Correlation of Cord Blood Bilirubin Values with Neonatal Jaundice in Health New-Borns: A Prospective Observational Study

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Abstract

Objective: The present study was conducted to investigate the predictability of pathological jaundice on cord blood bilirubin values.

Methodology: It was a prospective observation study conducted in Kurji holy family hospital on 289 healthy new-borns. Babies were divided into two groups. Group A who developed Physiological Jaundice and Group B who developed pathological jaundice. Cord blood bilirubin was estimated in all new-born who were then followed up-to 5th day of life. Babies who developed jaundice requiring treatment were admitted in NICU for phototherapy. Rest where checked regularly up-to 5th day of life and value recorded on 5th day by estimation of serum bilirubin.

Results: Incidence of pathological hyperbilirubinemia in our study was 11.2%. Statistically significant correlation between cord blood bilirubin and development of pathological jaundice. Gender, age, mode of delivery and birth weight has no correlation with cord bilirubin and the subsequent development of jaundice. Cord blood bilirubin <2.5mg/dl when compared with subsequent development of jaundice has high specificity (83.92%) and negative predictive value (87.35 %). Cord blood value of >3.5mg/dl has high sensitivity (97.06%), specificity (99.22%), Positive predictive value (94.29%) and negative predictive value (99.61 %) in predicting future development of future pathological jaundice.

Conclusion: 87.35% negative Predictive Value in the present study suggests that in Healthy Term babies (Cord Blood Bilirubin $\leq$ 2.5mg/dl) cord serum bilirubin can help to identify those new-borns who are unlikely to require further evaluation and intervention. These new-borns can be discharged with assurance to Parents. Babies with CBB level $\geq$ 3mg/dl should be followed more frequently. Thus, this study concludes that cord blood total bilirubin levels reliably predict the occurrence of pathological hyperbilirubinemia.

Keywords: Cord blood serum bilirubin; Pathological Jaundice; Physiological jaundice; Phototherapy

Introduction

Hyperbilirubinemia is the most common clinical condition requiring evaluation and treatment in the new-

born and a frequent reason for hospital readmission during the first week of life. Although generally a benign, postnatal, transitional phenomenon, a few neonates develop marked potentially hazardous bilirubin levels

that can pose a direct threat of serious brain injury [1]. Acute bilirubin encephalopathy (ABE) may ensue and evolve into kernicterus (chronic bilirubin encephalopathy), a permanent disabling neurologic condition classically characterized by (1) the movement disorders of dystonia and/or choreoathetosis, (2) hearing loss caused by auditory neuropathy spectrum disorders, and (3) oculomotor pareses¹. The genesis of neonatal hyperbilirubinemia reflects the interplay of developmental red blood cell (RBC), hepatic, and gastrointestinal immaturities that result in an imbalance favoring bilirubin production over hepatic enteric bilirubin clearance.

Almost all newborn infants have a serum or plasma total bilirubin (TB) level >1 mg/dL in contrast to normal adults in whom the normal TB level is <1 mg/Dl. Physiological jaundice usually appears on the 2nd – 3rd day, peaking between the 5th and 7th days of life. Jaundice may appear at birth or may appear any time during neonatal period depending upon the cause [2]. Since we know hyperbilirubinemia has a deleterious effect like Kernicterus, chore athetoid cerebral palsy, hearing impairment and cognitive impairment if not treated at the time. So meticulous screening of newborn is required to detect hyperbilirubinemia. Since the peak bilirubin level typically occurs at 72 to 96 hours, after healthy newborns are discharged from their birth hospital, follow-up is essential. Infants discharged before 72 hours should be seen within the next 2 days. Infants at lower gestational ages or who have other risk factors should be seen earlier [2]. This is practically impossible in underdeveloped and even in developing nations because of poverty, low education and cultural practice. Here comes the role of prediction of neonatal hyperbilirubinemia.

Early discharge of healthy term newborns after delivery has become a common practice, because of medical and social reasons and economic constraints [3]. Thus, the recognition, follow up and early treatment of jaundice has become more difficult as a result of early discharge from the hospital. Severe jaundice and even kernicterus can occur in some full term healthy newborns discharged early with no apparent early findings of haemolysis [4].

Methodology

This Prospective hospital-based study was conducted in Dept. of Paediatrics and Neonatology, Kurji Holy Family Hospital, Patna Bihar from 17 January 2016 to 30th

December.2018. A total of 289 New-born, fulfilling the predefined inclusion criteria, delivered in our hospital were studied. Proper ethical and scientific clearance was taken from concerned hospital department. Proper consent was taken from Parents of babies after explaining the risks and benefits of neonatal jaundice, phototherapy and blood sampling.

