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Prediction of early neonatal hyperbilirubinemia using 24-hour serum bilirubin level

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Abstract

Objective: To evaluate the predictive value of TSB=6 mg/dl at 24±6 hours of age in identifying those infants belonging to Bihar and border areas of Nepal who would not develop hyperbilirubinemia subsequently.

Methods: Serum bilirubin was estimated for all enrolled cases within 18 to 30 hour of life spectrophotometrically using twin Beam method. The babies were then followed up clinically by 2 observers for the appearance and progression of jaundice every 12 hour till discharge from the department of obstetrics and gynaecology and were then admitted with their mothers in step down of NICU. Here they were followed up daily upto fifth day of life. TSB estimation was repeated if the clinical assessment of jaundice was more than 10 mg/dl by any observer using Kramers Rule. Hyerbilirubinemia was defined as TSB level 12 mg/dl between 24 to 48 hour of life 15 mg/dl between 48 to 72 hour of life and 17 mg/dl beyond 72 hours of life.

Results: A total of 152 neonates were enrolled in the study. Of these, 23 neonates (i.e., 15.13%) developed hyperbilirubinemia. Sensitivity of TSB >6mg/dl at 24+6 hours in identifying those who will develop hyperbilirubinemia was 91.3%. Specificity was 76.74%.Positive predictive value was 41.2%. Negative predictive value was 98%. Therefore the test is useful in identifying the infants who are unlikely to develop hyperbilirubinemia.

Conclusion: Incidence of hyperbilirubinemia in healthy term and near term babies is 15.23%. TSB at 24+6 hours <6mg/dl has a high predictive value in identifying those infants who are unlikely to develop subsequent hyperbilirubinemia. This study, thus, will help obstetricians and doctors posted in nursery in planning an early discharge of healthy term newborns. They will be justified in discharging healthy term infants with TSB on 2nd day <6mg/dl early.

Keywords: Hyperbilirubinemia; Neonates; Kernicterus.

Introduction

Jaundice is the commonest abnormal physical finding in the first week of life and is a cause of concern for the parents as well as for the pediatricians. Jaundice is the visible form of hyperbilirubinemia. It appears in Newborn skin at Serum Bilirubin >5 mg/dl. Jaundice occurs in 60% of term and 80% of preterm infants. However, significant jaundice occurs in 6% of term babies and is the most common reason for readmission after early hospital discharge.

Physiologic jaundice usually appears on the 2nd to 3rd day of life, usually peaking by 3rd to 4th day to 6-8 mg/dl and then falls. In premature infants, the peak may be 10-12 mg/dl on the fifth day of life, possibly rising over 15mg/dl without any specific abnormality.

Bilirubin is a product of the breakdown of heme portion of hemoglobin. Three fourths of bilirubin is derived from hemoglobin in dying red cells while the rest is from hemoglobin released by ineffective erythropoiesis and heme containing tissue proteins. This bilirubin which is a non-polar compound is bound to albumin and carried to liver, where it is taken up by hepatocytes. Bound to a cytoplasmic protein, ligandin, it is carried to the endoplasmic reticulum for conjugation with glucoronide. This is done by the enzyme UDP-Glucuronyl Transferase (UDPG-T).

Unconjugated hyperbilirubinemia may be caused by any factor that increases the load of bilirubin (like hemolytic anemias, polycythemia, increased enterohepatic circulation, infection; factors reducing activity of conjugating enzymes (genetic deficiency, hypoxia, infection, hypothermia and hypothyroidism), factors competing for transferase enzyme (drugs).

Concerns regarding jaundice have increased after reports of Bilirubin induced brain damage occurring in healthy term infant. High levels of unconjugated bilirubin are potentially neurotoxic and can lead to widespread brain damage, most severely to Basal ganglia (Kernicterus).Also, conjugated bilirubin, though not neurotoxic usually indicates some serious underlying pathology.

Early discharge of healthy term newborn after delivery has become a common practice because of economic constraints, few hospital beds and large patient load. Thus the concept of prediction of Jaundice offers an attractive option to pick up babies at risk of neonatal hyperbilirubinemia. It is very important and life saving in context of developing country like India and especially for states like Bihar where costly investigations and regular follow up is beyond the reach of the vast majority.

