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Original Research Article

A Retrospective Study to Evaluate the Prediction of Early Neonatal Hyperbilirubinemia using 24-Hour Serum Bilirubin Level

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Abstract

Aim: The aim of the present study was to evaluate the prediction of early neonatal hyperbilirubinemia using 24-hour serum bilirubin level.

Methods: The present study was a retrospective study and was carried out at the NICU of Upgraded Department of Pediatrics, Patna Medical College and Hospital, Patna, Bihar, India. The study was carried out from December 2013 to November 2014. We enrolled 100 infants. All healthy term neonates were to be assayed for TSB levels at 24 hours (Between 24+6hours) and again at 5 days.

Results: There were 55 (55%) male neonates. 70 (70%) were delivered by normal vaginal delivery (NVD) and 30 (30%) delivered by LSCS. ABO incompatibility was present in 25% neonates. A TSB of <6mg/dl at 24 +6hours was present in 65 infants (65%). Out of these only 5 infants developed hyperbilirubinemia subsequently. In the rest 35 (35%) cases the TSB at 24+6 hours was >6 mg/dl. Out of this group 10 cases ultimately went on to develop a positive study outcome. All the neonates were classified into four groups depending on the 24 hour serum bilirubin levels <3mg/dl (group-1), 3-4.9mg/dl (group-2), 5-6.9mg/dl (group-3), and >7mg/dl (group-4). Majority 52 of newborns had mean 24hr bilirubin level between 3-4.9mg/dl. 25 (25%) newborns had 24 hours blood bilirubin level between <3mg/dl. 43 newborns had 24 hours blood bilirubin level between 5-6.9 mg/d. 14 neonates had 24 hours bilirubin levels >7mg/dl. The range of bilirubin value within 24 hours was 2.1 to 8.1mg/dl. There was statistically highly significant ($p<0.001$) association between requirement of phototherapy and higher 24hours serum bilirubin levels. Newborn babies with 24 hours serum bilirubin level of >4.75 mg/dl had a significant risk of developing neonatal hyperbilirubinemia.

Conclusion: 24 hour bilirubin level of more >4.75mg/dl can reliably predict neonatal hyperbilirubinemia in healthy term neonates.

Keywords: Hyperbilirubinemia, Serum bilirubin, neonatal

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. [1] National Neonatal Perinatal Database (NNPD) reported 6.1% incidence of significant hyperbilirubinemia in inborn neonates & 27.9% in out born in the year 2002. Sixty percent of the term healthy neonates have clinical jaundice in first week of life 6.1% healthy term newborns without identified risk factors have a maximal serum bilirubin level >12.9 mg/dl. [2] Neonatal brain is susceptible to toxicity from unconjugated bilirubin resulting in "kernicterus" or bilirubin induced brain damage (BIBD). [3,4] Bilirubin toxicity to immature brain in term newborns can be easily prevented if identified early. 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). [5] High levels of unconjugated bilirubin are potentially neurotoxic and can lead to widespread brain damage, most severely to Basal ganglia (Kernicterus). [6] Also, conjugated bilirubin, though not neurotoxic usually indicates some serious underlying pathology. Bilirubin toxicity to immature brain in term newborns can be easily prevented if identified early. Early initiation of treatment is cost effective and highly effective in preventing the neurological sequelae. Follow up of neonates discharged early is essential to identify neonates at risk of hyperbilirubinemia. [7]

Various methods were used to identify significant hyperbilirubinemia. Cord blood bilirubin levels, predischarge hour specific bilirubin values and transcutaneous bilirubin estimation used by many investigators to accurately identify at risk neonates. [8,9,10] There have been reports of a significant correlation between 24 hour bilirubin values and subsequent development of severe Hyperbilirub inemia. Hence the present study was conducted to evaluate 24 hour serum bilirubin level for predicting significant hyperbilirubinemia.

The aim of the present study was to evaluate the prediction of early neonatal hyperbilirubinemia using 24-hour serum bilirubin level.

Materials and Methods

The present study was a retrospective study and was carried out at the NICU of Upgraded Department Of Pediatrics, Patna Medical College and Hospital, Patna, Bihar, India. The study was carried out from December 2013 to November 2014. We enrolled 100 infants. 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 analyzed. 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 labor 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 gynecology and were then admitted with their mothers in step down of NICU. Here they were followed up daily up to fifth day of life. TSB estimation was repeated if the clinical assessment of jaundice was more than 10 mg/dl by any observer using Kramer's Rule. Hyperbilirubinemia 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 was calculated.

Results

Table 1: The baseline characteristics of the study population

Characteristic	No.	Percentage
Caesarean	30	30
Vaginal	70	70
Gender		
Male	55	55
Female	45	45
Parity		
=1	26	26
=2	34	34
=3	25	25
>4	15	15
Oxytocin used		
Used	80	80
Not used	20	20
Near term (35-37 wks)	7	7
ABO incompatibility		
Present	25	25
Absent	75	75

There were 55 (55%) male neonates. 70 (70%) were delivered by normal vaginal delivery (NVD) and 30 (30%) delivered by LSCS. ABO incompatibility was present in 25% neonates.

Table 2: Showing the distribution of Hyperbilirubinemia cases

TSB at 24+6hours	No. of cases who developedTSB >17mg/dl	No. of cases who did notdevelop TSB >17mg/dl	Total
>6mg/dl	10	15	35
<6mg/dl	5	60	65
Total			100

A TSB of <6mg/dl at 24 +6hours was present in 65 infants (65%). Out of these only 5 infants developed hyperbilirubinemia subsequently. In the rest 35 (35%) cases the TSB at 24+6 hours was >6 mg/dl. Out of this group 10 cases ultimately went on to develop a positive study outcome.

