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The Study of Cord Blood Albumin as a Risk Predictor of Neonatal Hyperbilirubinemia

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Abstract

Objective: To study correlation between umbilical cord blood albumin (CBA) and neonatal hyperbilirubinemia. ***Methods:*** From January 2023 to December 2023, a prospective observational study was conducted on 150 neonates, clinically stable babies delivered either vaginally or by caesarean section with birth weight ≥2 kg. At birth, CBA was analysed and neonate was followed up till 72 hours of birth for hyperbilirubinemia. Detailed analysis was done to correlate CBA with significant hyperbilirubinemia requiring treatment according to >35 weeks charts (AAP guidelines 2022). The statistical analysis used were Microsoft Excel and SPSS software. A p-value of less than 0.05 was considered statistically significant. ***Result:*** On the basis of CBA obtained, all the neonates were classified into 3 groups, 1st of 2-2.5g/dl, 2nd of 2.51 – 3g/dl and 3rd of >3g/dl. Significant hyperbilirubinemia (requiring phototherapy) was observed in 45 (30%) neonates and 105 neonates (70%) had no hyperbilirubinemia. The association between CBA levels and neonatal hyperbilirubinemia had strong statistically significant relationship ($p<0.05$). ***Conclusion:*** It was concluded that, CBA level of 2.15mg/dl belonging to group 1 had the highest sensitivity (95%) and specificity (100%) to predict appearance of significant neonatal hyperbilirubinemia and was statistically significant (p value<0.05).

Keywords: ***Hyperbilirubinemia, Cord Blood, Albumin, Phototherapy.***

Introduction

Neonatal hyperbilirubinemia is a major concern for parents and the pediatricians as it causes readmission in neonatal intensive care unit [1]. It is most commonly observed in the first week of life affecting nearly 60% of term and 80% of preterm neonates. 6.1% of well term neonates have a serum bilirubin more than 12.9 mg% at around 72 hours of life. Serum bilirubin value over 15 mg% is found in mostly 3% of normal term new-borns [2]. It basically occurs due to liver immaturity along with it reduced life span of red blood cells.

These harmful levels of bilirubin cross the blood brain barrier and damages the brain tissue which can lead to serious neurological condition called bilirubin induced neurologic dysfunction (BIND) manifesting in form of acute bilirubin encephalopathy and kernicterus. Therefore, early detection and treatment of neonatal hyperbilirubinemia is very important to prevent these life-threatening complications.

Unconjugated bilirubin is insoluble in water, so it gets transported by albumin to liver. The bilirubin bound to albumin does not cross the blood brain barrier making it less toxic. Thus lower the levels of albumin, more is the chances of increased hyperbilirubinemia due to lower binding of the bilirubin leading to lethal effects of it. Hence this study has been proposed to evaluate role of cord blood albumin levels as a risk predictor of neonatal hyperbilirubinemia

Materials and method

This prospective observational study was conducted in the Postnatal Ward of a tertiary care Hospital from January 2023 to December 2023 in Gujarat. The research was reviewed and approved by the Institutional Ethics Committee (Permission letter dated 19 July 2023)

Sample size calculation: Considering 5% level of significance, power of 90% and allowing for loss of data, sample size was calculated as 125. Hence the sample collected were 150 neonates considering feasibility and rounding off figures.

Inclusion Criteria: After written informed consent of parents, neonates with gestational age >36 weeks of both genders, delivered vaginally or by caesarean section with birth weight ≥2 kg were included.

Exclusion Criteria: Neonates with gestational age <36 weeks, those with perinatal asphyxia, neonates having Rh-negative mother or diabetic mother, twin/triplet neonates, those having meconium aspiration syndrome and respiratory distress syndrome were excluded from the study

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Procedure: All neonates enrolled in the study were first analysed with detailed history (antenatal, birth history and specific history regarding risk factors for neonatal hyperbilirubinemia) and was noted in preformed proforma. Along with that, clinical examination was done thoroughly. At birth, cord blood albumin was taken and analysed by autoanalyzer named Tabbot Architect C14000. The dye used in this analyser was Bromocresol green method and based on principle of colorimetry. Within 72 hours of birth, clinical assessment for hyperbilirubinemia was done. In neonates with clinically significant hyperbilirubinemia, further investigations were sent in form of complete blood count, serum bilirubin, ABO Rh grouping. Management was done in form of phototherapy, exchange transfusion and supportive care. Detailed analysis was done to know the correlation of cord blood albumin with significant neonatal hyperbilirubinemia (requiring treatment), according to >35 weeks charts (AAP 2022 guidelines) and was followed up till treatment was completed.

