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Correlation of Cord Blood Bilirubin Values with Neonatal Hyperbilirubinemia in Healthy Term Newborns in a Setting of Abo Incompatibility

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ABSTRACT

Background: Newborns with hyperbilirubinemia are at greater risk of kernicterus. Neonatal screening for hyperbilirubinemia helps to prevent kernicterus.
Aim: To find the correlation between cord blood bilirubin at birth and serum bilirubin at 72 hours of a neonate.
Method: Cord blood was drawn from 353 neonates, shortly after birth. The sample was then tested for both blood grouping and typing and total bilirubin levels. After 72 hours of birth, a second serum bilirubin test was carried out, and data was analysed to determine the correlation.
Results: In our study, neonates with significant hyperbilirubinemia (>15 mg/dl) around 72 hours of life had significantly elevated levels of cord blood bilirubin (≥2.5mg/dl. Cord Blood Bilirubin < 2.5 mg/dl can help to identify those newborns who are unlikely to require further evaluation and intervention.
Conclusion: Babies with Cord Blood Bilirubin level ≥ 2.5 mg/dl should be followed more frequently to reduce morbidity due to Neonatal hyperbilirubinemia.

Key Words: *ABO incompatibility, Cord Blood Bilirubin, kernicterus Neonatal hyperbilirubinemia, Neonatal jaundice*

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INTRODUCTION

Neonatal hyperbilirubinemia remains a public health concern for parents as well as for pediatricians as documented by recent reports of kernicterus in otherwise healthy term and near- term newborns. Kernicterus in such newborns is preventable, provided excessive hyperbilirubinemia for age is promptly identified and appropriately treated [1, 2]. With the intent to facilitate such identification and treatment, universal screening of babies for significant neonatal hyperbilirubinemia will identify at-risk neonates during the first week after birth [3]. Neonatal hyperbilirubinemia affects nearly 60% of term and 80% of preterm neonates during the first week of life [4]. Early discharge of healthy-term newborns after delivery has become a common practice because of medical and social reasons as well as economic constraints [5, 6]. Severe jaundice and even kernicterus can occur in some full-term healthy newborns discharged early with no apparent early findings of hemolysis [7]. The American Academy of Pediatrics (AAP) recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaundice and other problems [8] and this is not possible in our country due to limited follow-up facilities in the community. Early treatment of jaundice with phototherapy is effective, simple, and cheap [9, 10]. The concept of prediction of jaundice offers an attractive option to pick up babies at risk of NH. The present study was conducted to evaluate the predictive value of cord bilirubin level involving Group O positive Mothers and A positive or B positive healthy term neonates in Kolar for subsequent hyperbilirubinemia

AIMS AND OBJECTIVES

Aim: To find the correlation between cord blood bilirubin at birth and serum bilirubin at 72 hours of a neonate.
Objectives:
1) To estimate the cord blood bilirubin at birth and serum bilirubin value at 72 hrs after birth among neonates.
2) To correlate cord blood bilirubin and neonatal hyperbilirubinemia (serum bilirubin values at 72 hours) in a setting of ABO incompatibility.

MATERIALS & METHODS

This was a prospective study performed at S.N.R District Hospital, Kolar, Karnataka, India, from July 2021 to June 2022

Study population: Babies born with blood groups having A Positive or B Positive to O Positive mothers in S.N.R District Hospital, Kolar including both cesarean and vaginal delivery
Sampling Method: Convenient Sampling
Sampling size: According to a study by Kannan Ramamoorthy et al., the sample size was calculated to be 351 newborns, with an error of 1% and a 95% confidence interval. This estimate is based on cord serum bilirubin of 2.15 mg/dl with a sensitivity of 92.3%.

Inclusion criteria:

1) Healthy full-term inborn neonates with blood group A positive and blood group B positive born to healthy mothers with blood group o positive.

Exclusion criteria:

1) Neonates associated with Rh incompatibility.
2) Neonates with blood group other than A positive or B positive
3) Neonates with other significant illnesses that require NICU admission
4) Major high-risk congenital malformations
5) Neonates of mothers with chronic illness
6) Mothers of neonates that are not willing for follow-up
7) Mothers of neonates who refuse to give consent.

Ethical considerations: The study protocol was approved by the Institution's Ethical Committee.

Method of collection of data:

Informed consent was obtained from the parents of the new-born that satisfy the inclusion criteria, before enrolling them in the study. Demographic profile and relevant information of mothers was collected by using structured proforma by interviewing the mother. The gestational age of the newborn was assessed by using the New Ballard score. The cord blood sample was taken soon after birth and subjected to blood grouping-typing, total, and direct bilirubin. Total and direct serum bilirubin estimation was repeated at 72 hours of age. All babies were assessed daily for clinical Jaundice and its severity till discharge. Blood samples collected were stored away from light. The sample was refrigerated between 2-8 degrees Celsius until serum bilirubin was estimated. Serum bilirubin estimation was done within 12 hours of the collection of samples by Diazotized sulfanilic test.

