e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(11); 97-102

Original Research Article

Assessing the Predictive Value of 24-Hour Serum Bilirubin Levels in the Early Detection of Newborn Hyperbilirubinemia with in a Hospital Setting

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Received: 03-06-2023 Revised: 22-07-2023 / Accepted: 18-08-2023

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Conflict of interest: Nil

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 prospective study and was carried out at the NICU of Department of Pediatrics. The study was carried out for one year. 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: A bilirubin level over 4.75mg/dl during a 24-hour period may serve as a dependable indicator for the presence of newborn hyperbilirubinemia in healthy term infants.

Keywords: Hyperbilirubinemia, Serum bilirubin, neonatal.

Introduction

Jaundice is the most prevalent atypical physical observation during the first week of an infant's life, prompting anxiety among both parents and clinicians. Jaundice is the observable manifestation of hyperbilirubinemia. Elevated levels of serum bilirubin above 5 mg/dl have been seen in the skin of newborns. The incidence of jaundice is seen in 60% of full-term neonates and 80% of preterm infants. [1] In the year 2002, the National Neonatal Perinatal Database (NNPD) documented an incidence of severe hyperbilirubinemia in inborn neonates at a rate of 6.1%, whereas out born neonates had a higher prevalence of 27.9%. In the first week of life, around 60% of infants classified as healthy have clinical jaundice. A study found that 6.1% of healthy term babies who did not have any established risk factors had a maximum blood bilirubin level over 12.9 mg/dl. [2] neonatal brain is vulnerable to the harmful effects of unconjugated bilirubin, which may lead to the development of "kernicterus" or bilirubin-induced brain damage (BIBD). [3,4] The prevention of bilirubin toxicity in the undeveloped brain of term babies may be effectively achieved by early identification. Unconjugated hyperbilirubinemia can arise from various factors that contribute to an increased bilirubin load, such as hemolytic anemias, polycythemia, heightened enterohepatic circulation, and infection. Additionally, factors that diminish the activity of conjugating enzymes, including

genetic deficiencies, hypoxia, infection, hypothermia, and hypothyroidism, can also play a role. Furthermore, the presence of drugs that compete for transferase enzymes can contribute to this condition. [5] Elevated concentrations of unconjugated bilirubin has the potential to induce neurotoxicity, hence resulting in extensive cerebral impairment, particularly in the Basal ganglia region, ultimately culminating in Kernicterus. [6] Moreover, the presence of conjugated bilirubin, while often non-neurotoxic, often suggests the presence of a significant underlying pathological condition. The prevention of bilirubin toxicity in the undeveloped brain of term babies may be effectively achieved by early identification. [7] The prompt beginning of therapy at an early stage has been shown to be both cost-effective and highly efficacious in avoiding the development of neurological sequelae. The importance of post-discharge follow-up for newborns cannot be overstated, as it plays a crucial role in identifying neonates who may be at risk of developing hyperbilirubinemia. The user's text is too brief to be rewritten in an academic manner.

Multiple techniques were used to ascertain noteworthy hyperbilirubinemia. Many researchers use cord blood bilirubin levels, hour-specific bilirubin values before discharge, and transcutaneous bilirubin estimates as reliable methods for reliably identifying newborns who are at risk. [8-10] There have been documented instances of a significant association between 24-hour bilirubin levels and the eventual onset of acute hyperbilirubinemia. Therefore, the current research was undertaken to assess the 24-hour serum bilirubin level as a predictor of severe hyperbilirubinemia.

The objective of the current investigation was to assess the ability to forecast the occurrence of early newborn hyperbilirubinemia by using the 24-hour serum bilirubin level.

Materials and Methods

The present study was a prospective study and was carried out at the NICU of Department of Pediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India. The study was carried out for one year. 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 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 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	f cases who developed TSB >17mg/dl	No. of cases who did not develop 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	<0.0001
>4.75mg/dl	30	14	16	

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

Discussion

The occurrence of neonatal hyperbilirubinemia is a matter of apprehension for both parents and clinicians alike. The incidence of this condition is seen in around 5-10% of healthy term newborns [1,11], making it the primary cause for readmission after early hospital discharge. [12] There has been a growing apprehension about jaundice due to the emergence of data indicating the occurrence of bilirubin-induced brain damage in healthy full-term newborns, even in the absence of hemolysis. [13] The levels of total serum bilirubin (TSB) in newborns who are released within 48 hours of birth often exhibit a progressive rise, and a subset of these children subsequently experience the development of hyperbilirubinemia. In a study conducted by Alpay et al., a group of 500 children who were born at full term and in good health were examined. The researchers discovered that hyperbilirubinemia, defined as a serum bilirubin level above 17mg/dl, only manifested when the infants reached 72 hours of age. [14] According to the guidelines set out by the American Academy of Pediatrics, it is recommended that babies who are released from the hospital within a period of 48 hours should have a follow-up visit within 2-3 days. This visit serves the purpose of identifying any notable instances of jaundice or other potential issues. [15]

