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**Research Article**

# A study of cord blood albumin as a predictor of significant neonatal hyperbilirubinemia in term and preterm neonates

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## ABSTRACT

**Background:** Neonatal hyperbilirubinemia (NH) is the commonest abnormal physical finding which affects nearly 60% of term and 80% of preterm neonates during the first week of life. Although hyperbilirubinemia is more prevalent in preterm infants due to multiple factors, it can occur even in healthy term infants. Albumin is synthesized by liver and it helps in transport of unconjugated bilirubin. Early prediction of hyperbilirubinemia will help in early discharge and prevent hospitalization of babies and mothers for a longer period.
**Methods:** Observational study was performed on 175 newborns, divided in to term and preterm. Cord blood was collected from the newborns for cord serum albumin level measurements. Total serum bilirubin was measured during 72-96 hours of life, or earlier if clinically indicated, and assessed clinically daily for NH and intervened.
**Results:** Study cohort was grouped in to term and preterm, and each was further divided into 3 groups based on Cord Blood Albumin level (CBA) ≤2.8 g/dL, 2.9-3.3 g/dL and ≥3.4 g/dL, respectively. In these groups, the CBA levels of newborns with significant hyperbilirubinemia that required intervention was correlated with cord serum albumin levels. It showed that CBA level ≤ 2.8 g/dL is critical, with a good sensitivity and positive predictive value, in both term and preterm neonates. CBA level ≥ 3.4 g/dL was found to be relatively safe for neonates.
**Conclusions:** There is a correlation between CBA level and hyperbilirubinemia in both term and preterm newborns. Cord blood albumin level of ≤2.8 g/dL can predict the development of neonatal hyperbilirubinemia.

**Keywords:** Cord blood albumin, Neonatal hyperbilirubinemia, Term and preterm, Prediction

## INTRODUCTION

Neonatal hyperbilirubinemia (NH) is usually a normal physiologic condition occurring during the transitional period after birth. It is not a singular disease in itself, but a physical finding associated with multiple possible etiologies.[1] In most infants, unconjugated hyperbilirubinemia reflects a normal physiological phenomenon and is of little consequence. But in some infants the bilirubin levels may become extremely high and can lead to many complications.[2] Hyperbilirubinemia in preterm infants is more prevalent, more severe, and its course more protracted than in term neonates, as a result of exaggerated neonatal red cell, hepatic, and gastrointestinal immaturity.[3] Albumin is a major binding protein in the human neonate.[4] Low production of albumin will lower its transport and binding capacity, especially in preterm neonates.[5]

The concept of prediction of Jaundice offers a valuable option to pick up babies at risk of developing neonatal hyperbilirubinemia. By predicting the newborns likely to develop significant neonatal jaundice early at birth, we can design and implement the follow-up program in these high risk groups effectively. The present study was designed to evaluate the predictive value of cord blood albumin (CBA) among both term and preterm newborns with subsequent hyperbilirubinemia, in rural Bangalore.

## METHODS

This was a prospective study carried out over a period of two years from December 2012 to May 2014, at MVJ Medical College and Research Hospital, Bangalore. The study group consisted of 150 newborns of which 75 were term babies and 75 preterm babies, irrespective of gender. All term babies and preterm babies whose gestational age was more than 32 weeks, irrespective of their gender and mode of delivery was included in the study. VLBW babies, SGA babies, babies with hemolytic disease (Rh and ABO), instrumental delivery (forceps and vacuum) babies and those babies with significant illnesses like neonatal sepsis, birth asphyxia, respiratory distress syndrome, and meconium aspiration syndrome were excluded from the study. Those babies whose apgar score was <7 at 1 minute and who developed neonatal jaundice within 24 hours of life were also excluded.

The neonates were categorized in to two: 1) Term neonates 2) Preterm neonates >32 weeks of gestation. Both Term and Preterm groups were further divided in to three groups each, based on their CBA levels (≤2.8 g/dL, 2.9-3.3 g/dL and ≥ 3.4 g/dL respectively.

Informed consent was obtained from the parents of the newborn before enrolling them in the study. Demographic profile and relevant information was collected by interviewing the mother and from mother's case sheet. Gestational age was assessed by New Ballard score and correlated with the LMP. Cord Serum Albumin level was estimated at birth. All enrolled babies were followed up for 5 days and clinically assessed for jaundice according to Kramer dermal scale.[6] Total Serum Bilirubin (TSB) estimation was done at 72-96 hours of age, or earlier if it was indicated, for estimation of serum total bilirubin and indirect bilirubin. The babies were followed up daily and the level of serum bilirubin was estimated and interventions undertaken as per hyper-bilirubinemia management guidelines.