The main outcome of the study was inferred in terms of hyperbilirubinemia. Serum bilirubin >15 mg/dl at 3rd day of life (at 72 hrs of life) was taken as hyperbilirubinemia needing phototherapy and treatment is advised for all those full-term healthy babies with a serum bilirubin level of >15 mg/dl at 72 hours of life, as per the American academy of pediatrics practice parameter, 2004. Data entry was done in Microsoft Excel 2013 and statistical analysis was performed with the help of SPSS, Version 22. Descriptive statistical analysis has been carried out in the present study. Continuous variables were presented as the mean and standard error of the mean (SEM), while categorical variables are presented as numbers and percentages

RESULTS

The study was conducted on a total of 353 newborns after obtaining written consent from the parents. Proforma was filled for each newborn and the data were analyzed using the appropriate statistical software SPSS Version 22. The gender distribution of 353 newborns in the study group was 43.91% (155 neonates) were females and 56.09% (198 neonates) were male newborns and of them, maximum babies were with blood groups A+ (52.97%= 187) and B+ (47.03% = 166).

The below table 1, shows the distribution of Cord Blood Bilirubin levels (mg/dl) among the studied newborns. Maximum newborns had cord blood bilirubin between 2-2.9 mg/dl (52.97%) followed by 1-1.9 mg/dl (30.31%), 3-3.9 mg/dl (16.15%) and ≥4 mg/dl (0.57%).

Table 1: Levels of Cord Blood Bilirubin levels (mg/dl) of Neonates Studied

	Levels	No. of Patients	%	Mean ± SD
Cord Blood Bilirubin	1-1.9 mg/dl	107	30.31	**2.33 ± 0.64**
	2-2.9 mg/dl	187	52.97	
	3-3.9 mg/dl	57	16.15	

	≥4 mg/dl	2	0.57	
	Total	353	100.00	

The table 2 shows the distribution of Serum Bilirubin on Day 3 ≥15 mg/dl and Cord Blood Bilirubin levels (mg/dl) among the studied newborns.

Table 2: Levels of Cord Blood Bilirubin levels (mg/dl) of Neonates Studied among neonates with Serum Bilirubin on Day 3 - ≥15 mg/dl

Serum Bilirubin on Day 3	CBB Levels	No. of Patients	%
≥15 mg/dl	1-1.9 mg/dl	0	0.00
	2-2.9 mg/dl	5	20.00
	3-3.9 mg/dl	18	72.00
	≥4 mg/dl	2	8.00
	Total	25	100.00

Maximum newborns had cord blood bilirubin between 3-3.9 mg/dl (72.00%), followed by 2-2.9 mg/dl (20.00%) and ≥4 mg/dl (8.00%).

The present study infers that Cord Serum bilirubin levels of the babies with neonatal hyperbilirubinemia (≥15 mg/dl) are significantly higher (Cord Blood Bilirubin ≥2.5 mg/dl) than the babies without hyperbilirubinemia.Out of the total population, 25 neonates (7.08%) developed significant jaundice at 3 days of age

Table 3: Correlation of Cord Blood Bilirubin with Day 3 Serum Bilirubin

Cord Blood Bilirubin	Serum Bilirubin on Day 3		P-Value
	<15 mg/dl	≥15 mg/dl	
<2.5 mg/dl	211 (64.33%)	1 (4.00%)	<0.001
≥2.5 mg/dl	11 (35.67%)	24 (96.00%)	
Total	328 (100.00%)	25 (100.00%)	

True Positive: 24 New-borns with CBB ≥ 2.5mg/dl who developed significant Jaundice at postnatal 72 hours. **True Negative**: 211 neonates with CBB < 2.5mg/dl who did not develop significant Jaundice. **False Positive**: 117 Neonates with CBB ≥ 2.5mg/dl who did not develop significant Jaundice at post-natal 72 hours. **False Negative**: 1 Neonate with CBB <2.5mg/dl who developed significant Jaundice at postnatal 72 hours.

Table 4: Diagnostic Probability of Cord Blood Bilirubin for Significant Hyperbilirubinemia

Cord Blood Bilirubin	Serum Bilirubin on Day 3		P-Value
	<15 mg/dl	≥15 mg/dl	
<2.5 mg/dl	211	1	<0.001
≥2.5 mg/dl	117	24	
True Positive	True Negative	False Positive	False Negative
24	211	117	1
Sensitivity%	Specificity%	PPV %	NPV %
96.00%	64.33%	17.02%	99.53%

Sensitivity: If a neonate develops significant hyperbilirubinemia, the probability that the cord blood bilirubin was higher than 2.5 mg/dl was 96.00%. **Specificity**: The probability that the cord blood bilirubin was <2.5 mg/dl was 64.33% in a Non-hyperbilirubinemia neonate. **Positive Predictive Value**: In the present study, the probability that a neonate with cord blood bilirubin ≥ 2.5 mg/dl would later develop hyperbilirubinemia was 17.02%. **Negative Predictive Value**: The probability that a neonate with cord blood bilirubin <2.5 mg/dl would not develop hyperbilirubinemia was 99.53%.

