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Cord blood albumin as a predictor of significant neonatal hyperbilirubinemia in normal term healthy newborn

[1]Dr. Dharmagadda Sai Krishna, [2]Dr. Hemant Gupta, [3]Dr. Neelam Grover, [4]Dr. Bharti Kawatra, [5]Dr. Kiranjeet Kaur

[1]Junior Resident, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh, India
[2]Associate Professor, Department of Paediatrics, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh, India
[3]Professor and Head, Department of Paediatrics, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh, India
[4,5]Professor, Department of Biochemistry, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh, India

Corresponding Author: Dr. Hemant Gupta, Associate Professor, Department of Paediatrics, Maharishi Markandeshwar Medical College and Hospital, Solan, Himachal Pradesh, India
Email: hemant.solan@gmail.com
Mobile: 9418469707

Abstract

Introduction: Hyperbilirubinemia is the most common morbidity in normal term healthy newborn. There is evidence that cord blood albumin (CBA) level can act as a potential marker for the prediction of hyperbilirubinemia in neonates. The present study was therefore designed to establish a correlation between the level of cord blood albumin (CBA) and total serum bilirubin (TSB) so that albumin level could be standardized as a prediction marker for the neonatal hyperbilirubinemia.
Methods: CBA and TSB levels were analysed in 500 normal term healthy newborns with birth weight ≥2500 grams and APGAR score ≥ 7/10 at 1 min and 5 mins, after obtaining consent from their parents. Albumin levels were analysed from the cord blood at the time of birth and TSB levels were analysed from venous blood. Pearson's correlation coefficient was used to analyse the correlation between CBA and TSB levels.
Results: The mean CBA was 2.94 ± 0.34 g/dl and mean TSB was 11.17 ± 2.52 mg/dl. The relationship between CBA and TSB values was statistically significant on further analysis of CBA with the modality of treatment, the results were again statistically significant. The correlation between CBA and TSB was also observed with negative correlation of r = - 0.43 with p value of <0.0001 which was highly significant.
Conclusion: Newborns with high CBA levels have low risk of developing neonatal hyperbilirubinemia and can be discharged early from hospital. Whereas low CBA is an indicator for developing neonatal hyperbilirubinemia in the first week of life.

Keywords: Albumin, Bilirubin, Hyperbilirubinemia, Neonates

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Introduction

Jaundice occurs in sixty percent of term and eighty percent of preterm newborns in the 1st week of life, it is the common morbidity and reason for readmission after discharge. [1] Jaundice in neonates is visible in skin and eyes when total serum bilirubin concentration exceeds 5-7 mg/dl. A relatively shorter life span of red blood cells (RBCs), increased RBC mass, immature conjugation of bilirubin, with higher levels of monoglucuronidase, paucity of intestinal bacteria, enhanced beta-glucuronidase activity in the gut and decreased motility of intestines, all contribute to the so-called "physiological" jaundice of the newborn. Physiological jaundice is visible between 24-72 hours of age, in term babies. With the maximum magnitude seen on 3rd day of life, total serum bilirubin doesn't exceed 15mg/dl and it may take weeks before the total serum bilirubin (TSB) levels fall under 2 mg/dl. Physiological jaundice never appears before 24 hours of life. [2] Normal healthy term neonates are discharged early after a normal vaginal delivery due to issues like hospital acquired infections, various social as well as economic issues. [3] Every newborn discharged from hospital within 48 hours of delivery should have a follow-up visit after 48-72 hours as recommended by American Association of Paediatrics (AAP) to look for any significant jaundice and other problem. [4]
Several studies have shown the co-relation between decreased serum albumin and increase serum bilirubin, but to measure the serum albumin, the baby has to be pricked. This can be avoided if the CBA is checked. In this study CBA level was estimated and used in anticipation of significant neonatal jaundice subsequently, so that treatment could be initiated with phototherapy or exchange transfusion. In normal term healthy neonates bilirubin induced encephalopathy (BIE) has been reported without any hemolysis and it is a major concern to the clinician when discharging neonates early after birth. [5] By predicting the newborn developing significant neonatal jaundice early at birth, we can design and implement the follow up program in high-risk groups effectively and thus prevent kernicterus. [6]
Aim of the present study was to investigate the effectiveness of CBA as a predictor of significant neonatal hyperbilirubinemia in normal term healthy newborn and to establish a correlation between levels of CBA and TSB thereafter as a predictor of significant neonatal hyperbilirubinemia.

