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Cord blood bilirubin level as a predictor of development of pathological hyperbilirubinemia in newborns

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Abstract---Background: Early discharge of healthy term newborns after delivery has become a common practice because of medical and social reasons and economic constraints. Thus, the recognition, follow-up, and early treatment of jaundice has become more difficult as a result of earlier discharge. This study is done to know the cut-off value of cord blood bilirubin and establish correlation between cord blood bilirubin level and development of significant neonatal hyperbilirubinemia without having significant risk factors and its treatment modality and outcome. Methods: This prospective study performed on 150 eligible term newborns born to mothers with 'A' Positive, 'B' Positive and 'AB' Positive blood group. Cord blood was collected from healthy term newborns delivered by caesarean section for total serum bilirubin and blood group. Serum bilirubin estimation was repeated at 72 hrs after birth by peripheral venous blood Results: Subjects were categorized into hyperbilirubinemia and non-hyperbilirubinemia newborns. Babies with serum bilirubin level of $\geq 17\text{mg/dl}$ after 72 hrs of life were considered for phototherapy and it is taken as significant hyperbilirubinemia in the present study. By ROC analysis, cord blood bilirubin level of $\geq 2.6\text{mg/dl}$ was determined to have high sensitivity of 100%, specificity of 99.3% and negative predictive value of 100% for predicting new born with significant hyperbilirubinemia. Conclusions: This study showed significant correlation between cord blood bilirubin level and hyperbilirubinemia

in healthy term newborns without having significant risk factors. Cord blood bilirubin level of $\geq 2.6\text{mg/dl}$ can predict the development of significant hyperbilirubinemia.

Keywords---cord blood bilirubin, hyperbilirubinemia, newborns.

Introduction

Neonatal Hyperbilirubinemia (NNH) is observed commonly during the 1st week of birth in approximately 80% of preterm and 60% of term infants¹. Serum bilirubin over 15mg/dl is found in 3% of normal term infants. As a result of earlier discharge of the newborn from the hospital, the recognition, follow up and early treatment of Jaundice has become more difficult². As per recommendation from the American Academy of Pediatrics (AAP) that newborns discharged within 48hrs should have a follow-up visit after 2-3 days to detect significant jaundice and other problems³. Due to limited follow-up facilities in the community, this recommendation is not possible in our country. Therefore, under these circumstances in order to start early treatment and thereby minimize the risk of bilirubin dependent brain damage it would be desirable to predict the risk of jaundice⁴

Methods

Source of Data

This study will be performed at the Department of Paediatric, Cheluvamba Hospital, attached to Mysore Medical College & Research Institute.

Study Design

Type of study - Purposive sampling

Period of study- January 2019 to June 2020 Eligible term neonates born to "A" Positive, "B" Positive, 'AB' Positive mothers at this hospital will be prospectively enrolled in the study. After taking informed consent 2ml of cord blood will be drawn for bilirubin. This study will involve newborns born to mothers with blood group 'A' Positive, 'B' Positive and 'AB' Positive. Serum bilirubin estimation will be done at 72 hours of age. Babies will be followed up as and when clinically indicated along with-it treatment modalities and outcome will be observed in those who develop hyperbilirubinaemia. The demographic profile and relevant information of individual patient will be collected using structured Proforma by interviewing the mother and an informed consent will be obtained. Gestational age will be assessed by new Ballard score.

Inclusion criteria

- Term neonates delivered by LSCS at Cheluvamba hospital, Mysuru (as normal vaginal delivery mothers will be discharged within 48 hrs, so it is difficult for sampling and follow up, whereas LSCS mothers are easy for follow up due to long stay of duration)

- Born to mothers with 'A' Positive blood group
- Born to mothers with 'B' Positive blood group
- Born to mothers with 'AB' Positive blood group
- Cases with informed, written parental consent.

Exclusion criteria

- Pathological jaundice due to causes like ABO incompatibility, Rh incompatibility, G6PD deficiency etc
- Other Significant illness requiring NICU admission.
- Major congenital malformations.
- Chronic maternal illness (like DM).
- Birth weight less than 2.5kg.
- Any maternal complications like Preeclampsia, hypothyroidism etc

Method of collection of data

The demographic profile and relevant information of individual patient was collected and a predrawn proforma was explained to the mother or the caregiver. Informed consent regarding participation in the study was obtained in the regional language. All details were filled in the proforma. Eligible term neonates born to mothers with blood group A 'Positive', B 'Positive' and AB 'Positive' at this hospital was prospectively enrolled in the study. After taking informed consent 2ml of cord blood was drawn for bilirubin and blood grouping of the neonate. Serum bilirubin estimation was done at 72hrs of life. Babies were followed up as and when clinically indicated along with its treatment modalities and outcome was observed in those who developed hyperbilirubinemia. Babies were clinically examined for age, sex, gestational age, birth weight, evidence of jaundice, day of onset of jaundice with its risk factors