Statistical Analysis: Data analysis was done in Microsoft Excel and SPSS software. Categorical variables between the groups were compared using Chi Square, Z test and ANOVA test. A p-value of less than 0.05 was considered statistically significant.

Results

In this study, a total of 150 neonates were enrolled during the study period of around 1 year from January 2023 to December 2023. After analysing the total data obtained, there was a higher percentage of females, 85 (56.7%) compared to males. The distribution of birth weight of neonates, majority, 58 (38.7%) weighed between 2.6-3 kg, 51 (34%) weighed more than 3 kg and 41 (27.3%) weighed 2 - 2.5 kg. With comparison to other studies, Rehna T et al depicts majority weighed between 2.5–3.5 kg (76.69%) [3]. While, Huda et al shows that majority 60.7% weighed between 2.5 – 3 kg, which was similar to present study [5].

Table 1: Distribution of neonates as per gestational age

Gestational Age (Weeks)	Frequency	Percentage (%)
36-37	18	12
37-39	79	52.7
39-42	53	35.3
Total	150	100

Table 1 shows majority of neonates, 79 (52.7%) were born between 37-39 weeks, followed by 53 (34%) born between 39-42 weeks and 18 (12%) were born between 36-37 weeks. In previous studies, Rizwan et al, the mean gestational age observed was 38.95+/- 2.31 in Group 1 and 37.98+/- 2.33 in Group 2 of neonates distributed according to cord blood albumin levels [6]. In another study, Mashad et al done on 75 neonates, the mean gestational age obtained was 37.26+/- 4.28 [7].

The majority (66.7%) of neonates were delivered vaginally, while 33.3% were delivered by caesarean section. In other studies, like Meena JK et al, Gupta et al and Anupriya KS et al, majority of vaginal deliveries (53%, 59.9%, 53%) was observed similar to this study [4,8,9].

Table 2: Distribution of cord blood albumin level in study neonates

Cord albumin Level (g/dl)	Frequency	Percentage (%)
2-2.5	31	20.7
2.5-3	20	13.3
3-3.5	36	24
>3.5	63	42
Total	150	100

As shown in Table 2, the distribution of cord blood albumin levels of neonates indicated that majority 63 (66%) had levels > 3.5 g/dl and least, 20 (13.3%) were in the range of 2.5-3 g/dl.

Table 3: Association between cord blood albumin and gestational age

Cord blood albumin(g/dl)	Gestational Age (weeks)			Total	Value	Df	P Value*
	36-37	37-39	39-42				
2-2.5	8	12	14	34	26.139	6	0.00
	44.5%	15.2%	26.4%	22.7%			
2.5-3	1	12	7	20			
	5.5%	15.2%	13.3%	13.3%			
3-3.5	7	17	9	33			
	38.8%	21.5%	16.9%	22.0%			
>3.5	2	38	23	63			
	11.1%	48.1%	43.4%	42.0%			
Total	18	79	53	150			

As mentioned in Table 3, out of 18 neonates of gestational age, 36 – 37 weeks, majority, 8 neonates had cord blood albumin level of 2-2.5g/dl (44.4%), thus signifying lower gestational age neonates had lower levels of cord blood albumin which was also statistically significant (p value<0.05). Also, out of 53 neonates of gestational age 39 – 42 weeks, majority, 23 (43.4%) had cord albumin level of >3.5g/dl.

In this study, 30% (n=45) of babies developed significant hyperbilirubinemia (requiring phototherapy), while the remaining 70% (n=105) did not develop significant hyperbilirubinemia. On comparison with the previous studies, Meena JK et al and Anupriya KS et al showed similar proportion of development of hyperbilirubinemia, 30 (30%) and 29 (29%) to this study [8,9]. Hyperbilirubinemia rates seem to vary across gestational age groups, for neonates born 36-37 weeks, the rate is 27.8% which is greater than all other groups.

Neonates delivered via caesarean section, 42%, had a higher proportion of hyperbilirubinemia compared to those delivered vaginally, 24%. The data shows a statistically significant association (p value<0.05). In a study by Gupta et al, similar observation was seen, a significant association between caesarean delivery and significant hyperbilirubinemia in neonates at third day of life [10].

