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To study the correlation between various levels of cord blood albumin & serum bilirubin at 48 hrs of age in term healthy newborns

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Introduction: Neonatal Hyperbilirubinemia is the most common abnormal physical finding and the major cause of neonatal morbidity during the early neonatal period. Early identification of infants at risk might help in providing preventative therapy and follow-up. We aimed to assess whether arterial umbilical cord albumin level at birth predicts the development of neonatal hyperbilirubinemia in term newborns at 48 hrs of life. **Methods:** This prospective observational cohort study was conducted in a tertiary care hospital over 1 year in 200 term healthy neonates. Cord blood albumin was estimated at birth followed by serum bilirubin level on the 3rd postnatal day(48 hrs of age). **Results:** Total of 200 neonates were divided into three groups based on cord blood albumin level of <2.8 g/dl(group I), 2.8-3.4 g/dl(group II) and >3.4 g/dl(groupIII) with 32, 100 and 68 in three respective groups. 19 newborns (59.4%) in group I,14 in group II, and 7 newborns (10.3%) in group III developed serum bilirubin levels above an intermediate high-risk zone in Bhutani nomogram at 48 hrs of age. newborn with low cord albumin (<2.8g/dl) were significantly associated with higher bilirubin levels at 48 hrs of age. **Conclusion:** Neonates with cord blood albumin <2.8 gm/dl had a significant association of the development of hyperbilirubinemia at or above intermediate high-risk zone according to Bhutani nomogram at 48 hrs of life.

Keywords: Neonatal hyperbilirubinemia, Cord blood albumin, Pathological hyperbilirubinemia, Serum bilirubin.

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Introduction

Neonatal Hyperbilirubinemia is the most common abnormal physical finding and public health concern during the early neonatal period as many of the otherwise healthy term and near term newborn develops significant hyperbilirubinemia and kernicterus. About 60-70 % of term and 80 % of preterm have clinical jaundice. The incidence of significant hyperbilirubinemia is 15% among preterm and 3% normal term newborns. It is also the most common cause of readmission to the hospital during the early neonatal period [1,2]. Our hospital is a baby-friendly hospital with approximately 3000 deliveries per year. Healthy full-term newborns born following an uncomplicated delivery are discharged within 48 hours of life.

Hour-specific monitoring as used by developing countries is not applicable in most busy government settings. Under these circumstances, it is also not reliable to discharge full-term newborns examining only by visual assessment of hyperbilirubinemia by Kramer's rule applying cephalo-caudal progression of bilirubin and may also have observer variability. If newborns at risk of hyperbilirubinemia can be identified using reliable predictors, they can be timely treated and can be provided better follow-up care, band observing closely before discharge will further reduce morbidity and readmission rate in such newborns.[3].

Albumin helps in bilirubin clearance via increasing hepatic transportation. Low serum bilirubin may decrease the hepatic clearance and thus will increase significant hyperbilirubinemia. The lower Normal limit for serum albumin in term babies is 2.8gm/dl. The mean serum albumin level at term is 3.1gm/dl. Hence the normal range of Serum albumin at term is 3.1±3g./dl.[4]. The present study was conducted to find out the correlation between cord blood albumin and serum bilirubin at 48 hrs of life and to study whether low serum cord albumin level at birth can be used as a predictor for the development of hyperbilirubinemia above the high intermediate risk zone (>75th percentile) in healthy newborns.[2,5,6].

Methods

Setting: This was a prospective study, conducted at Mahatma Gandhi Memorial Medical College and Maharaja Yashwant Rao Holkar Hospital Indore. The study includes 200 term healthy neonates delivered at the hospital from July 2018 to May 2019.

Inclusion Criteria: 200 term healthy newborns with birth weight ≥2.5 kg.

Exclusion Criteria: Newborns with a congenital anomaly, birth asphyxia, traumatic birth, respiratory distress, sepsis, metabolic diseases, pathological hyperbilirubinemia before 24 hrs, infant of a diabetic mother, and haemolytic diseases requiring admission in NICU were excluded from the study.

