

Original Research Article

Cord blood bilirubin used as an early predictor of hyperbilirubinemia

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ABSTRACT

Background: Neonatal hyperbilirubinemia is among the commonest symptoms found in neonates. The information about risk of high bilirubin in infants allows simpler methods for reduction of bilirubin to be implemented before hyperbilirubinemia becomes significant and could help to take a decision for early discharge from Hospital. Thus, the authors were aimed at the assessment of the usefulness of the cord blood bilirubin as an early predictor of neonatal hyperbilirubinemia and the usefulness of 1st day bilirubin in predicting the neonatal hyperbilirubinemia.

Methods: The present study was planned to conduct in Department of Pediatrics, Government Thiruvarur Medical College and Hospital, Thiruvarur among neonates delivered from 1st August 2011 to 1st December 2013. These neonates were followed from birth to 2nd postnatal day. Cord blood was collected at birth and bilirubin estimation was done within 12 hours of collection of the blood.

Results: Cord blood bilirubin level of ≥ 2.15 mg/dl has a sensitivity of 73.08% and specificity of 59.49%, positive predictive value 14.6% and negative predictive value of 95.88% in predicting the risk of neonatal hyperbilirubinemia. 1st day bilirubin level of ≥ 5 mg/dl has a sensitivity of 92.3% and specificity of 71.16% and positive predictive value of 23.3% and negative predictive value of 98.9% in predicting the risk of neonatal hyperbilirubinemia.

Conclusions: The use of the critical cord bilirubin level of 2 mg/dl in all healthy term newborns will predict significant hyperbilirubinemia.

Keywords: Bilirubin, Cord blood, Hyperbilirubinemia, Predictors

INTRODUCTION

Neonatal hyperbilirubinemia or neonatal jaundice is among the commonest symptoms found in newborns.¹ Every newborn develops an unconjugated serum bilirubin level >1.8 mg/dl initial week of life after birth which is among the major causes.² Jaundice is reported among in about sixty percent of term and eighty percent of preterm infants in their first week of life.³ The concentration of total serum bilirubin (TSB) is the standard method to evaluate hyperbilirubinemia in neonates. When the TSB concentration will be more than 5 mg/dl, yellow coloration of skin could be visible which indicates jaundice.⁴ The potential risk of developing bilirubin

encephalopathy or even kernicterus is high in babies with elevated serum bilirubin level. The sequelae could be serious as patients may develop cerebral palsy, sensorineural deafness and mental retardation.

The information about risk of developing jaundice in infants allows simple methods for reduction of bilirubin to be implemented before hyperbilirubinemia becomes significant and could help to take a decision for early discharge from Hospital. Predicting higher risk for neonatal jaundice could also help in detecting neonates at lower risk for postnatal jaundice.⁵ Physical examination is not a reliable measure of the serum bilirubin. Under these circumstances it would be desirable to be able to predict

the risk of jaundice, in order to implement early treatment and thereby minimize the risk of bilirubin dependent brain damage.⁶

Thus, the authors were interested to assess the usefulness of the cord blood bilirubin as an early predictor of neonatal hyperbilirubinemia and the usefulness of 1st day bilirubin in predicting the neonatal hyperbilirubinemia. The aims were also to study the association between various levels of cord blood albumin and significant neonatal jaundice requiring interventions like phototherapy or exchange transfusion and to predict the proportion of new born requiring intervention for neonatal jaundice (phototherapy or exchange transfusion) based on cord blood albumin level.

METHODS

The present study was planned to conduct in Department of Pediatrics, Government Thiruvarur Medical College and Hospital, Thiruvarur among neonates delivered from 1st August 2011 to 1st December 2013. These neonates were followed from birth to 2nd postnatal day.

Inclusion criteria

- Healthy term neonates delivered at Department of Pediatrics, Government Thiruvarur Medical College and Hospital, Thiruvarur
- Hospital stay of more than 5 days.
- Cases with informed, written parental consent.

Exclusion criteria

- Clinical jaundice on the first postnatal day
- Sick babies or babies admitted to NICU
- Babies receiving drugs that are known to affect serum bilirubin levels
- More congenital anomalies in newborn
- Maternal gestational diabetes mellitus
- Pathological jaundice
- Rh incompatibility.

Considering above selection criteria, 300 consecutive term neonates delivered at Department of Pediatrics, Government Thiruvarur Medical College and Hospital, Thiruvarur were selected for the study. Informed written parental consent was obtained from all cases. Data was collected as per the Performa. Questionnaire method, maternal case file and examination of the newborn were used to obtain the required data.