Material & Methods

The present study was a prospective study and was carried out at the NICU of Department of Pediatrics at a tertiary care hospital, Patna. The study was carried out for two years. All healthy term neonates were to be assayed for TSB levels at 24 hours (Between 24+6hours) and again at 5 days. If clinical jaundice appeared in between TSB assay was done immediately and then daily till 5 days of age and the highest reading was recorded as Peak TSB. Hyperbilirubinemia was defined as TSB level >17 mg/dl. A cut off value of TSB at 6mg/dl at 24 hour was fixed arbitrarily and the significance of TSB>6mg/dl at 24 hours in predicting the development of hyperbilirubinemia was analysed. Criteria for inclusion of infants in the study were as follows-

All infants with-

a. Gestational age ≥ 35 weeks (based on last Menstrual Period) and neonatal assessment by expanded New Ballard Score.
b. Absence of significant illness – Requiring NICU admission for >12 hours.
c. Absence of major congenital malformations.
d. Residing at Patna or nearby whose parents agree to come for follow up.
e. Infants of Rh-negative mothers would be included only if they are also Rh-negative.

If an infant was initially included in the study but later developed significant illness requiring NICU admission and those who were found to have Rh-incompatibility were excluded. Infants of Rh-negative mothers were included only if the child was also Rh-negative.

Procedure

All babies delivered the previous day between 4 am and 4pm in the labour room of Dept. of Obstetrics and Gynecology 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 venous site. Blood sample of mother was simultaneously collected and sent for Blood Grouping if it was not known from before. The blood sample of infant was sent for grouping and TSB estimation.

The babies were then followed up clinically by 2 observers for the appearance and progression of jaundice every 12 hour till discharge from the department of obstetrics and gynaecology and were then admitted with their mothers in step down of NICU. Here they were followed up daily upto fifth day of life. TSB estimation was repeated if the clinical assessment of jaundice was more than 10 mg/dl by any observer using Kramers Rule. Hyerbilirubinemia was defined as TSB level ≥12 mg/dl between 24 to 48 hour of life ≥15 mg/dl between 48 to 72 hour of life and 17 mg/dl beyond 72 hours of life.

Whenever jaundice was clinically noticed to be >10 mg/dl, bilirubin estimation was repeated immediately and then everyday till 5 days of age and the highest reading was recorded as peak TSB.

Bilirubin Estimation: Blood samples were drawn by venipuncture into a micro-capillary, which was centrifuged in RM 12 C micro-centrifuge, at the rate of 10000 rpm for 5 min. Bilirubin estimation was done spectrophotometrically using twin beam method (455 and 575 nm wave lengths) and analyzed by Wako Bilirubin Tester Model SE 101 DII. Wako Bilirubin Tester requires only 0.05 ml of serum that can be analyzed directly in the capillary tube after whole blood sample in the micro-capillary has been centrifuged.

Statistical Analysis: The value of first day serum bilirubin which will predict, with reasonable accuracy, the neonates at risk of subsequent hyperbilirubinemia was determined. The sensitivity, specificity, positive and negative predictive values of the test were calculated.

Sample Size: Assuming the incidence of hyperbilirubinemia to be 1-3% in infants with TSB ≤ 6 mg/dl at 24 ± 6.

Hours with alpha value of 0.05 and beta value of 0.1, it was estimated that a sample size of 150infants would be sufficient. To account for dropouts, we enrolled 201 infants.

Results

A total of 201 neonates were initially enrolled. Out of these 38 cases did not turn up for follow up. They were therefore lost due to attrition. Eight infants were admitted to NICU later with a diagnosis of septicemia and were dropped from study. Three infants were admitted with complaints of seizures apart from those who had septicemia; one of these was due to documented hypoglycemia. All these three cases were excluded from study. Complete data was available for 152 infants (75.6%).

Table 1: The baseline characteristics of the study population

Characteristic	No.	Percentage
Caesarean	105	69.1
Vaginal	47	30.9
Parity		
=1	38	25.0
=2	54	35.5
=3	37	24.3
>4	23	15.2
Oxytocin used	120	78.9
Near term (35-37 wks)	8	5.2
ABO incompatibility	38	25.0

Table 2: Showing the incidence of Clinical Jaundice and significant Hyperbilirubinemia

Total enrollments	Clinical Jaundice present	Percentage	Significant Hyperbilirubinemia (>17mg/dl)	Percentage
152	109	71.71	23	15.13

Significant Hyperbilirubinemia (TSB>17mg/dl) was present in 21.1% cases of those babies who developed jaundice.

Table 3: Showing the distribution of Hyperbilirubinemia cases

TSB at 24+6hours	No. of cases who developed TSB >17mg/dl	No. of cases who did not develop TSB >17mg/dl	Total
>6mg/dl	21	30	51
<6mg/dl	2	99	101
			152

A TSB of <6mg/dl at 24 +6hours was present in 101 infants (66.45%). Out of these only two infants developed hyperbilirubinemia subsequently.