Inclusion Criteria

- Gestational age 35weeks and above. (Based on last Menstrual period).
- The absence of major congenital malformations.
- Residing at Patna or nearby whose parents agree to come for follow up.

Exclusion Criteria

- Presence of significant illness, (i.e. sepsis & hypothyroidism).
- Rh incompatibility
- ABO incompatibility
- Newborns with obvious life-threatening congenital malformation (trachea- esophageal fistula (TOF), anorectal malformation).
- Babies with conjugated hyperbilirubinemia.

All babies delivered in KHFH were examined and a detailed antenatal and postnatal history was taken. Cases were selected if they fulfilled all the criteria set out above. Informed consent was taken from the parents and blood was collected from cord blood at birth. Blood sample of the mother was simultaneously collected and sent for Blood Grouping if it was not known from before. The cord blood sample of the infant was sent for grouping and TSB estimation and then all babies were examined by senior registrars and experts for clinical assessment of bilirubin as per Kramer's scale and by transcutaneous bilirubinometer for continuous 5 days. Babies were divided into two groups: Group A developing jaundice within physiological range and Group B developing jaundice which needs treatment (pathological jaundice). Babies suspected of having high bilirubin were cross checked by serum bilirubin level and admitted for treatment if needed as per AAP nomogram for hyperbilirubinemia management. Remaining babies were checked for serum bilirubin on 5th day of life.

Bilirubin Estimation

The Serum Bilirubin was estimated by micro-bilirubin (Jendrassik & Grof method) for that venous blood is taken

in four microcapillaries and centrifuged at the rate of 10000 rpm for 5 minutes. Bilirubin estimation is done spectrophotometrically using beam method (55 nm wavelength) (micro la-300, Merck, Netherland). Calibration of bilimeter is done daily using labeternal solution.

Statistical Analysis

Data Analysis was carried out using Microsoft excel sheet. In case of Quantitative data, mean and standard deviation, as well as range (minimum & maximum value), is computed. Sensitivity, specificity, positive and negative predictive value of different cut-points of cord blood serum bilirubin was derived. For determining the significance of each test p-value of <0.05 was used.

Results

Out of 300 new-borns enrolled, 11 could not be included in the study because of refusal of consent, drop in follow up, Rh/ABO incompatibility and admission in NICU because of cause other than hyperbilirubinemia. All new born were exclusively breast fed. A total of 289

subjects were followed up for the first five days of life with clinical assessment and laboratory investigations. Of the enrolled subjects, 169 (58.48 %) were males and 120 (41.52%) were female with mean cord blood bilirubin and serum bilirubin during evaluation up to 5 days of (2.6 ± 0.8 & 13.9 ± 2.4) and (2.5 ± 0.4 & 12.9 ± 1.8) respectively with P value of 0.89 thus, no statistical significance (Table 1).

208 (71.179%) were babies >37 weeks of age and 81 (28.03%) were 35-37weeks babies. Gestational age included in study has no statistically significant effect when comparison between cord blood and serum bilirubin when estimated up to 5th day (Table 1) (P value 0.95) as revealed by our study in which out of total 34 babies who developed pathological jaundice meriting intervention wherein 35-37 weeks age and rest 25 where of age group > 37 weeks with no statistical significance. Similarly birth weight and mode of delivery comparison of cord blood bilirubin and serum bilirubin when estimated up to 5th day has no statistical significance with P value of 0.78 and 0.999 respectively as depicted in Table 1.

CHARACTERISTICS		NUMBER	%	Cord blood bilirubin Mean $\pm$ SD	Bilirubin during monitoring upto 5 th day of life Mean $\pm$ SD	P Value
GENDER	MALE	169	58.48	2.6 ± 0.8	13.9 ± 2.4	0.89
	FEMALE	120	41.52	2.5 ± 0.4	12.9 ± 1.8	
GESTATIONAL AGE	>37WEEKS	208	71.2	2.7 ± 0.8	13.7 ± 2.2	0.95
	35 -37 WEEKS	81	28.03	2.4 ± 1.4	13.2 ± 2.2	
MODE OF DELIVERY	VAGINAL	188	65.05	2.9 ± 1.3	11.9 ± 2.0	0.78
	LSCS	101	34.94	2.6 ± 0.8	12.9 ± 2.4	
BIRTH WEIGHT	1.5-2.5	98	33.91	2.5 ± 1.9	14.21 ± 1.4	0.999
	2.6-3.5	146	50.52	2.9 ± 1.4	12.3 ± 1.7	
	>3.5	45	15.57	2.87 ± 0.4	12.5 ± 2.8	

Table 1: Distribution of the enrolled new-born's according to gender, gestational age, birth weight and mode of delivery.