Table 3: Association between first day serum bilirubin and significant neonatal hyperbilirubinemia

First day serum Total bilirubin levels	Total	Hyperbilirubinemia		P Value
		Yes	No	
Group 1 (<3mg/dl)	25	2	23	<0.001
Group 2 (<3-4.9mg/dl)	52	4	48	
Group 3 (<5-6.9mg/dl)	18	9	9	
Group 4 (>7mg/dl)	5	2	3	

All the neonates were classified into four groups depending on the 24 hour serum bilirubin levels <3mg/dl (group-1), 3-4.9mg/dl (group-2), 5-6.9mg/dl (group-3), and >7mg/dl (group-4). Majority 52 of newborns had mean 24hr bilirubin level between 3-4.9mg/dl. 25 (25%) newborns had 24 hours blood bilirubin level between <3mg/dl. 43 newborns had 24 hours blood bilirubin level between 5-6.9 mg/d. 14 neonates had 24 hours bilirubin levels >7mg/dl. The range of bilirubin value within 24 hours was 2.1 to 8.1mg/dl. There was statistically highly significant ($p<0.001$) association between requirement of phototherapy and higher 24hours serum bilirubin levels.

Table 4: Predictive ability of 24 hours serum bilirubin for assessment of severe hyperbilirubinemia

First day serum bilirubin levels Mean	Total	Hyperbilirubinemia		'p' value
		Yes	No	
<4.75mg/dl	70	5	65	
>4.75mg/dl	30	14	16	<0.0001

Newborn babies with 24 hours serum bilirubin level of >4.75 mg/dl had a significant risk of developing neonatal hyperbilirubinemia.

Discussion

Neonatal hyperbilirubinemia is a cause of concern for the parents as well as for the pediatricians. It occurs in 5-10% of healthy term infants [1,11] and is the most common reason for readmission after early hospital discharge. [12] Concerns regarding jaundice have increased after reports of bilirubin induced brain damage occurring in healthy term infants, even without hemolysis. [13] Total serum bilirubin (TSB) in infants discharged within 48 hr of age generally shows an increasing trend and some of these infants later develop hyper-bilirubinemia. In a cohort of 500 healthy term infants, Alpay, et al found that hyper-bilirubinemia (serum bilirubin >17mg/dl) occurred only after 72 hr of age. [14] The American Academy of Pediatrics recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaundice and other problems. [15]

There were 55 (55%) male neonates. Amar T et al, in a study on 200 neonates with 82 males and 118 females found no association between gender of the newborn and the neonatal hyperbilirubinemia (≥15mg/dl). [16] In contrast study by Rudy S et al, showed significant association between the sex of the newborn and neonatal hyperbilirubinemia. They observed significant hyperbilirubinemia in male neonates. [17] 70 (70%) were delivered by normal vaginal delivery (NVD) and 30 (30%) delivered by LSCS. In study by Singhal V et al, observed statistically significant hyperbilirubinemia in caesarean delivered babies. [18]

ABO incompatibility was present in 25% neonates. A TSB of <6mg/dl at 24 +6hours was present in 65 infants (65%). Out of these only 5 infants developed hyperbilirubinemia subsequently. In the rest 35 (35%) cases the TSB at 24+6 hours was >6 mg/dl. 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. [19] In a study by Agarwal et al [20] 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.

Out of this group 10 cases ultimately went on to develop a positive study outcome. All the neonates were classified into four groups depending on the 24 hour serum bilirubin levels <3mg/dl (group-1), 3-4.9mg/dl (group-2), 5-6.9mg/dl (group-3), and >7mg/dl (group-4). Majority 52 of newborns had mean 24hr bilirubin level between 3-4.9mg/dl. 25 (25%) newborns had 24 hours blood bilirubin level between <3mg/dl. 43 newborns had 24 hours blood bilirubin level between 5-6.9 mg/d. 14 neonates had 24 hours bilirubin levels >7mg/dl. The range of bilirubin value within 24 hours was 2.1 to 8.1mg/dl. There was statistically highly significant ($p<0.001$) association between requirement of phototherapy and higher 24hours serum bilirubin levels. Newborn babies with 24 hours serum bilirubin level of >4.75 mg/dl had a significant risk of developing neonatal hyperbilirubinemia. According to Grover et al [21] 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 [22] 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.

For optimal utilization of the limited neonatal care facility available in our country, it is essential to have practical guidelines to predict which healthy newborn would develop significant hyperbilirubinemia and to avoid preventable neurological damage. From the present study, it can be concluded that 24 hour bilirubin >4.75mg/dl will help predict nearly all healthy term newborns that have significant hyperbilirubinemia and will require a phototherapy treatment later during first few days of life. Oxytocin, induction of labour, male gender and order of delivery must consider in healthy neonates before discharge. The main limitation of this study was small sample size. Further clinical follow up of neonates have done which is not ideal. Ideally follow up measuring serum levels of bilirubin would have been more appropriate.

Conclusion

The present study proved that a 24 hour total serum bilirubin (TSB) of less than 4.75 mg/dl predicts the risk of subsequent Hyperbilirubinemia. Oxytocin use, male sex and order of delivery are risk factors while contemplating early discharge of healthy neonates. To ease the burden on limited neonatal health care facilities it is necessary to have practical guidelines to predict significant hyperbilirubinemia in neonates.

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