V made final corrections of manuscript before submission.
- All authors approved the submission of this version of the manuscript and takes full responsibility for the manuscript. None of the authors have any conflict of interest.

What this study adds to existing knowledge?

There were no clear standard cut-off values for cord blood bilirubin and albumin levels in prediction of subsequent hyperbilirubinemia. Our study contributes to establish cut-off values for cord blood bilirubin and albumin levels.

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