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Original Article

Predictive Value of Umbilical cord Blood Albumin in early Identification of Neonatal Hyperbilirubinemia: An Observational Study

Priyamvada Singh[1], Kirtika Balhara[2], Parveen Kumar Antil[1], Satya Kiran Kapur[3]

1 Assistant Professor,
2 Resident,
3 Professor,
All from Department of Paediatrics, Faculty of Medicine and Health Sciences (FMHS), Shree Guru Gobind Singh Tricentenary University (SGT University), Budhera, Gurugram-Badli Road, Gurugram – 122505, Haryana, India

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Abstract

Introduction: Neonatal hyperbilirubinemia is clinically characterized by the yellowish discoloration of the skin and sclera. Early identification of neonates at risk for significant hyperbilirubinemia is crucial. Evaluating cord blood albumin levels has emerged as a predictive tool to assess the risk of developing hyperbilirubinemia.

Methods: A total of 266 eligible neonates were enrolled in this prospective observational study. Cord blood albumin (CBA) levels were measured and categorized into three distinct groups: Group A: CBA < 2.8 g / dL; Group B: CBA 2.8 – 3.3 g / dL; Group C: CBA > 3.3 g / dL. All neonates were followed from 24 hours to 72 hours of age. Kramer's rule was utilized to assess the progression of jaundice. If the neonate's jaundice reached Zone 2 on Day 1 or Zone 3 on Day 2 or Day 3, venous blood was collected for serum bilirubin estimation.

Results: On the second day of life, 30 out of 31 neonates in Group A (cord blood albumin < 2.8 g / dL), 25 out of 28 in Group B (cord blood albumin 2.8 – 3.3 g / dL), and 3 out of 141 in Group C (cord blood albumin > 3.3 g / dL) required phototherapy. By the third day, the need for phototherapy decreased to 8 in Group A, 1 in Group B, and none in Group C. Notably, 1 neonate in Group A required double-volume exchange transfusion on day 3, whereas none in Groups B and C required this intervention.

Conclusions: This study demonstrates cord blood albumin levels as a prognostic indicator for estimation of serum bilirubin which allows a more tailored approach to neonatal care.

Correspondence

Priyamvada Singh
Assistant Professor,
Department of Paediatrics,
Faculty of Medicine and Health Sciences (FMHS),
Shree Guru Gobind Singh Tricentenary University (SGT University),
Budhera, Gurugram-Badli Road,
Gurugram – 122505,
Haryana,
India
Email- priyam017singh@gmail.com

Introduction

Neonatal hyperbilirubinemia arises from elevated total serum bilirubin, clinically presenting as yellowish discoloration of the skin and sclera. It affects nearly 60% of the term and 80% of the preterm neonates within the initial week of life.[1] In most infants, unconjugated hyperbilirubinemia reflects a normal physiological phenomenon.[2] Physiological hyperbilirubinemia arises in neonates due to their limited uridine diphosphoglucuronosyl transferase (UDPGT) activity, approximately 1% of that found in adults. Additionally, the liver of neonate is not mature enough to handle the increased load of bilirubin.[3] However, it is important to distinguish physiological jaundice from a more severe condition called "pathological jaundice".

In term babies, physiological jaundice is seen to appear between 36 to 72 hours

of age, with maximum intensity on 4th day of life. It never appears before 24 hours of life.[4] In certain conditions, the bilirubin levels may exceed this duration and may cause complications like bilirubin encephalopathy and associated neurological sequel (kernicterus) which can be prevented if detected and treated early. Thus, the concept of prediction of jaundice by assessment of cord albumin offers an attractive option to pick up babies at risk of neonatal hyperbilirubinemia in order to implement early treatment and thereby minimize the risk of bilirubin induced brain damage.[5] The American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit after 48 - 72 hours of life to detect significant jaundice and other problems.[6] Loss to follow-up leads to delay in recognition of jaundice which might cause bilirubin induced brain damage resulting in sequel like cerebral palsy, sensorineural deafness and intellectual disability.[7,8]

Albumin is a preproprotein which accounts for about 60% of the total plasma proteins, with roughly 40% found in the plasma and the remainder in the extracellular space.[9] All fetal albumin is produced by the fetus, as it does not cross the hemochorial placenta, as evidenced in studies on rats, guinea pigs, and in vitro perfused human placentas.[10] Neonates have low albumin concentrations (2.5 g / dL), which reach adult levels (3.5 g / dL) after several months.[11] Albumin contributes to 70 - 75% of plasma oncotic pressure, possesses antioxidant properties, and transports substances such as bilirubin, free fatty acids, and cysteine.[12] Plasma albumin level increases as postnatal age increases.[13] Adult level is reached by about 5 months of age.[14]

The present study has been planned to study the co-relation between cord blood albumin level and neonatal hyperbilirubinemia in healthy full-term neonates and to co-relate cord blood albumin levels with neonatal hyperbilirubinemia in first 72 hours of life.

