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Original Research Article

Cord Blood Albumin as a Marker for Predicting Neonatal Jaundice in Healthy Term Newborns

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Abstract

Background: Neonatal jaundice is a commonly witnessed condition in the first week of neonatal life. Because of the medical, social and economic constraints, healthy term neonates are increasingly being discharged prior to 48 hrs of life, thereby increasing number of readmissions due to hyperbilirubinemia. Early discharge of healthy term neonates raises a concern of delayed recognition of hyperbilirubinemia that can induce brain damage resulting in sequelae like chronic bilirubin encephalopathy. Therefore, it is important to identify markers to predict hyperbilirubinemia early in the neonates.

Methods and Materials: A prospective study was conducted on 1000 healthy term neonates (gestational age ≥37 weeks) with an Apgar score of ≥7 at first and fifth minutes of life; irrespective of mode of delivery, birth weight and gender. Neonates with ABO and/or Rh incompatibility, those with congenital malformations (e.g. CDH, TEF, ARM etc), conjugated hyperbilirubinemia or any significant illness (like sepsis, perinatal asphyxia etc) were excluded from the study. Based on cord blood albumin levels, 3 groups were formed; namely Group A (<2.8 gm/dl), Group B (2.8 - 3.3 gm/dl) and Group C (>3.3 gm/dL). These groups were then assessed for development of clinically significant jaundice until they reach day of life 5 or until discharge, whichever is later.

Results: Group A, B, and C had 240, 350, and 410 neonates respectively. In group A, 199 (82.9%) neonates developed significant jaundice (Kramer's Zone ≥3), of which 178 (74.2%) neonates required phototherapy and 3 (1.25%) neonates needed exchange transfusion; whereas 127 (36.3%) neonates in group B developed significant jaundice (Kramer's Zone ≥3), of which 88 (25.1%) neonates needed phototherapy and 2 (0.5%) neonates required exchange transfusion. In group C, 112 (27.3%) neonates developed significant jaundice (Kramer's Zone ≥3), of which 22 (5.4%) neonates required phototherapy while none of them required exchange transfusion (p value ≤0.0001).

Conclusion: The risk of developing subsequent neonatal jaundice can be predicted early using umbilical cord blood albumin levels. Neonates with cord blood albumin levels >3.3 gm/dl can be safely discharged early. However, if cord blood albumin level is ≤3.3 gm/dl, neonates will need a closer follow-up to look for development of jaundice.

Keywords: Neonatal jaundice, cord blood albumin, hyperbilirubinemia, kernicterus.

Introduction

60-70% of term and about 80% of preterm neonates develop clinical jaundice [1]. Healthy term neonates are increasingly being discharged within 48 hrs of normal vaginal delivery owing to medical reasons like prevention of nosocomial infections, social reasons like early naming ceremony and also due to financial constraints. American Academy of Paediatrics (AAP) recommends, "neonates discharged within 48 hours should have a follow-up visit after 48 to 72 hours of discharge to look for any significant jaundice and other problems." [2].

Low resources, limited follow-up clinics and poor compliance by the parents causes delay in recognition of jaundice in these neonates. Reports of bilirubin induced brain damage in healthy term neonates even without haemolysis adds on to the concern of paediatrician regarding early discharge. Identification of early markers for prediction of neonates at risk of developing significant neonatal hyperbilirubinemia is an attractive option.

Albumin helps in hepatic transportation and clearance of bilirubin. Low serum albumin level is associated with decreased bilirubin clearance, thereby increasing the risk of significant hyperbilirubinemia [3]. Cord blood albumin levels as an early predictor of severity of neonatal jaundice has not been adequately studied. Hence, the present study was conducted to bridge this gap and determine whether cord blood albumin can be used as an early predictor of subsequent significant neonatal jaundice requiring medical interventions like phototherapy or exchange transfusion.

Materials and Methods

A prospective study was conducted in a tertiary care hospital of Southern Rajasthan to study and correlate cord blood albumin levels with the risk of subsequent development of significant neonatal jaundice in healthy term neonates. Prior approval from the Institutional Ethics Committee was taken. A total of 1000 healthy term neonates (gestational age ≥ 37 weeks) with an Apgar score of ≥7 at first and fifth minutes of life, irrespective of mode of delivery, gender and birth weight, were included in the study. Neonates with Rh or ABO incompatibility, those with congenital malformations requiring immediate surgical intervention (e.g., congenital diaphragmatic hernia, tracheoesophageal fistula, anorectal malformation etc), those with conjugated hyperbilirubinemia, or with significant illness (like sepsis, perinatal asphyxia, etc.) that could aggravate hyperbilirubinemia were excluded from the study.