Maternal variables like history of jaundice, first trimester bleeding, gestational hypertension, mode of delivery and uses of drugs during pregnancy were collected. Medication during labour, details of delivery, APGAR score and maternal blood group were collected from the maternal file. Babies were examined daily and looked for evidence of jaundice, sepsis, illness or birth trauma.

Weight of the new-born was recorded, and gestational age calculated. All the babies were followed up daily for first 5 postnatal days because peak serum bilirubin occurs between 1st and 2nd day.

Cord blood was collected at birth. First day serum bilirubin was estimated using blood drawn between 12-24 hours after birth. Blood was also drawn on 1st and 2nd day. Peripheral venous blood was used to measure serum bilirubin.

Blood sample collected was stored away from light. The sample was refrigerated between 2-8 °C till serum bilirubin estimation is done. Serum bilirubin estimation was done within 12 hours of collection of sample by Diazotized sulfanilic test. The main outcome of the study was inferred in terms of hyperbilirubinemia. Serum bilirubin ≥ 15 mg/dl after 48 hours of life was taken as hyperbilirubinemia needing phototherapy and treatment is advised to all those full term healthy babies with serum bilirubin level of ≥ 15 mg/dl after 48 hours of life, as per the American academy of paediatrics practice parameter, 2004.

IAP-NNF also recommends considering phototherapy with neonatal serum bilirubin levels of ≥ 15 mg/dl after 48 hours of life. So, in the present study babies with serum bilirubin level of ≥ 15 mg/dl are considered hyperbilirubinemia and needs phototherapy after 48 hours of postnatal life. Maternal, neonatal and natal variables were compared between neonates with 2 days follow up.

Statistical analysis

Statistical data were analyzed with the independent sample 't' test and the descriptive analysis and chi-square tests. Sensitivity, specificity, negative and positive predictive value of the test was calculated. The critical cord bilirubin level having the highest sensitivity and specificity was determined with the Receiver operating characteristics (ROC) curve analysis. Cord serum bilirubin and first day serum bilirubin concentration were used for developing 'prediction test'. The sensitivity and specificity were calculated for predicting hyperbilirubinemia.

RESULTS

The following results were made from the study. The study group consisted of 300 healthy term newborns that were followed up for first 2 postnatal days. The study results were analyzed using appropriate statistical methods and compared with the previous studies.

In the present study, there is no significant difference in the number of male and female babies. This implies uniform distribution of cases in the study group (Table 1).

Figure 1 presents the mean serum bilirubin level and the sex of the newborn. Hyperbilirubinemia was found in

48.9 There is no significant difference ($p = 0.67$) in the serum bilirubin level of both the sexes. Hence the present study infers that the serum bilirubin level is independent of the sex of the new-born.

Table 1: Sex wise distribution of cases (n = 300).

Gender	Frequency	%	Valid %	Cumulative %
Male	195	65	65	65
Female	105	35	35	100
Total	300	100	100	

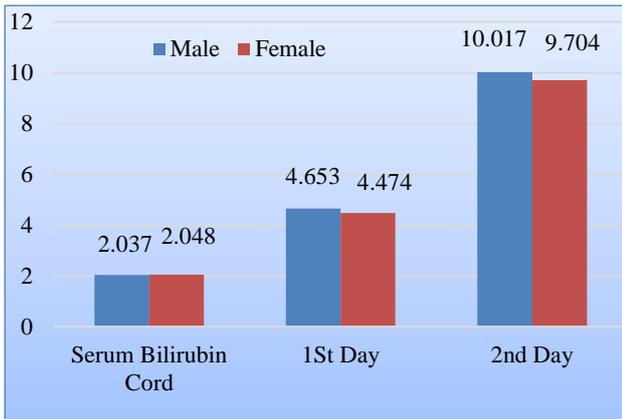


Figure 1: Association between the mean serum bilirubin level and the sex of the new-born (n = 300).

Association between the mode of delivery and the percentage neonatal hyperbilirubinemia is presented in Figure 2. Neonatal hyperbilirubinemia was found in 48.3% vaginal delivery and 43.1% caesarean section. There is no significant association ($p=0.568$) between the neonatal hyperbilirubinemia (≥ 15 mg/dl) and the mode of the delivery either the vaginal delivery or the caesarean section. This implies that neonatal hyperbilirubinemia is independent of the mode of delivery.