DISCUSSION

The study was conducted on 353 newborns after obtaining written consent from the parents. Our study hypothesized that a high serum bilirubin level at birth would also predict a high peak later in life. Our aim was to quantify the relationship between Cord blood bilirubin with peak serum bilirubin levels in the first three days. We Chose cord blood estimation for initial serum bilirubin estimation because it is a non-invasive way and the results are available within a few hours after birth. Furthermore, the most important is that the data are available immediately after birth. The babies at risk for developing hyperbilirubinemia can be detected at birth in a non-invasive way if the neonate leaves the hospital within the first few postnatal days. Keeping these factors in consideration our study was conducted on term healthy neonates

wherein the outcome was hyperbilirubinemia. We have considered peak serum bilirubin level >15 mg/dl on 72 hours of life as significant hyperbilirubinemia since specific treatment is considered at or above this level.

Hyperbilirubinemia varies from 10.30% to 14% in the studies showed in table 5. However, in the present study, hyperbilirubinemia is 7.08% which is the least among the above studies because our study group consisted of neonates with no risk factors. In the majority of the above studies, even high-risk neonates are also taken into consideration hence Hyperbilirubinemia is seen on the higher side compared to our study. In our present study neonates with significant hyperbilirubinemia (>15 mg/dl) at 3 days of age had significantly elevated levels of cord blood bilirubin (≥2.5mg/dl).

Table 5: Comparison of Presence of Hyperbilirubinemia

Studies	Year	No. of Cases	Presence of Hyperbilirubinemia
Ramesh Agarwal et al [16]	2002	213	10.30
Knuffer M et al [17]	2005	1100	10.60
Randew S et al [12]	2010	200	12
Pradhan A et al [13]	2017	202	12.87
Mohammad Rafi et al [14]	2019	300	14
Present	2021	353	7.08

In relation to Sensitivity this present study is in correlation with the study done by Rina Triasih et al. [11], Shivani Randew et al. [12], Pradhan A et al. [13], Mahammad Rafi et al [14] and contrary findings are seen in the study done by Zakia Nahar et al. [15], Asper Specificity is concerned similar findings are seen in Rina Triasih et al [11] whereas contrary findings are seen in the study done by Zakia Nahar et al. [15], Shavian Randew et al. [12], Pradhan A et al. [13], and Mahammad Rafi et al. [14]. The positive predictive value of this study is in correlation with none of the above studies whereas contrary findings are seen in the study done by Rina Triasih et al. [11], Zakia Nahar et al. [15], Shivani Randew et al. [12]. Pradhan A et al [13] and Mahammad Rafi et al. [14], This could be as the majority of the studies are taking not just healthy neonates, even high-risk neonates are taken into consideration. As per Specificity is concerned similar findings are seen in most of the studies by Rina Triasih et al. [11], Zakia Nahar et al. [15], Shivani Randew et al. [12], and Mohammad Rafi et al [14] except the study done by Pradhan A et al [13] where the findings are contrary. Thus cord blood bilirubin level appears as a risk indicator in predicting neonatal hyperbilirubinemia. Cord Blood Bilirubin < 2.5 mg/dl can help to identify those newborns who are unlikely to require further evaluation and intervention. Babies with Cord Blood Bilirubin level ≥ 2.5 mg/dl should be followed more frequently to reduce mortality and morbidity due to Neonatal hyperbilirubinemia.

Table 6: Comparison studies on the predictive ability of cord blood bilirubin level and Neonatal Hyperbilirubinemia

Studies	Cut off Cord STB (mg/dl)	Cut off neonatal hyperbilirubinemia (mg/dl)	Repeat Sample taken	Sensitivity	Specificity	PPV	NPV	P Value
Present	≥2.5	≥15	72 hrs	96.00%	64.33%	17.02%	99.53%	<0.001
Rina Triasih et al [11]	>4.5	≥12.9	5 days	90%	71.9%	50%	96.8%	<0.05
Zakia Nahar et al [15]	≥2.5	≥17	72 hrs	77%	98.6%	91%	96%	<0.05
Shivani Randew et al [12]	>6.4	≥17	Beyond 72 hrs	87%	80.11%	37.5%	97.92%	0.000
Pradhan A et al [13]	≥2.5	≥15	72 hrs	84.1%	88.5%	98%	45.1%	0.000
Mahammad Rafi et al [14]	≥2	≥15	5 days	90.48%	84.88%	49.35%	98.21%	<0.0001

CONCLUSION

From our study it can be concluded that cord blood bilirubin estimation is a non-invasive and reliable investigation for early prediction of neonatal hyperbilirubinemia. So babies with cord blood bilirubin ≥2.5mg/dl define the risk group prone to develop significant hyperbilirubinemia and may likely require appropriate intervention to control neonatal hyperbilirubinemia at 3 days of the age of neonate

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