Method: The minimum sample size of 167 was calculated using EpiInfo software by Kelsey method at a confidence limit of 80%, with an estimated prevalence of 15%, with a margin of error at 5%, eligible newborns were included consecutively whose parents gave consent to participate in the study over the study period. Approval was taken from the institutional ethics committee before conducting the study. Informed consent was obtained from the parents of the newborn for demographic profile and relevant information was collected in predesigned proforma. Cord blood was collected at birth and analysed by auto analyser method for Cord Serum Albumin level. Venous blood samples were collected from the baby at 48 hours of life. Serum bilirubin estimation is done within 12 hours of collection of a sample by Diazotized sulfanilic test. Gestational age was assessed using Ballard score, SGA, AGA and LGA were defined using Fenton chart. Newborns were dived into 3 groups for data analysis according to their cord albumin levels (<2.8, 2.8-3.4, and >3.4 g/dl), And were analysed to find out association with 3 risk zone according to Bhutani nomogram (Low-risk zone, low intermediate risk zone and High intermediate-risk zone and above). Bilirubin level at or above high intermediate risk zone (over 75th percentile cutoff value11.3mg/dl) at 48 hrs of age was considered a cutoff value to find out the association with cord blood albumin level. [2,6,7].

Statistic Analysis Data: was entered on the computer using Microsoft Office Excel Software program for Windows, then transferred to the Statistical Package of Social Science Software (SPSS) program and Stata 10.0 to be statistically analysed. Comparison between groups was performed using the Manne Whitney test for quantitative variables while comparison for qualitative variables was performed through Chi-square or Fisher's test. P values less than 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves were used to evaluate the accuracy of cord blood albumin.

Sensitivity, specificity, likelihood ratio for a positive Test and likelihood ratio were calculated.

Results

Table-1: Demographic profile of study population according to cord blood albumin at birth

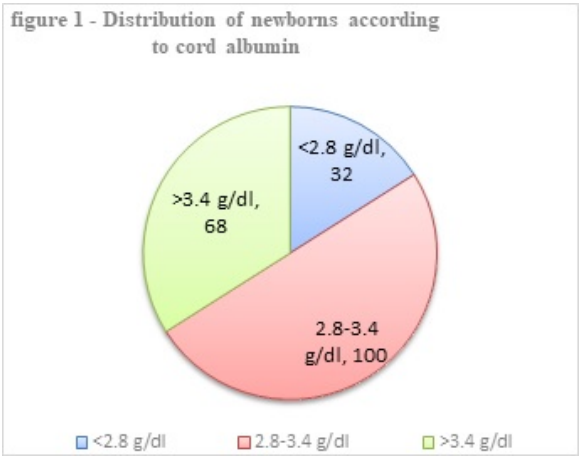
		Cord blood albumin(g/dl)			total	
		<2.8	2.8-3.4	>3.4		
Gender	Male	17 (15.3%)	59 (53.1%)	35 (31.5%)	111(55.5%)	>0.05
	Female	15 (16.8%)	41 (46%)	33 (48.5%)	89(12.3%)	
Birth Weight	2.5-3	24 (36.9%)	35 (53.8%)	6 (9%)	65 (32%)	<0.05*
	3.1-3.5	6 (7%)	62 (80%)	9 (13.2%)	77 (38%)	
	>3.5	2 (3%)	3 (4%)	53(91%)	58 (29%)	
Gestational age	mean age	37.5	38	38.3	149(74.5%)	>0.05
	37-40 wk	32(21%)	104(69%)	13(8%)		
	>40 wk	18(35%)	21(41%)	12(23.5%)	51(25.5%)	
newborns with higher birth weight had a significantly lesser incidence of low cord albumin(<2.8)* Gestational age and gender were not associated with low cord albumin at birth.						

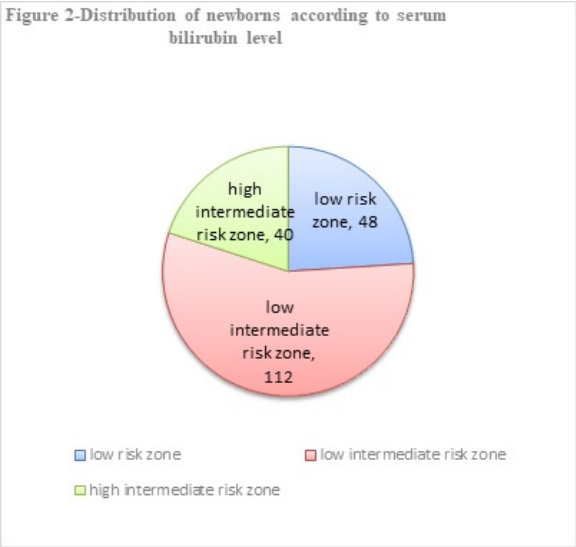
Table-2: Comparison of Cord blood albumin at birth and Total serum bilirubin at 48 hrs of age