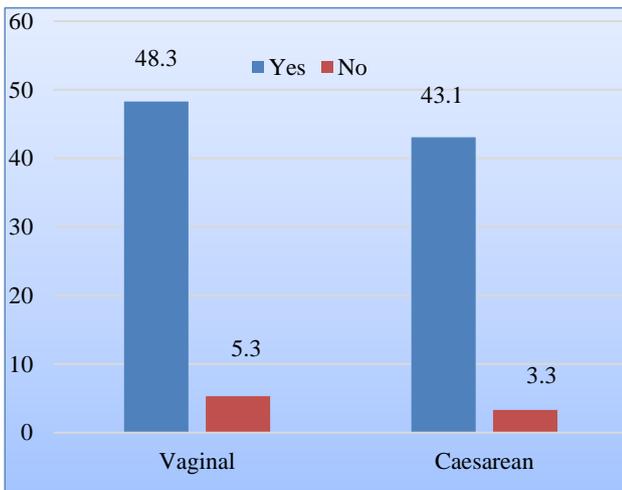


Figure 2: Association between the mode of delivery and the neonatal hyperbilirubinemia (≥ 15 mg/dl).

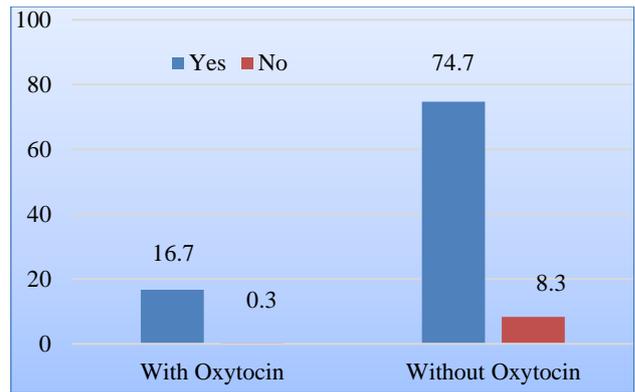


Figure 3: Association between the neonatal hyperbilirubinemia (≥ 15 mg/dl) and the oxytocin induction of labour.

Association between the percentage of neonatal hyperbilirubinemia and the oxytocin induction of labour is showed in Figure 3. Neonatal hyperbilirubinemia was found in 74.7% cases if without using oxytocin. There is no significant correlation ($p > 0.05$) between the babies given fluids and other medications (except oxytocin) with the neonatal hyperbilirubinemia (≥ 15 mg/dl). But there is significant correlation ($p < 0.05$) between the neonatal hyperbilirubinemia and the Oxytocin induction of labour.

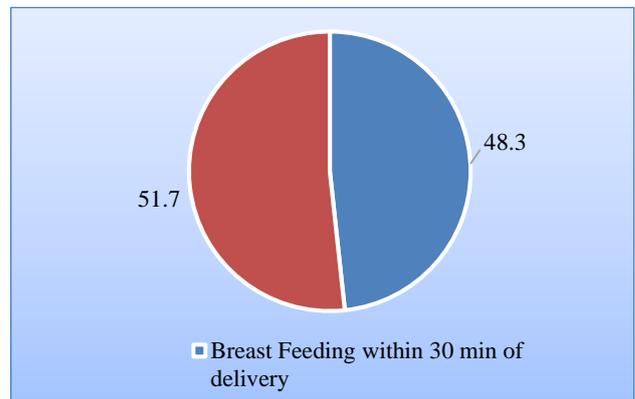


Figure 4: Association between the time of initiation of breast feeding and neonatal hyperbilirubinemia (≥ 15 mg/dl).

In the present study the maternal gestational hypertension has no significant correlation ($p=0.967$) with the development of neonatal hyperbilirubinemia (Figure 4). Hence the study inferred that the neonatal hyperbilirubinemia is independent of the maternal gestational hypertension.

Table 2 presents association between the gestational hypertension and the neonatal hyperbilirubinemia. 83.7% neonatal hyperbilirubinemia was found in mothers without hypertension. The maternal gestational hypertension has no significant correlation ($p=0.967$) with the development of neonatal hyperbilirubinemia. Hence the study inferred that the neonatal

hyperbilirubinemia was independent of the maternal gestational hypertension.

Table 2: Association between the gestational hypertension and the neonatal hyperbilirubinemia (≥ 15 mg/dl).

Maternal Gestational Hypertension	Neonatal Hyperbilirubinemia (≥ 15 mg/dl)		Total
	No	Yes	
Without maternal Hypertension (%)	7.3	83.7	91
With maternal Hypertension (%)	1.3	7.7	9
Total	8.6	91.4	100

The cord serum bilirubin levels of the babies with neonatal hyperbilirubinemia (≥ 15 mg/dl) is significantly higher than the babies without hyperbilirubinemia (Figure 5). Bilirubin profile in the first 2 days of postnatal life infered that the babies with neonatal hyperbilirubinemia had significantly higher bilirubin levels compared to babies without hyperbilirubinemia.