Methods

This was an observational study conducted in the Department of Paediatrics and Department of Obstetrics and Gynaecology, SGT University, Gurugram, India over a period of 18 months (September 2021 - March 2023). Ethical clearance was obtained from Institutional Ethics Committee, SGT University (IEC/FMHS/MD/ S/2022-42). Sample size was calculated using the formula 4pq/d2 (based on previous studies) where 'p' is prevalence of neonatal hyperbilirubinemia, 'q' is 100-p, 'd' is 10% of p (precision of the estimate). Thus, ideal sample size = 4 X 60 X 40 / 6 X 6 = 266. Convenient sample size of minimum 100 consecutive healthy full term newborns was taken. The inclusion criteria was full-term neonates (37 – 42 weeks) who had normal vaginal delivery / Caesarean section) with birth weight > 2500 gm and APGAR Score > 7 at 1 min and 5 min. Exclusion criteria included LBW / SGA babies, babies requiring NICU admission and those with maternal history of drugs intake during the third trimester. A structured proforma was used to collect. 2 - 3 ml of cord blood was taken for serum albumin estimation by auto analyzer method. The neonates were divided into three study groups based on cord blood albumin: group A (cord blood albumin < 2.8 g / dl), group B (cord blood albumin 2.8 - 3.3 g / dl) and group C (cord blood albumin > 3.3 g / dl). The neonates were followed starting at 24 hours till 72 hours. If Kramer's score exceeded zone 2 on day 1 or zone 3 on day 2 / day 3, then 1 ml of venous blood was for serum bilirubin estimation.

Results

A total of 266 eligible neonates were enrolled, where 155 were male and 111 were female babies. 200 newborns were delivered by normal vaginal route and 66 newborns were delivered by LSCS. Out of 266, 126 mothers had first baby, 100 had two babies and 40 mothers had more than two babies. 93 mothers had O+ blood group, 75 had B+ blood group, 53 had A+ blood group, 34 had AB+ blood group, 5 had A- blood group, 4 had O- blood group and 2 had B- blood group. The serum bilirubin levels and the cord blood albumin levels have been shown in Tables 1 and 2 respectively.

Table 1: Total serum bilirubin on the study population

TSB (mg / dl)	Days		%
	Day 1	Day 2 / 3	
≤ 10	42	44	32.3
10 - 14	46	55	38
15 - 17	7	9	6
≥ 17	21	42	23.7
Total	116	150	100

Table 2: Cord blood albumin (g / dl) levels of the study population

CBA (g / dl)	CBA- group	No. of new born	%
< 2 . 8	Group-A	41	15.4
2.8 - 3.3	Group-B	37	14
> 3 . 3	Group-C	188	70.6
Total		266	100

The biochemical parameters of the babies requiring phototherapy is illustrated in Table 3. The different maternal variables and their correlation with the need of phototherapy is shown in Table 4. The different maternal variables based on cord blood albumin levels are shown in Table 5. Table 6 represents the relationship between different clinical neonatal variables and the need of phototherapy. Table 7 demonstrates the relationship between clinical neonatal variables and cord blood albumin level. Table 8 shows the different neonatal

hyperbilirubinemia parameters based on cord blood albumin levels.

Table 3: The serum bilirubin level of babies

Variable	Need of phototherapy		P - value
	No	Yes	
TSB (mg / dl) (Mean ± SD)	9.81 ± 2.9	18.05 ± 1.41	< 0.001
CBA Levels (g / dl) (Mean ± SD)	4.16 ± 0.42	2.7 ± 0.55	< 0.001

Table 4: Maternal variables and their association with the need of phototherapy

Clinical variables No		Need of phototherapy		P value
		Yes		
Mode of delivery N (%)	LSCS	44 (16.5%)	22 (8.3%)	0.0388
	VD	145 (54.5%)	55 (20.7%)	
Parity (Mean ± SD)		1.73 ± 0.79	1.68 ± 0.95	0.457
	A+	48 (18%)	5 (1.9%)	
	AB+	25 (9.4%)	9 (3.4%)	
	B-	2 (0.75%)	0 (0%)	
	B+	52 (19.5%)	23 (8.6%)	
	O-	4 (1.5%)	0 (0%)	
	O+	53 (20%)	40 (15%)	