Thorough clinical examination of the baby is done to identify:

- Pallor
- Temperature
- Icterus
- Hepatosplenomegaly
- Extravasation of blood (cephalhematoma/ subgaleal bleed)
- Excessive bruising
- Neurological signs like opisthotonos

Results

The following results were made from the study. An Observational study consisted of 150 healthy term newborns that were followed up for first 5 postnatal days. The study results were analysed using appropriate statistical methods.

Table 1. Study population and significant jaundice

Total	Number	Percentage
150	10	6.6

Table 2. Maternal details (N = 150)

Mothers details		Number of Mothers	Total %	Correlation	
				Cord blood bilirubin	Total blood bilirubin at 72 hours of life
Gravida	Gravida 1	43	28.7	P Value 0.430	P Value 0.914
	Gravida 2	64	42.7		
	Gravida 3	36	24.0		
	Gravida 4	6	4.0		
	Gravida 5	1	0.7		
Blood Group	A+	43	28.7	P Value 0.658	P Value 0.306
	B+	58	38.7		
	AB+	49	32.7		

Table 3. Details of Neonates Studied (N = 150)

Details of Neonates		Number of Neonates	Total %	Correlation	
				CBB	Total blood bilirubin at 72 hours of life
Gender	Male	76	50.7	P value 0.958	P value 0.472
	Female	74	49.3		
Weeks of Gestation	37-38	50	33.3	Correlation Coefficient (rho) = -0.02 0.805	Correlation Coefficient (rho) = 0.04 P value 0.655
	38-39	60	40		
	39-40	40	26.6		
Birth weight(kg)	2.50-3.00	64	42.7	P value 0.714 Correlation Coefficient (rho) = 0.03	P value 0.045 Correlation Coefficient (rho) = 0.16
	3.01-3.50	56	37.3		
	3.51-4.00	30	20.0		
Blood Group	A+	53	35.3	P value 0.449	P value 0.405
	B+	50	33.3		
	AB+	47	37.3		

Table 4. Cord Blood Bilirubin, total blood bilirubin at 48 hr and 72 hour of life 4.2 of the Study Population

	Minimum	Maximum	Mean $\pm$ SD
Cord Blood Total Bilirubin	1.50	3.0	2.02 $\pm$ 0.36
Total Bilirubin at 72 hour of life	7.9	13.4	13.35 $\pm$ 10.23

Table 6. Diagnostic predictability of cord blood total bilirubin of >3 mg/dl for hyperbilirubinemia at 72 hours

Cord bilirubin at birth(mg/dl)	Serum bilirubin (mg/dl) at 72 hrs of life
≥ 2.5	17.70 $\pm$ 1.80
< 2.5	13.01 $\pm$ 10.54
p<0.001 w=86.0 (Wilcoxon-Mann-Whitney U Test)	

Table 7. Diagnostic statistics

Cut off	>2.5
Sensitivity (%)	100
Specificity (%)	99.3
Positive predictive value (PPV)	90.9
Negative predictive value (NPV)	100
Diagnostic accuracy	99.3
Positive likelihood ratio	140
Negative likelihood ratio	0

ROC Curve Analysis Showing Diagnostic Performance of CBB (mg/dL) in Predicting Phototherapy: Required vs Phototherapy: Not Required