Table 4: Association between neonatal hyperbilirubinemia and Cord blood albumin levels

Cord blood albumin(g/dl)	Neonatal Hyperbilirubinemia		Total	Value	df	P Value*
	Yes	No				
2-2.5	29	2	31	111.775	3	0.00
	93.50%	6.50%	100.00%			
2.5-3	14	6	20			
	70.00%	30.00%	100.00%			
3-3.5	1	35	36			
	2.80%	97.20%	100.00%			
>3.5	1	62	63			
	1.60%	98.40%	100.00%			
Total	45	105	150			
	30.00%	70.00%	100.00%			

As mentioned in Table 4, the association between low cord blood albumin levels and significant neonatal hyperbilirubinemia indicated strong statistically significant relationship ($p<0.05$). Thus, Cord Blood Albumin ranging between 2 – 2.5g/dl strongly suggests association with onset of significant neonatal hyperbilirubinemia.

This study cord blood albumin levels compared with previous studies depicts that, the cut off value for cord blood albumin is similar to the studies Gupta N et al (n=152) and Huda WM et al (n=150), which is, <2.33 and <2.8.41,43 Also in other studies, Anupriya KS et al (n=100), Sandhya J et al (n=60) and Meena JK et al (n=100) the cut off values for cord blood albumin were <3.3, <3.05 and <3.3 [5,8-11].

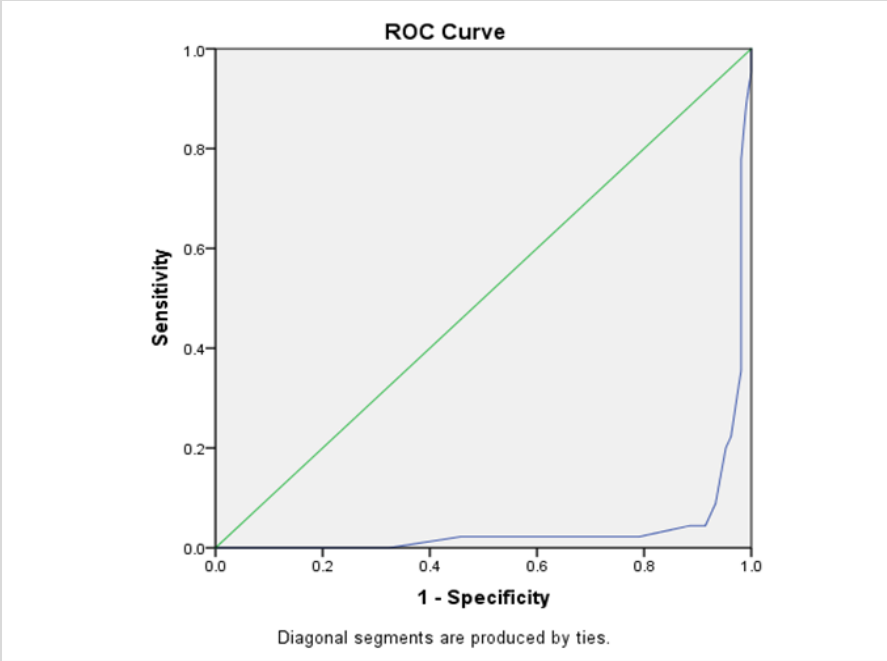

Fig 1: ROC curve to compare cord blood albumin level and to predict onset of neonatal hyperbilirubinemia requiring treatment

Table 5: ROC curve to compare cord blood albumin level and to predict onset of neonatal hyperbilirubinemia requiring treatment

Area	Std. Error	P Value*
0.042	0.018	0.00
Positive if Greater Than or Equal To[a]	**Sensitivity**	**1 - Specificity**
2.1500	.956	1.000
2.2500	.889	.990
2.3500	.778	.981
2.4500	.600	.981
2.5500	.356	.981
2.6500	.222	.962
2.7500	.200	.952
2.8500	.089	.933
3.0000	.044	.914
3.1500	.044	.886
3.2500	.022	.790
3.3500	.022	.752

The ROC curve analysis, as mentioned in Table 5, cord blood albumin and probability of requirement of subsequent treatment indicates a significant area under the curve (AUC) of 0.042 ($p < 0.05$), suggesting that cord blood albumin level is predictive of treatment requirement. The curve shows that the cord blood albumin level of 2.15mg/dl has the highest sensitivity (95%) and specificity (100%) to predict the requirement of treatment for hyperbilirubinemia among neonates.

Discussion

The findings of the present study revealed a significant association of lower cord blood albumin (CBA) with lower gestational age, birth weight, mode of delivery and significant neonatal hyperbilirubinemia. Cord blood albumin was significantly low (2-2.5g/dl) in neonates with gestational age of 36-37 weeks. At the time of the delivery, collected neonate's samples for cord blood albumin were classified into 4 groups, 1st group of 2-2.5g/dl, 2nd group 2.51 – 3g/dl, 3rd group 3.1 – 3.5 and 4th group >3.51 g/dl. These neonates were then followed up for occurrence of significant hyperbilirubinemia requiring treatment which was observed in 45 (30%) of neonates and 105 neonates (70%) did not develop hyperbilirubinemia. The treatment given to these neonates was phototherapy.