A total of 255 (84.5%) (Group A) developed jaundice which was in physiological range so went home without any treatment. The mean ($\pm$ SD) serum total bilirubin in cord blood, and on day 5 of the babies in this group were

1.6 (± 0.4) mg/dl and 11.9(± 2.4) mg/ dl respectively (Table 2). Statistical correlation revealed no significance with P value of 0.087.

GRUOP	NUMBER	%	Cord blood bilirubin	Bilirubin during monitoring upto 5 th day of life Mean $\pm$ SD	P Value
			Mean $\pm$ SD		
A	255	88.2	1.6 ± 0.4	11.9 ± 2.4	0.087
B	34	11.8	2.6 ± 0.8	16.7 ± 1.8	0.0001

Table 2: Mean $\pm$ SD at bilirubin levels in cord blood and 5th day blood of neonates and their association.
Group A: Physiological hyperbilirubinemia. Group B: Pathological hyperbilirubinemia

Total 34 (Group B) (11.76) infants developed hyperbilirubinemia up to 5th day with cord blood bilirubin with mean bilirubin of 2.6mg/dl with standard deviation of 0.8mg/dl and mean serum bilirubin when estimated up to 5th day of life of 16.7mg/dl with standard deviation of 1.8. Statistical correlation between these two was strong with p Value of 0.0001 (Table 2).

Table 3 illustrates babies having cord blood bilirubin of <2.5mg/dl where compared with their serum bilirubin which was recorded up to their 5th day of life Sensitivity 8.82 % (CI-1.86% to 23.68%) and specificity of 83.92% (CI- 78.83% to 88.21%) with Positive Predictive Value and negative predictive value of 6.82% (2.34% to 18.26%) and 87.35 % (85.99% to 88.59%) respectively.

STATISTICS	CORD BLOOD SERUM BILIRUBIN mg/dl					
	<2.5		2.5-3		>3	
	Value	CONFIDENCE INTERVAL	VALUE	CONFIDENCE INTERVAL	VALUE	CONFIDENCE INTERVAL
Sensitivity	8.82%	1.86% to 23.68%	66.67%	49.03% to 81.44%	97.06%	84.67% to 99.93%
Specificity	83.92%	78.83% to 88.21%	92.94%	89.07% to 95.76%	99.22%	97.21% to 99.91%
Positive Likelihood Ratio	0.55	0.18 to 1.68	9.44	5.72 to 15.60	124.24	31.20 to 494.69
Negative Likelihood Ratio	1.09	0.97 to 1.22	0.36	0.23 to 0.57	0.03	0.00 to 0.20
Disease prevalence	11.76%	8.29% to 16.05%	12.37%	8.82% to 16.71%	11.72%	8.26% to 16.00%
Positive Predictive Value	6.82%	2.34% to 18.26%	57.14%	44.67% to 68.77%	94.29%	80.56% to 98.50%
Negative Predictive Value	87.35%	85.99% to 88.59%	95.18%	92.55% to 96.91%	99.61%	97.36% to 99.94%

Table 3: Statistics of values of various cord blood bilirubin levels in predicting the development of significant hyperbilirubinemia.

Neonates having cord blood bilirubin level in the range of 2.5-3 when compared with their serum bilirubin recorded up to 5th day of life was having sensitivity, specificity Positive predictive value and negative predictive value of 66.67% (49.03% to 81.44%), 92.94 % (89.07% to 95.76%), 57.14% (44.67% to 68.77%), and 95.18 % (92.55% to 96.91%) respectively. Similarly cord blood bilirubin of >3mg/dl has sensitivity, specificity Positive predictive value and negative predictive value of 97.06% (84.67% to 99.93%), 99.22% (97.21% to 99.91%), 94.29% (80.56% to 98.50%), 99.61 % (97.36% to 99.94%) (Table 3).

Discussion

Jaundice is a common entity which needs attention up to some days of birth. Most of the jaundice which develops in new-born is in physiological range except small fraction that need intervention like phototherapy, exchange transfusion or new modalities of treatment. Although their fraction is low usually in the range of 8-10 %, as proved in our study with 11.2%. But, timely diagnosis and immediate treatment is very essential because it could have devastating effect on their future life

because of kernicterus, which lead to mental retardation, chore athetoid type of cerebral palsy or hearing defect. Since percentage of these side effects have dramatically decreased in last decade because of public awareness educational programs. But, still there is small fraction of new- born who fall prey to the devastating side effects of neonatal hyperbilirubinemia especially in developing country because of poor follow up, limited resources and most important parental emotional attachment, who did not want their child to get hurt even from a single needle prick. Keeping in view all these factors, the objective of this research was framed. Our study presumption was that a high serum bilirubin level at birth would also predict a high peak later in life.