Material and Methods

Patients recruitment: 500 normal term healthy newborns with birth weight ≥2500 grams and APGAR score ≥ 7/10 at 1 min and 5 mins, were recruited in the present study after obtaining consent from their parents. Neonates with low birth weight (< 2500 grams), preterm, ABO and Rh incompatibility, hemolytic anemias, birth asphyxia, congenital malformation, respiratory distress, meconium-stained amniotic fluid, cephalohematoma, extensive bruising, neonatal jaundice within 24 hours of life and neonatal sepsis were excluded from the study.

Cord blood albumin (CBA) and Total serum bilirubin (TSB): Two ml of cord blood was collected at Birth. Cord blood sample taken was centrifuged at 3000 rpm (revolutions per minute) and the resultant serum was sent for analysis in Autoanalyzer for albumin content. The Autoanalyzer is an automated analyser using a flow technique called continuous flow analysis (CFA). An auto analyser can analyse hundreds of samples every day with one operating technician. All the enrolled newborns were followed up for five days and clinical assessment for jaundice was done according to Kramer and dermal scale. From neonates who were included, 1.5 ml of blood from vein was drawn between 3 to 5 Days or earlier when indicated to measure the total and indirect serum bilirubins. The babies were followed up daily and the levels of serum bilirubin were estimated and intervention was undertaken when required as per hyperbilirubinemia management guidelines.

Statistical analysis was carried out using SPSS 25.0 (IBM, Trialware, USA). Measure of central

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tendency was used to measure all the quantitative variables. Qualitative variable was described in frequencies and proportions. Data was expressed as mean ± standard deviation for normally distributed continuous variables. Pearson correlation was used to analyse the correlation between quantitative variables. Whole data was presented in tables and graphs. All tests were tested at 5% level of significance and 95% confidence interval (significance level of $\alpha = 0.05$).

Results

Among total 500 neonates, 382(76.4%) neonates delivered via normal vaginal delivery (NVD) and 118 (23.6%) neonates delivered via lower segment caesarean section (LSCS). The males to female sex ratio was 1.02: 1 with male in higher number compared to females. 253 (50.6%) were males and 247 (49.4%) were females. CBA levels was <2.8 g/dL in 145(29%) neonates, 2.8-3.30 g/dL in 298(59.6%) and >3.30 g/dL in 57(11.4%) neonates. TSB levels was <15 mg/dL in 460(92%) neonates, 15-20 mg/dL in 39(7.8%) and >20 mg/dL in 1(0.2%) neonate. 40(8%) out of 500 neonates developed significant neonatal hyperbilirubinemia (Figure 1 and Table 1).

Seventy three (50.34%), 38(12.75%) and 3(5.26%) neonates received phototherapy who had CBA level less than 2.8 g/dl, between 2.8-3.3 g/dl and more than 3.3.g/dl accordingly (Figure 2 and Table 2). Neonates with high levels of CBA required less phototherapy when compared to neonates with low levels of CBA.

Amongst neonates who had TSB levels <15 mg/dL, 10.08% cases received the phototherapy. All the neonates who had TSB > 15 mg/dL received the phototherapy (Figure 3 and Table 3). Neonates with high levels of TSB required more phototherapy when compared to neonates with low levels of TSB.

The mean CBA was 2.94 ± 0.34 g/dl and mean TSB was 11.17 ± 2.52 mg/dl.

Statistically significant negative correlation with p value < 0.0001 was observed between CBA and TSB levels. Pearson correlation was mild to moderate with r = -0.4398 (Figure 4 and Table 4).