Table 3: Association between the neonatal hyperbilirubinemia (≥ 15 mg/dl) and the critical cord bilirubin level (≥ 2.15 mg/dl).

Neonatal Hyperbilirubinemia (≥ 15 mg/dl)	Cord blood bilirubin (mg/dl)		Total
	≥ 2.15	< 2.15	
Absent	37	54.3	91.3
Present	6.3	2.4	8.7
Total	43.3	56.7	100

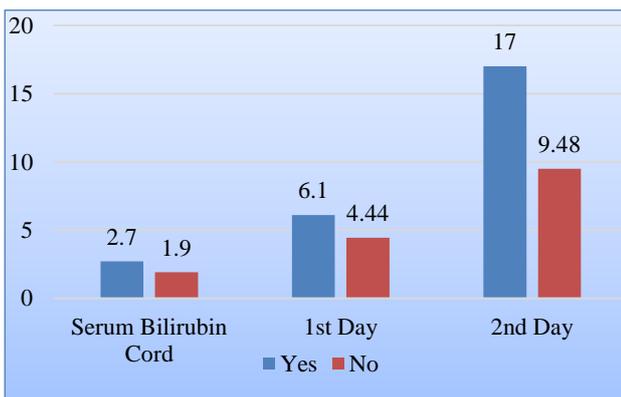


Figure 5: Mean bilirubin profile in the first two postnatal days.

Cord bilirubin level of ≥ 2.15 mg/dl cut off value is chosen based on the receiver operating characteristics (ROC) analysis (Figure 6). In the present study cord serum bilirubin of ≥ 2.15 mg/dl having, sensitivity = 92.3%, specificity = 71.16%, positive predictive value 23.3% and negative predictive value = 98.98%.

Table 4: Association of the neonatal hyperbilirubinemia (≥ 15 mg/dl) with the first day (24 hrs) bilirubin level (≥ 5 mg/dl).

		Neonatal hyperbilirubinemia		Total
		Yes	No	
1 st day ≥ 5	Count	24	79	103
	% Total	8	26.3	34.3
1 st day < 5	Count	2	195	197
	% Total	0.7	65	65.7
Total	Count	26	274	300
	% Total	8.7	91.3	100

So, the cord bilirubin level of ≥ 2.15 mg/dl can be used as an early predictor of neonatal hyperbilirubinemia.

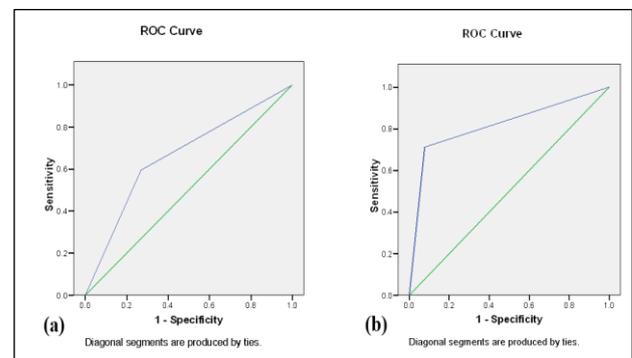


Figure 6: (a) Cord serum bilirubin (b) First day serum bilirubin level based on ROC curve analysis.

First day serum bilirubin level of ≥ 5 mg/dl cut off value was chosen based on ROC analysis (Figure 6). In the present study first day serum bilirubin level of ≥ 5 mg/dl has, sensitivity = 92.3%, specificity = 71.16%, positive predictive value = 23.3% and negative predictive value = 98.98%.

So, the first day (24 hours) serum bilirubin of ≥ 5 mg/dl can also be used as an early predictor of neonatal hyperbilirubinemia (≥ 15 mg/dl).

DISCUSSION

Jaundice in newborn is quite common affecting nearly 60% of term and 80% of preterm neonates during first week of life. Higher cord bilirubin levels among infants which later become jaundiced compared to cord blood bilirubin levels in non-jaundiced infants indicate that mechanisms of importance for the subsequent jaundice are already active in late fetal life. Nearly all fetal bilirubin is unconjugated, due to a limited ability of the fetal liver to conjugate bilirubin.

A total of 300 full term neonates delivered in the Department of Pediatrics, Government Thiruvapur Medical College and Hospital, Thiruvapur, from

December 1st August 2011 to 1st December 2013 were studied to assess the usefulness of the cord blood bilirubin as an early predictor of neonatal hyperbilirubinemia and the usefulness of 1st day bilirubin in predicting the neonatal hyperbilirubinemia.