The results of the present study are almost similar to the previous studies done in India. The distribution of groups according to cord blood albumin and its comparison with prospective development of significant hyperbilirubinemia came out to be statistically significant (p value<0.05). While no significant association was seen with gestational age, gender, oxytocin induction during delivery, any previous maternal illnesses and jaundice in sibling.

The cord blood albumin levels in present study, compared with previous studies depicts that the cut off value for cord blood albumin was similar to the studies Gupta N et al (n=152) and Huda WM et al (n=150), which is, <2.33 and <2.8 [4,5]. Also in other studies, Anupriya KS et al (n=100), Sandhya J et al (n=60) and Meena JK et al (n=100) the cut off values for cord blood albumin were <3.3, <3.05 and <3.3 [6,7,10]. Cross sectional study from northern India, done by Huda WM et al, showed that neonates who developed neonatal hyperbilirubinemia, 95.2% had CBA ≤ 2.8 g/dl. In this range, there was 29% probability of developing neonatal hyperbilirubinemia and CBA ≥ 3.4 g/dl, had 0% probability of developing neonatal hyperbilirubinemia [5].

A prospective study Eastern India, done by Ahmar R et al, 110 term babies, 80 % had CSA>2.8 g/dl and 20% had < 2.8 g/dl. 48% of all babies developed icterus, and 41% from 1st group and 15.5% from 2nd group developed icterus. The total bilirubin level was significant in 2nd group (p<0.001). 41.5% with icterus required phototherapy and majority were from later group (p<0.05). Only 1 baby from Group 2 required exchange transfusion. Sensitivity of cord albumin to detect hyperbilirubinemia was found to be 74.5%, while specificity was 63.6%. Positive predictive value (PPV) was 42.7% and negative predictive value (NPV) 91.8 % [8].

In general, postnatal albumin values follow the gestational trend and increase with gestational age. Considering the functions of albumin, which include acting as an antioxidant, transporting bilirubin and free fatty acids. After birth, fetal hemoglobin is rapidly broken down, thereby releasing large amounts of bilirubin that should need to be transported off by albumin. The bilirubin binds to albumin in an equimolar ratio. Free bilirubin is anticipated when the molar bilirubin-to-albumin ratio (BAR) is > 0.8. About 8.5mg of the bilirubin will bind tightly to 1g of albumin. It is free bilirubin which can cross the blood brain barrier. Little data is available regarding the reference ranges for serum albumin values in preterm and term infants. In term neonates, serum albumin of 2.8gm/dl is the lower normal limit whereas the mean serum albumin level at term is 3.1gm/dl[11]. Thus, the normal range of serum albumin value at term is 3.1±3gm/dl.

Conclusion

The ROC curve analysis of cord blood albumin and probability of requirement of subsequent treatment indicated a significant area under the curve (AUC) of 0.042 ($p < 0.05$), suggesting that cord blood albumin level is predictive of treatment requirement.

This study showed that the cord blood albumin level of 2.15mg/dl belonging to group 1 comprising of umbilical cord blood albumin of 2-2.5g/dl has the highest sensitivity (95%) and specificity (100%) to predict appearance of neonatal hyperbilirubinemia requiring treatment. As the neonates belonging to group 1 of 2-2.5g/dl cord blood albumin level, developed significant hyperbilirubinemia in higher proportion. Thus, signifying that cord blood albumin can be considered as a major risk factor for development of neonatal hyperbilirubinemia. In neonates with significantly low cord blood albumin level can be followed up intensively for appearance of significant neonatal hyperbilirubinemia. Hence, early detection of neonatal hyperbilirubinemia can help in timely management of neonatal hyperbilirubinemia and prevent the early as well as long term complications associated to neonatal hyperbilirubinemia.

Limitation

There is a scope for increasing of sample size with efficient laboratory facilities in our overburdened tertiary care institution. The group of early premature babies were not included in the study so we cannot comment on the level of umbilical cord blood albumin and its role in neonatal hyperbilirubinemia requiring treatment. We can do future study on group of early premature babies to evaluate umbilical cord blood albumin level as a risk predictor for all neonates developing hyperbilirubinemia.

Declarations

Funding

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Conflict of interest

None declared

Ethical Approval

The study was approved by the Institutional Ethics Committee

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