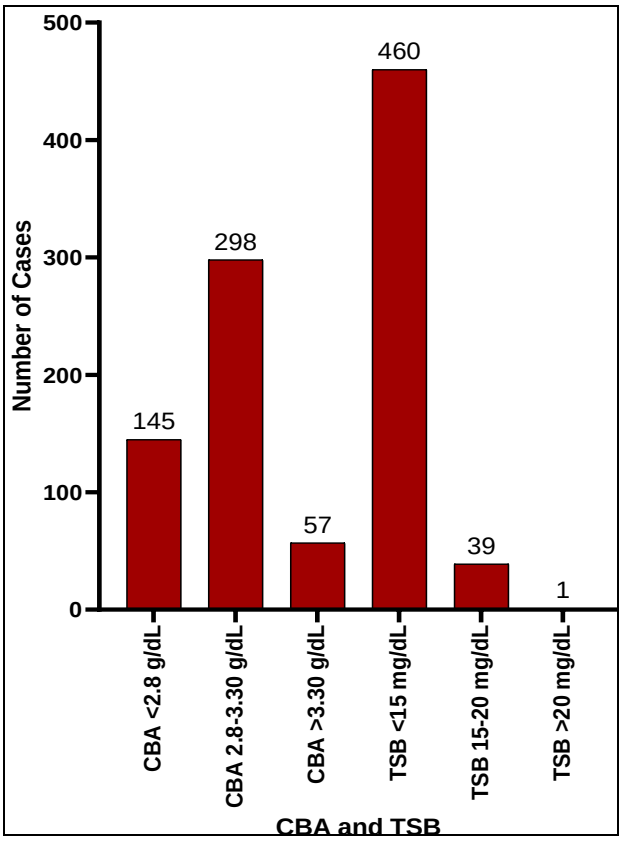

Figure 1: Distribution of CBA and TSB

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Table 1: Distribution of CBA and TSB

	Range	N (%)
Cord blood Albumin	<2.8 g/dL	145 (29%)
	2.8-3.30 g/dL	298 (59.60%)
	>3.30 g/dL	57 (11.40%)
	Total	500 (100%)
Total Serum Bilirubin	<15 mg/dL	460 (92%)
	15-20 mg/dL	39 (7.8%)
	>20 mg/dL	1 (0.2%)
	Total	500 (100%)

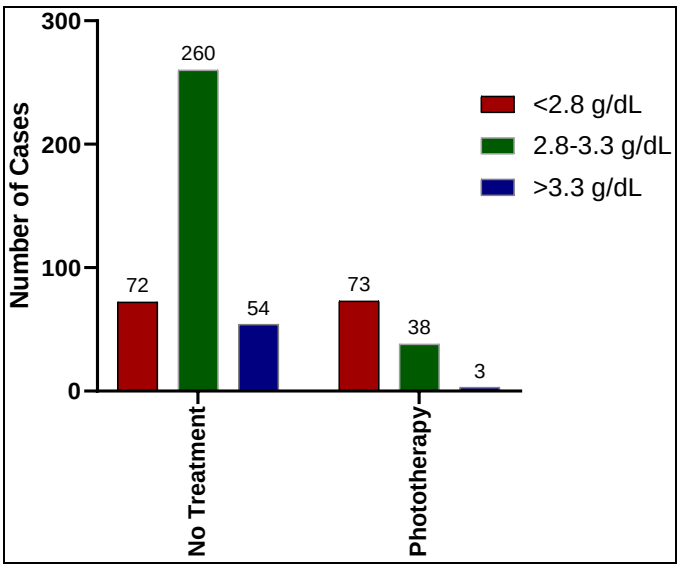

Figure 2: Treatment in study subjects according to CBA

Table 2: Treatment in study subjects according to CBA

Treatment	Cord blood Albumin				P value
	<2.8 g/dL	2.8-3.3 g/dL	>3.3 g/dL	Total	
No Treatment	72 (49.65%)	260 (87.24%)	54 (94.73%)	386 (77.2%)	
Phototherapy	73 (50.34%)	38 (12.75%)	3 (5.26%)	114 (22.8%)	0.0001***
Total	145 (29%)	298 (59.6%)	57 (11.4%)	500 (100%)	