Cord blood was collected at delivery in one EDTA and one plain vial and sent to laboratory for baby's blood group and estimation of serum albumin levels by COBAS C311 fully automated biochemistry analyser based on BCG (bromocresol green colorimetric) method. Relevant antenatal and perinatal history was taken, anthropometry and a thorough clinical examination was performed, and details were recorded in a pre-designed proforma for all the neonates included in the study.

Based on cord blood albumin levels, 3 groups were formed; namely Group A (<2.8 gm/dl), Group B (2.8 - 3.3 gm/dl) and Group C (>3.3 gm/dL). These groups were then assessed for development of clinically significant jaundice until they reach day of life 5 or until discharge, whichever is later, as serum bilirubin reaches its peak levels between 3rd to 5th day in healthy term newborns.[4] Visual assessment of serum total bilirubin

(STB) levels was done according to Kramer [5] dermal chart as follow – "Zone 1 - head and neck: 4 to 6 mg/dl; Zone 2 - chest and upper abdomen: 6 to 8 mg/dl; Zone 3 - lower abdomen and thighs: 8 to 12 mg/dl; Zone 4 - arms and legs: 12 to 14 mg/dl; Zone 5 - palms and soles: ≥ 15 mg/dl". Serum bilirubin levels were sent for neonates who developed clinical jaundice of Zone ≥3 according to Kramer dermal chart[5]. COBAS C311 Biochemistry Analyzer based on Diazo method was used for serum bilirubin level estimation. Other relevant blood investigations were sent whenever necessary.

The main outcome of the study was assessed in terms of number of neonates developing significant hyperbilirubinemia requiring phototherapy or exchange transfusion (ET). Qualitative data was derived in percentage while mean and standard deviation was used to summarise Quantitative data. The significance of difference between proportions and percentages was determined using Chi-square (X2) test. Z-test and t-test were used to compare the mean difference of various parameters. ANOVA was used inter-group and intra-group to show any significant difference in cord blood albumin levels. A significant difference was defined by 'P' value of less than 0.05.

Results

In our study, there were 240 neonates in Group A, 350 neonates in Group B and 410 neonates in Group C. The mean gestational age was 38.22 ± 1.10 weeks in Group A, 38.29 ± 1.06 weeks in Group B and 38.23 ± 1.05 weeks in Group C. The mean birth weight in Group A, B and C was 2.70 ± 0.41 kg, 2.74 ± 0.42 kg and 2.77 ± 0.43 kg respectively. 58.8% neonates in group A were exclusively breastfed whereas 41.3% received both formula feed and breast feed. Similarly, 55.7% neonates in group B received exclusive breast feeding and 44.3% neonates were given formula feed as well. In group C, 55.9% neonates were on exclusive breast feeding as compared to 44.1% neonates who were on mixed feeding. The onset of jaundice was noted on 2nd, 3rd and 4th postnatal day in 29 (2.9%), 316 (31.6%) and 404 (40.4%) neonates respectively; i.e. majority of neonates developed jaundice on 4thpostnatal day. All groups were comparable based on demographic characteristics except age of onset of jaundice (Table 1).

Table 1: Basic demographic characteristics of all three groups

		Group A (n=240) (Cord blood albumin <2.8gm/dl)	Group B (n=350) (Cord blood albumin 2.8-3.3gm/dl)	Group C (n=410) (Cord blood albumin >3.3gm/dl)	P-value
Gestational age (weeks)		38.22 ± 1.10	38.29 ± 1.06	38.23 ± 1.05	> 0.05
Birth weight (kg)		2.70 ± 0.41	2.74 ± 0.42	2.77 ± 0.43	> 0.05
Gender	M F	121 (50.4%) 119 (49.6%)	200 (57.1%) 150 (42.9%)	200 (48.8%) 210 (51.2%)	> 0.05
Mode of delivery	Nvd Lscs	119 (49.6%) 121 (50.4%)	159 (45.4%) 191 (54.6%)	194 (47.3%) 216 (52.7%)	> 0.05
Mode of feeding	Bf	141 (58.8%)	195 (55.7%)	229 (55.9%)	> 0.05

	Bf+tf	99 (41.3%)	155 (44.3%)	181 (44.1%)	
Age of onset of jaundice (postnatal days)		4.12 ± 0.933	3.86 ± 0.949	3.88 ± 0.869	≤ 0.0001

The incidence of clinical jaundice in all the groups and need for intervention in form of phototherapy and exchange transfusion is depicted in Table 2. The average serum bilirubin level in group A, B and C was 15.07 ± 3.9 mg/dl, 10.43 ± 3.9 mg/dl and 9.23 ± 2.3 mg/dl respectively (P value < 0.001).