In the rest 51(33.52%) cases the TSB at 24+6 hours was >6 mg/dl. Out of this group 21 cases ultimately went on to develop a positive study outcome.

Sensitivity of TSB at 24+6 hours >6mg/dl in identifying those who will develop hyperbilirubinemia =91.3%.

Specificity of TSB at 24+6hours>6 mg/dl in identifying those who will develop hyperbilirubinemia=76.74%.

Positive predictive value of TSB at 24+6hours >6 mg/dl in identifying those who will develop hyperbilirubinemia =41.2%.

Negative predictive value of TSB at 24+6hours >6 mg/dl in identifying those who will develop hyperbilirubinemia =98%

Discussion

The present study found that a TSB level ≤6 mg/dl at 24 ± 6 hour can be used to predict the decreased risk for subsequent hyperbilirubinemia (TSB > 17 mg/dl). Such infants could thus be discharged early without need to follow up for hyperbilirubinemia later.

Bhutani *et al* [10] showed in a large cohort that infants who develop hyperbilirubinemia have serum bilirubin levels, which are in higher percentiles soon after birth. The authors created percentile charts of serum bilirubin level at different postnatal ages in near-term and term infants who were direct Coombs test negative. They found that 6.1% of neonates had pre-discharge serum bilirubin [3]95th percentile; 32.1% of these infants showed hyperbilirubinemia subsequently. [10] Neonates with pre-discharge TSB levels in the low risk zone (< 40th percentile) did not show hyperbilirubinemia subsequently. However, there was an important source of bias in this study. Out of around 13,000 neonates, subsequent bilirubin estimation could be done in only around 25%. The infants included those who came for follow up or were referred by their primary physicians. A large number of infants were thus not included. It is likely that infants without significant problems were not included while developing these percentile charts.

Later Alpay, *et al* reported that TSB levels of ³6 mg/dl in the first 24 hour predicted jaundice in all newborns subsequently.[5]Awasthi *et al*. showed that TSB level of 3.99 mg/dl at 18-24 hour was able to predict subsequent hyperbilirubinemia (>15 mg/dl) with sensitivity and specificity of 67%each.[11]

In a study by Agarwal *et al*[12]the predictive ability of TSB =6mg/dl at 24±6 hour of life was evaluated and a sensitivity of 95%, specificity of 27.2% and negative predictive value of 99.3% were determined.

According to Grover et al. [13] 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. The difference was significant (p=0.000). 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%.

Lavanya et al. [14] showed the mean duration of onset of significant jaundice to be 61 ± 32 hours. The mean duration of phototherapy was 49 ±26 hours. Large for gestation, lower gestational age, birth trauma and previous sibling with jaundice predicted severe jaundice. TcB measured at 24-48 hours was a better predictor of 'significant jaundice with onset after 48 hours than clinical risk factors.

In the study done by Chawla et al[15]997 neonates (birth weight: 2627 ± 536 g, gestation: 37.8±1.5 weeks) were enrolled, of which 931 completed follow up. Among enrolled neonates 344 (34.5%) were low birth weight. Rate of exclusive breastfeeding during hospital stay was more than 80%. Bilirubin nomogram was constructed using 40th, 75th and 95th percentile values of hour-specific bilirubin. Pre-discharge STB of ≥95th percentile was assigned to be in high-risk zone, between 75th and 94th centile in upper-intermediate risk zone, between 40th and 74th centile in lower-intermediate risk zone and below 40th percentile in low-risk zone. Among 49 neonates with pre-discharge STB in high risk zone. 34 developed SHB (positive predictive value: 69.4%, sensitivity: 17.1%, positive likelihood ratio: 8.26). Among 342 neonates with pre-discharge STB in low risk zone, 32 developed PHB (negative predictive value: 90.6% and specificity: 42.5%, positive likelihood ratio: 0.37). Area under curve for this risk assessment strategy was 0.73.

Hour-specific bilirubin nomogram and STB measurement can be used for predicting subsequent need of phototherapy. Further studies are needed to validate performance of risk demarcation zones defined in this hour-specific bilirubin nomogram.

Conclusion

The present study proves that a TSB at 24+6 hours <6mg/dl has a high predictive value in identifying those infants who are unlikely to develop subsequent hyperbilirubinemia and these neonates can be discharged early from the hospital.

Incidence of hyperbilirubinemia in healthy term and near term babies is 15.23%.

The incidence increases by the use of oxytocin and at lower gestational age.

This study, thus, will help obstetricians and pediatricians posted in nursery in planning an early discharge of healthy term newborns. They will be justified in discharging healthy term infants with TSB on 2nd day <6mg/dl early.

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