Table 5: Maternal variables based on cord blood albumin levels

Clinical variable Group A (< 2.8)		CBA Levels (g / dl)		
		Group B (2.8 - 3.3)	Group C (> 3.3)	
Mode of delivery N (%)	LSCS	9 (3.4%)	13 (4.9%)	44 (16.5%)
	VD	32 (12%)	24 (9%)	144 (54.1%)
		P1: 0.656	P2: 0.459	
Parity (Mean ± SD)		1.70 ± 1.0	1.64 ± 0.9	1.74 ± 0.8
	P1: 0.847		P2: 0.131	
Blood group N (%)	A-	0 (0%)	1 (0.4%)	4 (1.5%)
	A+	0 (0%)	4 (1.5%)	49 (18.4%)
	AB+	5 (1.9%)	5 (1.9%)	24 (9%)
	B-	0 (0%)	0 (0%)	2 (0.8%)
	B+	12 (4.5%)	12 (4.5%)	51 (19.1%)
	O-	0 (0%)	0 (0%)	4 (1.5%)
	O+	24 (9%)	15 (5.6%)	54 (20.3%)
		P1: 0.014	P2: 0.617	

Table 6: Neonatal variables with the need of phototherapy

Clinical Variable No		Need of phototherapy		P - value
		Yes		
Blood group N (%)	A-	7 (2.6%)	1 (0.4%)	0.0172
	A+	45 (16.9%)	23 (8.6%)	
	AB+	25 (9.4%)	2 (0.8%)	
	B-	1 (0.4%)	1 (0.4%)	
	B+	49 (18.4%)	35 (13.2%)	
	O-	11 (4.1%)	0 (0%)	
	O+	51 (19.2%)	15 (5.6%)	

Table 7: Neonatal variables based on cord blood albumin levels

Clinical variables Group A (< 2.8)		CBA Levels (g / dl)		
		Group B (2.8 - 3.3)	Group C (> 3.3)	
Gender N (%)	Male	23 (8.6%)	24 (9%)	108 (40.6%)
	Female	18 (6.8%)	13 (4.9%)	80 (30%)
		P1: 0.846	P2: 0.459	
Blood group N (%)	A-	0 (0%)	1 (0.4%)	7 (2.6%)
	A+	8 (3%)	12 (4.5%)	48 (18%)
	AB+	1 (0.4%)	1 (0.4%)	25 (9.4%)
	B-	0 (0%)	1 (0.4%)	1 (0.4%)
	B+	21 (7.9%)	13 (4.9%)	50 (18.8%)
	O-	0 (0%)	1 (0.4%)	10 (3.8%)
	O+	11 (4.1%)	8 (3%)	47 (17.7%)
		P1: 0.099	P2: 0.509	

Table 8: Neonatal hyperbilirubinemia parameters based on cord blood albumin levels

Clinical variable	CBA Levels (g / dl)				
	Group A (< 2.8)		Group B (2.8 - 3.3)	Group C (> 3.3)	
Need of phototherapy – Day 2 N (%)	No	1 (0.4%)	4 (1.5%)		184 (69.2%)
	Yes	40 (15%)	33(12.4%)		4 (1.5%)
		P1: < 0.001		P2: < 0.001	
Need of phototherapy – Day 3 N (%)	NO	31 (11.7%)	36 (13.5%)		188 (70.6%)
	YES	10 (3.8%)	1 (0.4%)		0 (0%)
		P1: < 0.001		P2: 0.024	
Need of exchange transfusion N (%)	NO	40 (15%)	37 (13.9%)		188 (70.6%)
	YES	1 (0.4%)	0 (0%)		0 (0%)
		P1: 0.033		P2: NA	

Discussion

Early identification of neonates at risk is crucial for timely intervention in neonatal hyperbilirubinemia. Recent research suggests that umbilical cord blood albumin levels could serve as a predictive marker for neonatal hyperbilirubinemia, especially in healthy full-term neonates. Dhanjal et al noted that cord blood albumin levels < 2.8 g / dL were significantly associated with the development of significant hyperbilirubinemia requiring phototherapy. The sensitivity and specificity of CBA levels < 2.8 g / dL in predicting significant neonatal hyperbilirubinemia were 87.5% and 75.7%, respectively. This underscores the potential utility of CBA as a screening tool for identifying at-risk neonates.[15] Similarly, a study by Kumar et al observed that term neonates with CBA levels ≤ 2.8 g / dL had a higher incidence of significant hyperbilirubinemia requiring intervention. This finding further supports the role of CBA levels in predicting neonatal jaundice.[16] These studies highlight the importance of early screening for neonatal hyperbilirubinemia using CBA levels, enabling timely interventions and reducing the risk of severe outcomes.