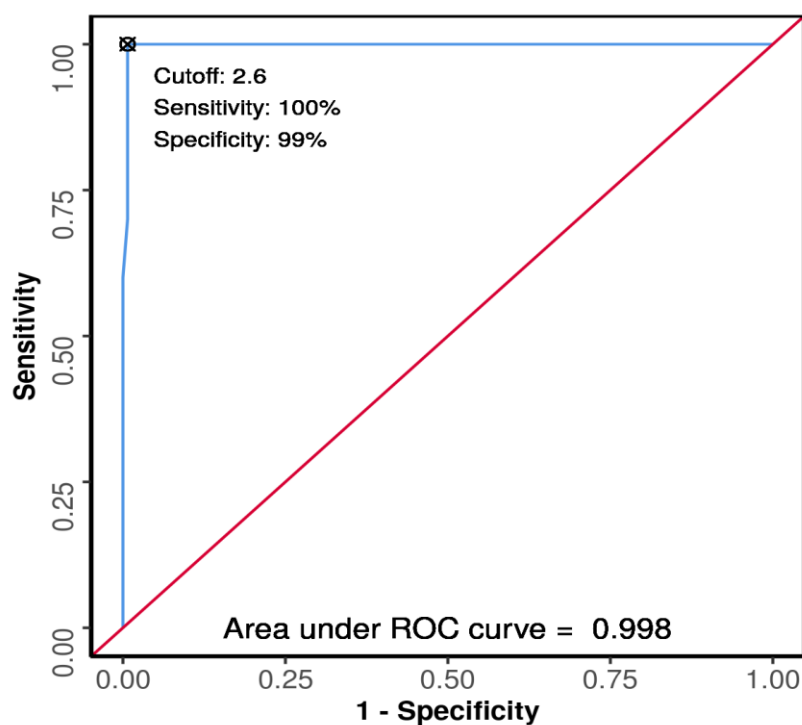


Table 8. Comparison of incidence of hyperbilirubinemia

Studies	Year	No. Of Cases	Incidence of Hyperbilirubinemia
Palmer et al. ⁵	1983	41057	10.70
Phuapradit et al. ⁶	1993	7644	8.35
Awasthi et al. ⁷	1998	274	12.80
Alpay et al. ⁸	2000	498	12.05
Agarwal et al. ⁹	2002	213	10.30
Knupfer M et al. ¹⁰	2005	1100	10.60
Amar T et al. ¹¹	2005	200	9.5
Randev S et al. ¹²	2010	200	12
Present Study	2019	150	6.6

Table 10. Comparison of cord serum bilirubin and significant jaundice

Studies	Cord blood bilirubin (mg/dl)	Mean Total serum bilirubin at 72 hours (mg/dl)	Significance
Present	≤2.5 mg/dL	13.01 ±1.54	p<0.001 w=86.0(Wilcoxon-Mann-Whitney U Test)
	>2.5 mg/dL	17.70 ±1.80	
Sehgal P et al ¹³	<2.02	10.56±3.18	Sensitivity – 87.5%

Amar T et al ¹¹			Specificity – 70.8%
	≥ 2.02	18.2±1.50	
	<2.02	13.50 ± 3.50	
Zakia nahar et al ¹⁴	≥ 2.02	18.3±0.82	PPV- 38.6% NPV-98.7% Sensitivity – 89.75% Specificity – 85.10%
	≤ 2.5	11.3 ±2.1	
	>2.5	17.8 ±0.8	Sensitivity-77% Specificity -98.6% PPV- 91% NPV-96%
Rudy Satrya et al ¹⁵	<2.54	7.89 ±1.25	
	≥ 2.54	15.2±0.80	Sensitivity-90.5% Specificity -85%

Table Comparison of studies on predictive ability of cord blood bilirubin level and significant hyperbilirubinemia

	Cut-off CBB (mg/dl)	Cutoff neonatal jaundice (mg/dl)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Present study	≥ 2.6	≥ 17	100.0	99.3	90.9	100
Amar T et al ¹¹	>2	≥ 17	89.5	85	38.8	98.7
Nilesh et al ¹⁶	>3	>15	100	98.17	66.67	100
Zakia nahar et al ¹⁴	≥ 2.5	≥ 17	77	98.6	91	96
Rudy Satrya et al ¹⁵	≥ 2.54	≥ 12.9	90.5	85	88.4	98.4
Rajput G et al ¹⁷	>2	>15	86	40	29	91
Pradhan et al ¹⁸	≥ 2.5	>15	84.1	88.5	98	45.1

Discussion

In most of the neonates hyperbilirubinemia is a common problem. During the 1st week of life jaundice is seen in approximately 60% of term infants and 80% of preterm infants. Under normal circumstances, the umbilical cord serum indirect bilirubin is 1-3 mg/dl and rises at a rate of <5 mg/dl/day, thus jaundice becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days at 5-6 mg/dl and decreasing to <2 mg/dl between the 5th and 7th days of life¹⁹. Our study presumption was 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 of the first five days. We chose cord blood estimation for initial serum bilirubin estimation as it is easy and a non-invasive way and the results are available within few hours after birth.

The increased cases of bilirubin related neurological damage occurred as a result of early hospital discharge of newborns. Therefore, it is must to have an easy and safe test to identify babies who are at risk for significant jaundice and will help in avoiding the fatal outcome. To address this issue AAP recommends that all newborns that were discharged within 48 hours of birth should be followed up within 2 to 3 days of discharge to hospital, health worker or at home³. It will be very difficult to document the benefits of this policy, given the rare incidence of kernicterus and less chances of adapting the advice especially in lower socioeconomic and rural areas.