Table 2: Incidence of clinical jaundice and requirement of phototherapy and exchange transfusion in three groups

	Group A (n=240) (Cord blood albumin <2.8 gm/dl)	**Group B (n=350) (Cord blood albumin 2.8-3.3 gm/dl)**	**Group C (n=410) (Cord blood albumin >3.3 gm/dl)**	**P-value**
Neonates developing clinical jaundice; Kramer dermal zone ≥ 3	199 (82.9%)	127 (36.3%)	112 (27.3%)	≤ 0.0001
Serum bilirubin levels in neonates (mg/dl)	15.07 ± 3.9	10.43 ± 3.9	9.23 ± 2.3	<0.001
Newborns requiring Phototherapy	178 (74.2%)	88 (25.1%)	22 (5.4%)	≤ 0.0001
Newborns requiring exchange transfusion	3 (1.25%)	2 (0.5%)	0	≤ 0.0001

In our study, there was a negative Pearson's correlation (r = -0.440) between cord blood albumin and serum total albumin, which was statistically significant (p-value 0.001) as depicted in Table 3.

Table 3: Correlation between Cord Blood Albumin and Serum Total Bilirubin Among Neonates with Jaundice (Kramer dermal zone ≥ 3)

Correlation	**r-value**	**p-value**	**Significance**
CBA v/s STB	-0.440	<0.001	S

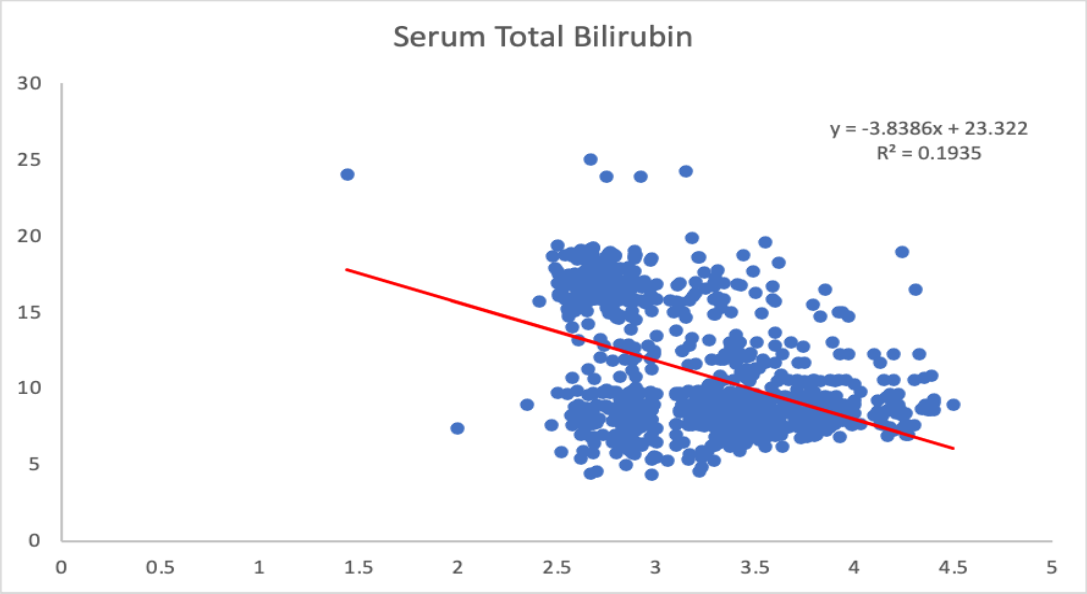

Figure 1: Correlation between Cord Blood Albumin and Serum Total Bilirubin

Discussion

In our study, out of total 1000 neonates, 521 were males and 479 were females. In a similar study by Trivedi *et al* [6], out of 605 neonates, 305 (50.41%) were males and 300 (49.59%) were females, with a slight male preponderance similar to our study.

In the current study, the mean gestational age for Group A, B and C was 38.22 ± 1.10 weeks, 38.29 ± 1.06 weeks, and 38.23 ± 1.05 weeks, respectively with p value >0.05. Similarly, Sindhu Sivanandan *et al* [7] found that mean gestation age in one group was 38 ± 1.3 weeks and another group was 37 ± 1.0 weeks with p value >0.05.