Incidence of pathological hyperbilirubinemia in our study was 11.2mg/dl. This is in accordance to studies conducted by other authors like was 12.80% in a study by Awasthi S et al. [5], 12.00% as per a study by Randev S, et al. [6], 11.4% in a study by Dhanwadkar et al. [7].

In our study there was no relation between cord blood bilirubin and bilirubin monitored up to 5th days of life when gender, gestational age, birth weight and mode of

delivery were compared. Similar findings were noted by Awasthi S, et al. [5] and Alpay F, et al. [8].

Incidence of pathological hyperbilirubinemia was 11.2 % in our study which is supported by research conducted by Knupfer M, et al. [9] & Awasthi, et al. [5], who derived incidence of 10.6 and 12.8 % respectively.

In our study mean cord blood bilirubin of those babies who developed pathological jaundice was 2.6 ± 0.6 (mean $\pm$ SD). This finding was in accordance of the research of Bernaldo and Segre [10] investigated the predictability of umbilical cord blood unconjugated bilirubin concentration on subsequent hyperbilirubinemia and need for therapy. Utilizing a cut-off point of un-conjugated bilirubin of 2.0 mg/dl, they showed that 53% babies needed phototherapy and raising the cut-off value to 2.5 mg/dl predicted that 72% babies need phototherapy. Zakia Nahar, et al. [11] 2009 found cord blood bilirubin of

$2.5 \text{mg/dl} \pm 0.5$ which can predict occurrence of pathological jaundice in neonates.

Present study revealed at cord blood bilirubin level of $<2.5 \text{mg/dl}$, sensitivity 8.82 % and specificity of 83.92% with positive predictive value and negative predictive value of 6.82% and 87.35 % respectively. Thus, at cord blood $<2.5 \text{mg/dl}$ probability of not developing hyperbilirubinemia is 83.92%. This finding was supported by Rosenfeld J, et al. [12] who found 4% incidence of NNH at cord blood bilirubin level of $<2 \text{mg/dl}$ with specificity of 98.23%. Knupfer M, et al. [9] derived incidence of just 0.30% at serum bilirubin level of 1.17-1.75mg/dl.

Other findings which we extracted from our study were sensitivity, specificity, positive predictive value and negative predictive value at cord blood serum bilirubin level of 2.5-3mg/dl and $>3 \text{mg/dl}$ and other studies which support this are shown in Table 4.

Studies	Cut off Cord STB (mg/dL)	Cut off Neonatal Hyperbilirubinemia (mg/dL)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
OUR Study	<2.5	<12	8.82%	83.92%	6.82%	87.35%
	2.5-3	14.5-15.6	66.67%	92.94%	57.14%	95.18%
	>3	>16	97.06%	99.22%	94.29%	99.61%
Amar Taksande et al ¹³ (2005)	>2	≥ 17	89.50%	85%	38.80%	98.70%
Knudsen ¹⁴ (1989)	>2.35	>15	13%	99%	85%	72%
Zakia Naharet al ¹¹ .(2009)	≥ 2.5	≥ 17	77%	98.60%		96%
Sun. G. et al ¹⁵ .(2007)	>2	≥ 17	68%		45.08%	
Satrya R et al ¹⁶ .(2009)	≥ 2.54	≥ 12.9	90.50%	85%		

Table 4: Studies on the predictive ability of cordblood bilirubin level and the neonatal hyperbilirubinemia.

As illustrated in Table 4 our study predicts with high probability at serum bilirubin level $>3 \text{mg/dl}$, chances of developing pathological neonatal hyperbilirubinemia are very high. Thus, these new-born must be meticulously checked on follow up. Cord blood bilirubin level of 2.5-3.5 also showed good specificity but due to decreased sensitivity, these new born can be categorised into intermediate risk. So our study can classify new-born into three risk categorise as per cord blood serum bilirubin (Table 5).

Cord blood bilirubin (mg/dl)	Risk category
<2.5	Low
2.5-3	Intermediate
$>3 \text{mg/dl}$	High risk

Table 5: Three risks categorise as per cord blood serum bilirubin.

Conclusion

The study concludes with result that there is significant correlation between cord blood serum bilirubin and development of neonatal jaundice. Cord blood bilirubin can be used to categorise neonates into risk group. Neonates with serum bilirubin <2mg/dl have low risk for neonatal hyperbilirubinemia, thus can be kept in low priority as compared to neonates with cord blood serum bilirubin >3mg/dl. Neonates with Cord Blood Bilirubin level ≥ 3 mg/dl should be followed more frequently to reduce morbidity and mortality due to neonatal hyperbilirubinemia [13-16].

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