Cord blood albumin(g/dl)	serum bilirubin at 48 hrs of age (mg/dl)				p-value
	Low-risk zone	Low intermediate-risk zone	High intermediate-risk zone	total	
<2.8	2 (6.3%)	11 (34.4%)	19 (59.4%) #	32(16%)	p <0.05*
2.8-3.4	3 (3%)	83 (83%)	14 (14%)	100(50%)	
>3.4	43 (63%)	18 (26.5%)	7 (10.3%)	68(34%)	
Total	48 (24%)	112 (56%)	40 (20%)	200	
[P=<0.05*] A significant number of newborns with cord albumin level <2.8 g/dl recorded serum bilirubin above high intermediate risk zone in Bhutani nomogram at 48 hrs of age. # 83.9% sensitivity, 81.7% specificity, and PPV 84.1% for cord blood albumin <2.8g/dl to detect hyperbilirubinemia at high intermediate risk zone.					

Out of the 200 infants enrolled in our study, 111(55.5%) were males and 89(44.5%). 16% newborn had cord albumin <2.8 ,50% recorded values between 2.8 to 3.4 and 68(34%) recorded cord albumin >3.4 g/dl. Newborns with higher birth weight had a significantly lesser incidence of low cord albumin (<2.8)*. gestational age and gender of the study population did not have a significant association with low cord albumin. (table 1, figure 1)

Out of 200 newborns, 48(24%) serum bilirubin levels were at the low-risk zone, 112(56%) at the low intermediate risk zone, while 40 (20%) were at the high intermediate risk zone at 48 hrs of age. 59.4% of newborns with cord albumin level <2.8 g/dl recorded serum bilirubin at or above high intermediate risk zone, while 11 were at low intermediate risk zone and 2 new-born were at low-risk zone at 48 hrs of age. This correlation was statistically significant. [$\chi 2$= 122.28; Likelihood Ratio=115.13; P=<0.05*] (table 2 figure2) We found that a cut-off level of cord blood albumin of 2.8g/dl had 83.9% sensitivity, 81.7% specificity, and PPV 84.1% for prediction of hyperbilirubinemia at high intermediate cut-off level with a p-value of <0.05 in term newborns, with NPV of 75% indicating its usefulness. ROC curve also analysis showed that the area under the curve was 0.872 of the total area making cord blood albumin a significant indicator to predict hyperbilirubinemia. (figure 3)





Discussion

According to recent AAP guidelines, healthy term newborns should be discharged within 48 hours of birth [2]. Hence it is necessary to identify the newborns at risk of developing hyperbilirubinemia following an early discharge from the hospital to avoid readmissions and complications as bilirubin encephalopathy and long term complications [3]. Albumin has a role in the transport and clearance of bilirubin. Albumin acts as a carrier protein for the transport of bilirubin, which eventually helps in the transfer of bilirubin to the liver where conjugation occurs.

Bilirubin binds to albumin in an equimolar ratio. Around 8.5 mg of bilirubin will bind covalently to 1 g of albumin, this process is interrupted due to decreased albumin levels in newborns. It is documented in the literature that newborns have an immature liver function as compared to adults leading to decreased production and synthesis of all the major proteins including albumin which has a major role in the conjugation of bilirubin.

And the neonatal liver is also immature with less ability to excrete and handle excessive production of bilirubin than can be caused by various aetiologies in newborns. Low production of albumin in newborns will lower its transport and binding capacity and may increase bilirubin in these newborns.[4]. In the present study we aimed to assess the correlation between cord blood albumin and serum bilirubin for early identification of hyperbilirubinemia and use of cord blood Albumin level as a tool for screening for the risk of subsequent Neonatal hyperbilirubinemia.