In our study of 266 neonates, 155 (58.3%) were males and 111 (41.7%) were females, indicating a slight male predominance. Among these, 30% males and 27% females required phototherapy or exchange transfusion. However, no statistically significant relationship was found between significant hyperbilirubinemia and the gender of the newborns. A study by Isa et al in Bahrain observed that male neonates had a higher incidence of hyperbilirubinemia compared to females (51.7% vs. 48.3%, respectively), but gender alone did not significantly predict the severity or need for treatment.[17] This reinforces the need to consider other factors and markers, such as umbilical cord blood albumin, for early prediction and intervention.

The present study noted a significant association between the mode of delivery and the need for phototherapy: 22 out of 66 LSCS-delivered infants required phototherapy, compared to 55 out of 200 NVD-delivered infants. This finding aligns with previous studies suggesting that the mode of delivery can influence neonatal bilirubin levels, potentially due to stress-related differences between delivery types. The parity of mothers also varied - 47.4% were primiparous, 37.6% were multiparous and 15% had more than two previous pregnancies. However, parity did not show a significant correlation with the need for phototherapy. This finding has also been substantiated by a study by Khatun et al where no significant difference in bilirubin levels was found among neonates born to primiparous versus multiparous mothers.[18]

The present study found statistically significant relationship between maternal blood group and the need for phototherapy. Specifically, 40 out of 93 newborns requiring phototherapy had O+ mothers, and 23 had B+ mothers, suggesting a higher risk of hyperbilirubinemia in these groups. This might

be related to ABO incompatibility, a well-documented risk factor for neonatal hyperbilirubinemia. ABO incompatibility occurs when a mother with blood group O has a baby with blood group A or B.[19] Early identification of at-risk pregnancies through maternal blood typing and fetal blood group determination, along with vigilant monitoring of bilirubin levels postnatally, are crucial steps in mitigating the risks associated with ABO incompatibility.

TSB levels among the 266 neonates were distributed as follows: 32.3% had TSB ≤ 10 mg / dL, 38% had levels between 10 – 14 mg / dL, 6% had levels between 15 – 17 mg / dL, and 23.7% had TSB ≥ 17 mg / dL. Of these, 29% developed significant hyperbilirubinemia requiring phototherapy, one required double volume exchange transfusion, and 70.6% needed no intervention. A significant correlation was observed between TSB levels and the need for phototherapy, highlighting the importance of TSB as a critical parameter in managing neonatal jaundice.

Elevated TSB levels indicate an imbalance between bilirubin production and clearance, often exacerbated by factors such as ABO or Rh incompatibility, prematurity, or breastfeeding challenges. The American Academy of Pediatrics (AAP) 2022 guidelines provide updated TSB thresholds for initiating phototherapy and exchange transfusion, tailored to the infant's age in hours and risk factors. For instance, phototherapy is recommended when TSB exceeds 15 mg / dL for infants aged 49 – 72 hours, and exchange transfusion is considered if TSB reaches 25 mg / dL.[20]

A significant correlation was observed between lower CBA levels and the development of significant hyperbilirubinemia. On day 2, 40 out of 41 neonates in Group A required phototherapy, compared to 33 out of 37 in Group B, and only 4 out of 188 in Group C. By day 3, the need for phototherapy significantly decreased, but the trend remained consistent with initial findings. A study by Sharma et al found that low CBA levels were predictive of subsequent hyperbilirubinemia requiring intervention, guiding timely therapeutic decisions to prevent adverse neurological outcomes.[21]

Although the present study has tried to see the correlation between cord blood albumin level and subsequent hyperbilirubinemia, the research is limited by a single centric small sample size. These findings need to be corroborated further in the future focussing on larger cohorts and diverse populations.

Conclusions

Neonates with CBA levels above 3.3 g / dL are at a lower risk of developing significant hyperbilirubinemia and may be considered for early discharge. Conversely, neonates with CBA levels below 3.3 g / dL require close monitoring for jaundice development. Neonates with CBA levels under 2.8 g / dL should not be discharged early, regardless of the presence or absence of other risk factors for neonatal jaundice.

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