In plasma, unconjugated bilirubin is tightly bound to albumin, which is the dominant bilirubin binding protein in plasma under normal circumstances no bilirubin deposition takes place in fetal tissue. Unconjugated bilirubin is rapidly transferred to the maternal circulation by the placenta, whereas only small quantities of conjugated bilirubin cross the placenta. Thus, bilirubin produced by the fetus is excreted by the mother, who presumably has a large reserve capacity for bilirubin excretion and only minor differences in maternal bilirubin concentrations can be expected. Raised cord blood bilirubin in ABO or non-ABO situation indicated ongoing in utero hemolysis. These babies are more likely to develop hyperbilirubinemia. A cord bilirubin level >2.5 mg/dl predicts development of pathological jaundice (defined as bilirubin >13 mg/dl) with sensitivity of 92.3% and specificity of 71.16%.

The study revealed the cord bilirubin level of >2 mg/dl had the highest sensitivity (93.3%) and this critical bilirubin level had a very high (98.9%) negative predictive value and fairly low (23.3%) positive predictive value. As per the findings of this study, a critical cut off level of cord bilirubin was 2 mg/dl predicted 90% of the newborns who developed jaundice. However, the cord bilirubin level of <2 mg/dl did not completely exclude the development of significant hyperbilirubinemia; only 2.05% of the newborns with cord bilirubin levels of <2 mg/dl developed jaundice. 98.9% negative predictive value in the present study suggested that measurement of cord serum bilirubin can help in identify those newborns that are unlikely to require further evaluation and intervention.

Alpay et al observed that a serum bilirubin >6 mg/dl on the first day of life had 90% sensitivity of predicting a subsequent TSB >15 mg/dl between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97%. No cases with TSB of <6 mg/dl in first 24 hours required phototherapy treatment value of measuring cord bilirubin concentration in ABO-incompatibility had been investigated by Riesenberget al who found that all infant with cord bilirubin level is higher than 68 mmol/l and development severe jaundice.⁷

Trisiah et al reported in their study that all the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5 mg/dl at 24 hours of life, whereas that risk was 6.6% in cases whose bilirubin level was 5 mg/dl at 24 hrs of life. The maternal and umbilical cord bilirubin concentration at delivery, a yellow skin colour during the first 24 hrs or postnatal life and carbon monoxide excretion are all associated with the later development of neonatal jaundice in healthy mature

newborn infant. The incidence of significant hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin and the incidence of breastfeeding.⁸ In the present study group, there were no significant hyperbilirubinemia with respect to these factors (such as hemoglobin level, haematocrit level, gender, delivery route, birth weight and gestational age) that might be associated with the risk of hyperbilirubinemia.

Trisiah et al reported in their study, with the 1st day bilirubin level of >4.5 mg/dl showed that it has a sensitivity 90%, specificity 71.9%, positive predictive value 50% and negative predictive value of 96.8% in predicting neonatal hyperbilirubinemia. In this study, 1st day or 24 hrs bilirubin levels \geq 5 mg/dl found to be used as an early predictor of neonatal hyperbilirubinemia.⁸

Randev et al found 24 neonates among 200 enrolled (i.e., 12%) developed hyperbilirubinemia. The mean first day TSB value in the neonates who subsequently developed hyperbilirubinemia was 7.716 mg/dl as compared to a value of 5.154 mg/dl in those who did not. Using Receiver operating characteristic (ROC) curve analysis, a value of 6.4 mg/dl (first day TSB) was determined to have the best predictive ability for subsequent hyperbilirubinemia with a sensitivity of 87.5%, specificity of 80.11%, positive predictive value of 37.5% and a negative predictive value of 97.92%.⁹

So, this can be concluded that the use of the critical cord bilirubin level of 2 mg/dl in all healthy term newborns will predict significant hyperbilirubinemia. There is a concern about increasing incidence of kernicterus in healthy term neonates and hyperbilirubinemia is one of the most common causes for readmission of the newborns. The need for early detection of hyperbilirubinemia in the early discharged new-borns from the hospital is therefore important. Knowledge of the infants at risk for developing jaundice allows simple bilirubin reducing methods to be implemented before bilirubin reaches critical levels.

Limitations of the study were, only full term healthy neonates were taken for the study. Since the peak bilirubin level reached on 1st and 2nd postnatal days, babies are followed till 5 days of delivery. In view of early discharge of the babies delivered vaginally, increased representation of babies extracted by caesarean section were taken.

CONCLUSION

The use of the critical cord bilirubin level of 2 mg/dl in all healthy term new-borns will predict significant hyperbilirubinemia.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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