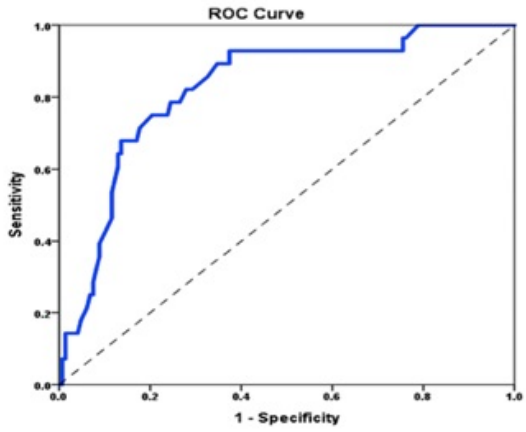
There are a few studies that predict Neonatal hyperbilirubinemia by estimating cord blood bilirubin levels but vary in opinion. In our study we found that a cut-off level of cord blood albumin of 2.8g/dl had 83.9% sensitivity, 81.7% specificity, and PPV 84.1% for prediction of hyperbilirubinemia for high intermediate cut-off level with a p-value of <0.05 in term newborns, with NPV of 75% indicating its usefulness. ROC curve analysis also showed that the area under the curve was 0.872 of the total area making cord blood albumin<2.8 g/dl a significant indicator to predict hyperbilirubinemia.[table 2, figure 3] Reshad M, Ravichander B et al[8] with the sample size of 175 terms and preterm newborn found that cord blood albumin level ≤ 2.8 g/dL is a sensitive limit, with good sensitivity and positive predictive value, in both term and preterm neonates and Cord blood albumin level ≥ 3.4 g/dL was found to be relatively safe for neonates.

Similar observations were made by Gaurav Aiyappa et al. [71.8%9] with 71.8% sensitivity and 65.1% with a sample size of 165 newborns. In the present study, there is a statistically significant correlation between birth weight and cord blood albumin and between birth weight and serum bilirubin in term neonates with good sensitivity and specificity. As we did not take preterm neonates making our results more specific to term newborns. Sahu et al [10]. the study of 40 neonates also showed that 70% of newborns who developed significant neonatal hyperbilirubinemia had cord serum albumin level < 2.8 g/dl, 30% newborns had cord albumin level 2.9-3.3 g/dl and none of the newborns with cord albumin >3.4g/dl developed neonatal hyperbilirubinemia, and 80% neonates with cord albumin less than 2.8 mg/dl required phototherapy.

Statistical significance was noted between cord albumin with development of significant hyperbilirubinemia (p-value <0.001). In a study by Trivedi et al. [11]. 205 newborns out of 605 developed neonatal hyperbilirubinemia with 58.35% (120/205) of the neonates with cord albumin level <2.8 g/dl developing significant neonatal hyperbilirubinemia required intervention with statistical significance of P <0.05. A study by Meena KJ et al. [12] found that cord bilirubin level >2.5 mg/dl had a sensitivity of 77%, specificity of 98.6% with NPV of 96% which supports the results of the present study. Pahuja et al. [13]. also observed that the predictive value of cord albumin to detect neonatal hyperbilirubinemia was 75% with 61.3% sensitivity, and 76.8% specificity following the

Present study. Similar observations were also made by Asit Kumar et al. [5]. Dr Pushpanjali et al[14]. Dhanjal SS et al[15] and Pathak NN et al [16]. The limitations of our study were that we restricted the duration of follow-up for only the first 48 hours, due to our early discharge policy for healthy term newborns, and maximum serum bilirubin concentration is seen at 72 to 96 hrs. The strength of the study is that this is the first study that evaluated the hyperbilirubinemia using Bhutani nomogram as a cutoff limit to predict hyperbilirubinemia of high intermediate risk zone, making our results more reliable and accurate for healthy term newborns as early as 48 hrs, who are discharged early and often with poor followup for development of subsequent hyperbilirubinemia.

Figure 3-ROC curve analysis to correlate cord blood albumin as a tool to identify serum bilirubin level above high intermediate risk zone according to Bhutani's nomogram with the area under curve is 0.872 which is statistically significant.



Conclusion

In summary, we have demonstrated the predictive usefulness and clinical value of cord blood albumin level of <2.8 g/dl. This can be used as a risk indicator and an easy tool to predict the significant hyperbilirubinemia as early as at birth and at risk newborns can be provided better pre-discharge advice and early treatment to prevent complications associated with significant hyperbilirubinemia. This can further reduce morbidity, cost of treatment and readmission in such at-risk newborns In a developing country like India with high neonatal mortality and morbidity, cord blood albumin can be used by clinicians and health workers for early identification and early referral of at-risk neonates To referral centres. Cord blood albumin being a cost-effective marker, can be implemented in daily clinical practice for better management of newborns at risk of developing hyperbilirubinemia.

What does the study add to the existing knowledge

Cord blood albumin measurement at birth is an easy and reliable tool for predicting hyperbilirubinemia in healthy full-term newborns.

Author's contribution

Dr Sunil Arya-Concept, study design, data analysis, Final approval of the manuscript, Dr Chetan Panwar-Wrote study protocol, data collection, data analysis, statistical analysis, Dr Jyoti Prajapati-Manuscript preparation, statistical analysis, Review of Literature

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