Majority of neonates (40.4%) included in our study developed clinically significant jaundice (Kramer's dermal zone ≥3) on 4th postnatal day. Meena JK *et al* [8] in their study noticed clinical jaundice on 3rd postnatal day. Anand *et al* reported that 45.7% neonates had onset of jaundice on 3rd postnatal day followed by 35.3% on 4th postnatal day. Sethi *et al* [9], reported development of jaundice on 3rd postnatal day of life in two-third neonates.

In our study, there was no significant difference in mean birth weight between all the three groups (P value >0.05). Mean birth weight of group A was 2.80 ± 0.44 kg as compared to 2.78 ± 0.42 kg and 2.76 ± 0.40 kg in group B and C respectively. Similarly, in study of Sindhu Sivanandan *et al*[7], mean birth weight in case group was 2.79 ± 0.351 kg and mean birth weight in control group was 2.923 ± 0.330 kg with p value >0.05. Wood B.S.B., Culley P.E. *et al* [10]. in another study found that as birth weight increase, there was gradual reduction in incidence of neonatal jaundice.

In our study, out of 472 cases with vaginal deliveries, 143 developed significant jaundice and out of 528 cases with caesarean section, 145 developed significant jaundice. However, there was no significant association between neonatal jaundice and mode of delivery with a p value of 0.323. In a study conducted by Amar Taksande *et al* [11] on 200 neonates, 8 out of 66 neonates born by caesarean section and 11 out of 144 neonates delivered by normal vaginal delivery developed significant jaundice (p

value 0.527). Similarly, Rostami *et al* [12] and Rudy Satrya *et al* [13] found that there was no correlation between mode of delivery and significant jaundice (p value >0.05).

In our study, out of 1000 neonates, 82.9%, 36.3% and 27.3% neonates developed clinically significant jaundice [Kramer's dermal zone ≥3] in group A, B and C respectively. In group A, 74.2% neonates required phototherapy and 1.25% neonates required exchange transfusion. In group B, 25.1% neonates received phototherapy and 0.5% neonates underwent exchange transfusion; while in group C, 5.4% neonates required phototherapy while none of them required exchange transfusion. In a study conducted by Meena JK *et al* [8], 95.5%, 79.4% and 36.4% neonates developed significant jaundice in group A (cord blood albumin <2.8 gm/dl), group B (cord blood albumin 2.8-3.3 gm/dl), and group C (cord blood albumin >3.3 gm/dl) respectively.

In group A, 81.8% required phototherapy and 9.1% required exchange transfusion. In group B and C, 26.5% and 2.3% neonates required phototherapy respectively. None of the neonates required exchange transfusion in both group B and C. Similarly, Suchanda *et al* [14] conducted a study on 40 neonates and found that 82% of neonates who had cord blood albumin levels less than 2.8 gm/dl developed hyperbilirubinemia requiring phototherapy while about 12% of them needed exchange transfusion.

At higher levels of cord blood albumin (i.e. 2.8 - 3.3 gm/dl), 40% received phototherapy whereas neonates with cord blood albumin >3.3 gm/dl did not require any medical intervention for hyperbilirubinemia. Similarly, in a study by Trivedi *et al* [6] on 605 infants, 205 neonates developed hyperbilirubinemia of which 120 (58.5%) neonates had cord serum albumin level < 2.8gm/dl, 59 (28.8%) neonates had cord serum albumin level in the range of 2.8 – 3.5 gm/dl, whereas 26 (12.7%) neonates developed hyperbilirubinemia even though cord serum albumin level was more than 3.5 gm/dl. (p <0.05).

In our study, there was a negative Pearson's correlation (r = -0.440) between cord blood albumin and serum total albumin, which was statistically significant (p-value <0.001). Trivedi *et al* [6] in their study found a positive correlation between cord serum albumin levels and cord serum conjugated bilirubin (r=0.2, p >0.05) whereas the correlation between cord serum albumin level and unconjugated bilirubin was found to be negative (r = - 0.1917).

There was no attrition and we could analyse all the patients enrolled in the study. However, this study was a single-centre study limited only to term neonates, so the results could not be validated for large populations. Large, multicentric trials are further required to validate the findings of this study.

Conclusion

Umbilical cord blood albumin level in healthy term neonates is a useful predictor of subsequent significant neonatal jaundice. Low cord blood albumin level is associated with increased incidence of neonatal hyperbilirubinemia requiring phototherapy and/or exchange transfusion. Early discharge can be safely planned in neonates with cord blood albumin level >3.3 gm/dl, whereas a closer follow-up is a must in neonates with albumin levels ≤3.3 gm/dL for early detection of significant jaundice. Hence, routine estimation of cord blood albumin level is recommended for all term neonates in institutional delivery. These levels will help to effectively design the follow-up plan for high risk group neonates who are being discharged early.

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