Experience suggests that asking mothers to look for yellowish discoloration (jaundice) in newborns is not reliable. Despite such instructions, it is difficult to recognize significant jaundice for many parents. Unfortunately, the presence of severe jaundice is often missed clinically, which means that the trigger for measuring the first serum bilirubin level and deciding subsequent recommendation is not set. This is a potentially a serious problem. Jaundice appears at various intervals in newborns after birth and ability to notice its severity, approximate range with cephalocaudal progression has been a topic of study for the past 60 years. Additionally, in most of the recently reported healthy term newborns that developed kernicterus, significant jaundice was almost certainly present before the first hospital discharge, judging from the height of TSB for age in hours at readmission. Either the early icterus had not been noted or its pathologic intensity for postnatal age was not appreciated.

Currently we do not have a reliable method of anticipating such levels of hyperbilirubinemia. Unfavourable outcomes can be prevented by regular, close and frequent follow up after birth and discharge from hospital, but to prevent rare cases of kernicterus to approach to surveillance of the newborn that is substantially more rigorous than has been practiced. The benefits, costs, feasibility and risks of such an approach need to be determined. Collection of umbilical cord blood is simple, easy and not associated with any pain. Most important is that the results of tests are available within hours of birth. Thus, the babies who are discharged within few days postnatally can be assessed for risk of hyperbilirubinemia in a non-invasive way at birth. Using Cord blood Bilirubin values may help to predict babies with low risk for hyperbilirubinemia and minimize an unnecessary stay in hospital.

Keeping these factors in mind our study was conducted on healthy full-term neonates with non-hemolytic jaundice. We have considered peak serum bilirubin level >17 mg/dl as "hyperbilirubinemia" since specific treatment is usually considered at or above this level. However, some neonatologists initiate phototherapy at slightly lower serum bilirubin levels, especially if they suspect a rising trend. Therefore, we have also predicted treatment with phototherapy. Incidence of hyperbilirubinemia varies from 3.5% to 12.8% in various Studies. Incidence of hyperbilirubinemia in the present study is 6.6%. There was no significant difference between the groups in terms of CBB (mg/dL) and blood

group of babies and this is correlating with studies by Amar T et al¹¹ and Rajput et al¹⁷.

There was statistically insignificant correlation between CBB and birthweight although there was weak positive correlation and also between CBB and gestational age although there was weak negative correlation and these findings were correlating with studies by Amar T et al¹¹ and Rajput et al¹⁷. There was no significant difference between the Total Bilirubin (72 Hours) gender groups, Gravida groups and Baby blood group. There was a weak positive correlation between Birth Weight and Total Bilirubin (72 Hours), and this correlation was statistically significant ($\rho = 0.16$, $p = 0.045$). For every 1 unit increase in Birth Weight (Kg), the Total Bilirubin (72 Hours) increases by 3.92 units. Conversely, for every 1 unit increase in Total Bilirubin (72 Hours), the Birth Weight (Kg) increases by 0.01 units

In the present study, there was a statistically insignificant weak positive correlation between the Total Bilirubin (72 Hours) to Gestational Age (Weeks). Other studies also reported the relation between raising levels of cord bilirubin and increased incidence of significant hyper bilirubinemia in later life. In the present study using serum bilirubin levels ≥ 2.5 mg/dL in the cord blood, hyperbilirubinemia could be predicted with sensitivity of 100%, specificity of 99.30 %, and positive predictive value of 90.9 % and Negative predictive value of 100%

Conclusion

In postnatal wards hyperbilirubinemia is one of the common problems seen. Neonatal hyperbilirubinemia occurs in 5-10 % of healthy term infants. Upto 4% of term newborns who are readmitted to the hospital during their first week of life, approximately 85% are readmitted for jaundice. Early identification of at risk newborn for significant hyperbilirubinemia by using simple predictors can help to prevent possible bilirubin induced neurological damage. A 100% Negative Predictive Value in the present study suggests that in healthy term babies (without RH and ABO incompatibility with Cord Blood Bilirubin <2.5mg/dl) cord serum bilirubin 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 morbidity and mortality due to neonatal hyperbilirubinemia.

Our study sample did not have a heterogeneous group of neonates. This is the strength of our study. It means that the Prediction test (72 hrs TSB ≥ 17 mg/dl) developed by us can be applied to the neonates of local rural population on whom it was developed. Thus prediction of neonatal hyperbilirubinemia will have widespread implication especially in our rural setup.

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