The cord blood (2 ml) collected at birth was analyzed by Erba EM200 auto analyzer for cord serum albumin level. The venous blood samples collected from the baby at 72 to 96 hours of life were subjected for total and direct serum bilirubin, by Diazotized sulfanilic test and for blood group analysis.

The main outcome of the study was inferred in terms of neonatal hyperbilirubinemia requiring intervention. Interventions like phototherapy and exchange transfusion were undertaken as per hyperbilirubinemia management guidelines.[7,8]

Data was tabulated in Microsoft Excel and analysed using SAS 9.2, SPSS 15.0, Stata 10.1 and R environment ver.2.11.1. Proportions and Chi square test was used to analyse data. P value less than 0.05 was considered significant.

## RESULTS

The study cohort consisted of 150 neonates who fulfilled the inclusion criteria. The study group was categorized in to two: Term neonates and Preterm neonates >32 weeks of gestation, which was further divided based on cord serum albumin level in to 3 groups (Table 1).

**Table 1: Groups based on cord serum albumin (g/dl) level.**

| CBA (g/dl) | Term | Preterm | Total | % |
|---|---|---|---|---|
| ≤ 2.8(group 1) | 26(34.7%) | 46(61.3%) | 72 | 48 |
| 2.9-3.3 (group 2) | 28(37.3%) | 26(34.7%) | 54 | 36 |
| ≥3.4(group 3) | 21(28%) | 3(4%) | 24 | 16 |
| Total | 75(100%) | 75(100%) | 150 | 100 |

**Table 2: Correlation of clinical variables with need for phototherapy-term.**

| Variables | Phototherapy | | P value |
|---|---|---|---|
| | Yes (n= 31) | No (n=44) | |
| Gender | | | |
| Male | 16 (51.6%) | 23 (52.3%) | 0.955 |
| Female | 15 (48.4%) | 21 (47.7%) | |
| Mode of delivery | | | |
| Vaginal | 16 (51.6%) | 25 (56.8%) | 0.656 |
| Cesarean | 15 (48.4%) | 19 (43.2%) | |
| Birth weight (kgs) | | | |
| <3 | 22 (70.9%) | 25 (56.8%) | 0.201 |
| 3-3.5 | 7 (22.6%) | 18 (40.9%) | |
| >3.5 | 2 (6.5%) | 1 (2.3%) | |
| CBA (Mg/dL) | | | |
| ≤2.8 | 19 (61.2%) | 7 (15.9%) | 0.001 |
| 2.9-3.4 | 10 (32.3%) | 18 (40.9%) | |
| ≥3.4 | 2 (6.5%) | 19 (43.2%) | |

**Table 3: Correlation of clinical variables with need for phototherapy-preterm.**

| Variables | Phototherapy | | P value |
|---|---|---|---|
| | Yes (n= 41) | No (n= 34) | |
| Gender | | | |
| Male | 25(61%) | 17(50%) | 0.34 |
| Female | 16(39%) | 17(50%) | |
| Mode of delivery | | | |
| Vaginal | 26(63.4%) | 20(58.8%) | 0.585 |
| Cesarean | 15(36.6%) | 14(41.2%) | |
| Birth weight (kgs) | | | |
| <2.2 | 23(56.1%) | 4(11.8%) | 0.0001 |
| 2.2-2.4 | 18(43.9%) | 21(61.8%) | |
| >2.4 | 0 | 9(26.4%) | |
| CBA (g/dL) | | | |
| ≤2.8 | 33(80.5%) | 13(38.2%) | 0.001 |
| 2.9-3.4 | 8(19.5%) | 18(53%) | |
| ≥3.4 | 0 | 3(8.8%) | |

The demographic variables and the variables, which influence neonatal hyperbilirubinemia directly or indirectly, for term and preterm neonates were compared and are shown in Table 2 and Table 3 respectively.

In Table 2, statistical significance can be seen between cord serum albumin and neonatal hyperbilirubinemia (P= 0.001). In table III, statistical significance can be seen with birth weight (0.001) and cord blood albumin (0.001) for the subsequent occurrence of neonatal hyperbilirubinemia.