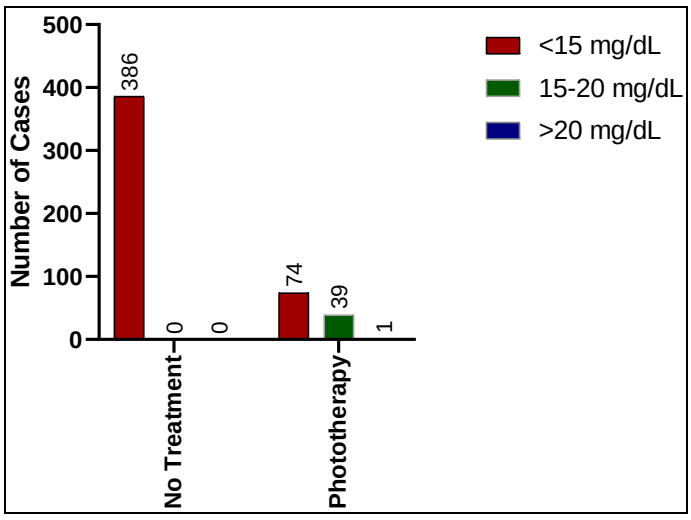

Figure 3: Treatment in study subjects according to TSB

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Table 3: Treatment in study subjects according to TSB

Treatment	Total Serum Bilirubin				P value
	<15 mg/dL	15-20 mg/dL	>20 mg/dL	Total	
No Treatment	386 (83.91%)	0	0	386 (77.20%)	
Phototherapy	74 (10.08%)	39 (100%)	1 (100%)	114 (22.80%)	0.0001***
Total	460 (92%)	39 (7.8%)	1 (0.2%)	500 (100%)	

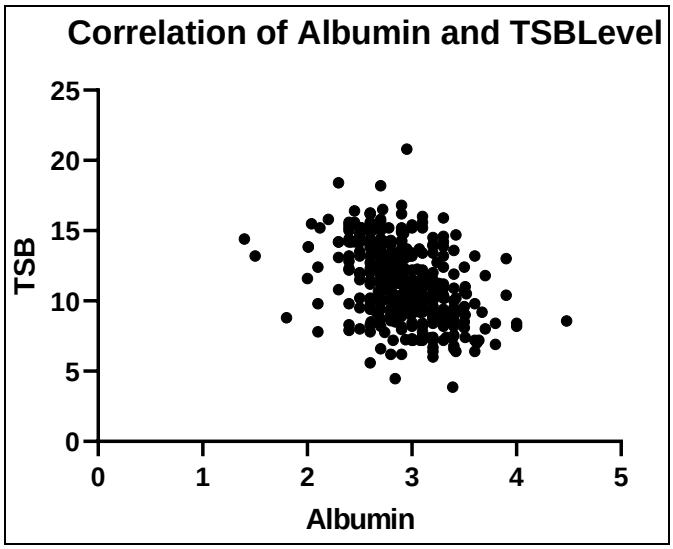

Figure 4: Correlation between CBA and TSB levels

Table 4: Correlation

Pearson correlation (r)	-0.4398
95% confidence interval	-0.5080 to -0.3661
R squared	0.1934
P (two-tailed)	<0.0001***

Discussion

In the present study, the TSB levels were <15 mg/dl, 15-20 mg/dl and >20 mg/dl in 460(92%), 39(7.8%) neonates and 1(0.2%) neonate respectively. Forty (8%) out of 500 neonates developed significant neonatal hyperbilirubinemia. Neonatal hyperbilirubinemia was observed in 64 percent of neonates in the study conducted by Awad *et al*. with 22 percent of newborns requiring phototherapy, one percent requiring exchange transfusion, and 77 percent requiring no intervention at all. [7] The study conducted by Khairy *et al*. [8] and Alalfy *et al*. [9] have found a high incidence of hyperbilirubinemia. The results of the present study are in concordance with those of Kumar *et al*. [10] and Thakur *et al*. [11] who also reported a lower incidence. This disparity can be attributed to the racial and ethnic disparities among the populations examined for jaundice by various researchers.