## DISCUSSION

Studies and literatures have shown that neonates have an immature liver function as compared to that of adults. As a result, there is decreased production and synthesis of all the major proteins in the newborns. On the other hand, liver at times may not be able to handle the excess production of bilirubin that may occur due to various reasons in newborn. The decrease in the production of various proteins means that there is a decrease in the production of albumin, which has a major role in the conjugation of bilirubin. Albumin acts a carrier protein for the transport of bilirubin, which eventually helps in the transfer of bilirubin to the liver where conjugation occurs. This process is interrupted due to decreased albumin levels in newborns. The impact is more so in preterm newborns, which have an even decreased albumin levels. In this present study, we assessed the Cord Serum Albumin (CSA) level as a tool for screening for the risk of subsequent NH, in both term and preterm neonates and compared its efficacy in both the groups.

In the present study, Term group had 31 males and 44 females, while preterm group had 41 males and 34 females respectively. There was no significant association between gender and NNHB in either of the two groups (0.955 in term; 0.343 in preterm). There was also no association found between neonatal hyper-bilirubinemia and the mode of delivery, in both term and preterm neonates with p value of 0.656 in term group and 0.585 in preterm group respectively.

In our study, in the term group, 22 out of 47 newborns with birth weight less than 3 kg developed significant neonatal hyperbilirubinemia. Only 2 newborns with birth weight more than 3.5 kg developed NH. With P =0.201, there was no significant association between birth weight and significant NH. Among preterm newborns, there was a significant association between birth weight and development of significant NH (P=0.0001). Romagnoli, et al in 1983 and Onwuanaku, et al in 2011, in their respective studies concluded that there was a significant association between birth weight and neonatal hyperbilirubinemia among preterm newborns. Rudy Satrya, et al in a study on 88 newborns, showed that there is no association (p 0.885) between birth weight and neonatal hyperbilirubinemia, among term newborns.[9-11] The present study is in correlation with these studies.

In the term group, 19 (61.2%) newborns with CSA < 2.8 g/dL developed neonatal hyperbilirubinemia. 13 (32.3%) newborns had CSA level between 2.9- 3.3 g/dL, and only 2 (6.5%) of the newborns with CSA level ≥3.4 g/dL developed significant neonatal hyperbilirubinemia. The P value was significant (0.001). In the preterm group, 33 (80.5%) newborns that developed significant hyperbilirubinemia had a CSA level <2.8 g/dL, 8 (19.5%) newborns had a CSA level between 2.9 and 3.3 g/dL. None of the newborns with CSA level >3.4 g/dL developed neonatal hyperbilirubinemia. There was a significant P value of 0.001.

Study of Sahu et al in 2011, showed that 70% (14/20) newborn who developed significant NH had CSA level <2.8 g/dL, 30% (6/20) newborn had CSA level 2.9-3.3 g/dL and none of the newborns with CSA level >3.4g/dL developed NH.[4] There was a Statistical significance noted between CSA and development of NH (p value <0.001). Trivedi et al in 2013, studied a total of 605 newborns and 205 newborns developed significant NH in study group with 58.35% (120/205) of the neonates with CSA level <2.8 g/dL developing significant NH (P= <0.05). Our study results correlated well with both these studies.[12]

Few studies were done on term newborns to find the correlation between CBA and NH, but none have been done on preterm newborns.[4,12,13] In the present study, it was found that there was a significant association between cord blood albumin values and the tendency to develop significant neonatal hyperbilirubinemia that may require intervention, and also the risk is the same for both term and preterm newborns when cord blood albumin levels are less than 2.8 g/dL. Between 2.9 g/dL, the risk is comparatively less, and with value above 3.4 g/dL, newborns have a very less chance of developing significant neonatal hyperbilirubinemia.

Our study had homogenous local rural population unlike heterogeneous group of neonates from Cosmopolitan Urban Bangalore. This is the strength of this study. It means that the Prediction test developed by us can be applied to the rural population as well. The limitation of our study was that it had a small sample size and only healthy neonates, in both term and preterm groups, were taken for the study.

## CONCLUSION

There is a significant association between cord blood albumin values and the tendency to develop significant neonatal hyperbilirubinemia in term as well as preterm neonates. Cord blood albumin can be used as a ‘surrogate marker’ for screening the newborns for development of neonatal hyperbilirubinemia. The evaluation of Cord Blood Albumin being a cost effective one, can be safely implemented in daily clinical practice, along with the presently available laboratory tests, for a better outcome in newborns developing hyperbilirubinemia.

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