Chandan and Praveen studied and found that roughly half of term and eighty percent of preterm newborns developed jaundice, typically two to four days after delivery and disappeared spontaneously after one to two weeks. In their study significant hyperbilirubinemia was found in 6.87 percent neonates and all the neonates had considerably lower CBA levels (< 3.8g/dl). As a result, based on CBA, a group of newborns at risk of developing jaundice at delivery could be identified. [12] In our investigation, there was no statistically significant association between birth weight and CBA level groups. The study conducted by Dhanjal *et al*. [5] and Aiyappa *et al*. [13], however revealed that when the neonate's birth weight was taken into account, the lower the birth weight, the lower the CBA levels and higher the chance of developing icterus. There was no significant association between albumin levels from cord blood and other factors such

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as gender, type of birth, feeding type, gestational period, mother age, or order of the newborn in the present study as also seen by Meena *et al*. [14] and Reshad *et al*. [6]

In the present study, neonates who had CBA <2.8 g/dL, 50.34% cases received the phototherapy whereas neonates who had CBA 2.8-3.3 g/dL, 12.75% cases received phototherapy and neonates who had CBA >3.3 g/dL, 5.26% cases received phototherapy. Neonates with high levels of CBA required less phototherapy when compared to neonates with low levels of CBA. The results of the present study relate with those of S. Sahu *et al*. [15] who concluded that neonates having CBA levels greater than 3.3 gm/dl are safe to discharge early. Umbilical cord albumin levels are useful in predicting the development of jaundice in healthy term infants. [15] In Sapkota and Gami trial, five out of 100 babies experienced substantial neonatal hyperbilirubinemia (TSB level 17 mg/dl), necessitating phototherapy. None of the neonates required exchange transfusion. [16] Their observations were similar to present study.

The prognostic usefulness for future hyperbilirubinemia by measuring CBA and bilirubin in newborns delivered ≥35 weeks of gestational age was investigated by Mashad *et al*. [17] They discovered that 81.8 percent of newborns developed severe hyperbilirubinemia who had CBA <2.8 g/dl, whereas CBA levels >3.3 mg/dl were considered safe and had no incidence of neonatal hyperbilirubinemia. According to the authors, to predict future significant hyperbilirubinemia in newborns, CBA could be helpful. Mishra and Naidu determined the association of CBA with TSB levels. [18] As per their results 95% of neonates who had hyperbilirubinemia, the albumin levels were <2.8 g/dl. Hence, they concluded that the development of neonatal hyperbilirubinemia could be predicted by measuring CBA levels at birth and could be used as a risk indicator. Chandan and Praveen have also concluded that there is an association between the amount of CBA and newborn hyperbilirubinemia. A CBA level of <3.8 g/dl is a risk indication for newborn hyperbilirubinemia development. [12]

In the present study, correlation was established between TSB and CBA. Out of one forty five; thirty (20.69%) neonates with CBA less than 2.8 g/dl, developed significant hyperbilirubinemia with TSB >15 mg/dl, ten (3.35%) out of 298 neonates in the group with CBA between 2.8-3.3 g/dl developed hyperbilirubinemia, none out of 57 neonates developed significant hyperbilirubinemia in the group with CBA >3.3 g/dl. This elucidates that with increased CBA, the number of neonates with TSB >15 mg/dl decreased and showed negative correlation with r = -0.439. Thus, higher the CBA the lower the TSB levels were found. This result was similar with Sapkota and Gami which showed negative correlation between CBA and TSB with r = -0.455 thereby concluding CBA level as a risk factor for developing severe jaundice. [16] A study by Hanan *et al*. [19] also showed similar negative correlation with r= -0.684. In the present study, strength of the correlation between CBA and TSB was moderately negative as the sample size was only 500 neonates. It could have been more significant, if the sample size is large. Hence, more studies are needed with large sample size to establish strong correlation.

Conclusion

In the present study, the CBA level and TSB levels shows negative correlation (r = -0.4398). Thus, low CBA levels are high risk indicators towards predicting neonatal hyperbilirubinemia. Source of CBA is the mother's circulation; 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. Neonates with high levels of CBA required less phototherapy when compared to neonates with low levels of CBA. Also neonates with high levels of TSB required more phototherapy when compared to neonates with low levels of TSB. The use of CBA values may help to detect the newborn at low or high risk for hyperbilirubinemia. CBA gives additional clue in visualizing future hyperbilirubinemia to protect them from latter age complications.

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