Fifty-five percent of the newborns were male. In research conducted by Amar T et al, a cohort of 200 newborns, consisting of 82 males and 118 females, was examined to see if there was a correlation between the gender of the newborn and the occurrence of neonatal hyperbilirubinemia (≥15mg/dl). The findings of the study revealed no significant link between the gender of the newborn and the occurrence of neonatal hyperbilirubinemia. [16] In contrast to the findings of Rudy et al., their investigation demonstrated a significant correlation between the sex of the infant and the occurrence of neonatal hyperbilirubinemia. Significant hyperbilirubinemia was detected in male newborns. [17] Seventeen out of seventy deliveries (70%) were conducted by normal vaginal delivery (NVD), whereas the remaining thirty deliveries (30%) were performed through lower segment cesarean section (LSCS). Singhal et al. conducted research in which they detected a statistically significant occurrence of hyperbilirubinemia in infants delivered through caesarean section. [18] The occurrence of ABO incompatibility was seen in 25% of the newborns. A total serum bilirubin (TSB) level of less than 6mg/dl at 24 hours and 6 hours afterwards was seen in 65 newborns, accounting for 65% of the sample population. Subsequently, only five newborns had hyperbilirubinemia within this group. In the other 35 instances, which accounted for 35% of the total, the total serum bilirubin (TSB) level at 24+6 hours exceeded 6 mg/dl. The study conducted by Awasthi et al. shown that a total serum bilirubin (TSB) level of 3.99 mg/dl between 18-24 hours after birth had the ability to accurately predict the occurrence of hyperbilirubinemia, defined as TSB levels above 15 mg/dl, with a sensitivity and specificity of 67% each. [19] The research conducted by Agarwal et al. (2020) aimed to assess the predictive capacity of total serum bilirubin (TSB) levels at 24±6 hours after birth. The results revealed a sensitivity of 95%, specificity of 27.2%, and negative predictive value of 99.3%. [20,21]

Among the members of this cohort, a total of 10 instances eventually exhibited a favorable result in the research. The newborns were categorized into four distinct groups based on their serum bilirubin levels during the first 24 hours after birth: group 1 included neonates with bilirubin levels below 3mg/dl, group 2 included neonates with bilirubin levels between 3-4.9mg/dl, group 3 included neonates with bilirubin levels between 5-6.9mg/dl, and group 4 included neonates with bilirubin levels beyond 7mg/dl. The majority, including 52% of neonates, had a mean 24-hour bilirubin level falling within the range of 3-4.9mg/dl. A total of 25 infants, accounting for 25% of the sample, had a blood bilirubin level between <3mg/dl during the first 24 hours after birth. A total of 43 neonates had blood bilirubin levels ranging from 5 to 6.9 mg/dL throughout a 24-hour period. A total of 14 newborns had bilirubin levels above 7mg/dl over a 24-hour period. The bilirubin values observed over a 24-hour period ranged from 2.1 to 8.1mg/dl. A statistically significant correlation ($p<0.001$) was seen between the need for phototherapy and elevated levels of blood bilirubin at the 24-hour mark. Infants who exhibit a serum bilirubin level over 4.75 mg/dl during the first 24 hours after birth are at a significant risk for the development of neonatal hyperbilirubinemia. Based on the findings of Grover et al. (2021), the average total serum bilirubin (TSB) level on the initial day of birth was 7.716 mg/dl for neonates who later experienced hyperbilirubinemia, whereas neonates who did not develop hyperbilirubinemia had an average TSB level of 5.154 mg/dl. There was a statistically significant difference observed ($p=0.000$). 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%. In a study conducted by Lavanya et al. [22] , it was observed that the average time for the onset of significant jaundice was found to be 61 ± 32 hours. The average duration of phototherapy

was found to be 49 ±26 hours. Several factors were found to be significant predictors of severe jaundice, namely a high birth weight for gestational age, a lower gestational age, a history of birth trauma, and having a previous sibling with jaundice. The measurement of total serum bilirubin (TcB) within the time frame of 24-48 hours was found to be a more reliable indicator for the occurrence of significant jaundice that manifests after 48 hours, compared to clinical risk factors.

In order to maximize the efficient utilization of the limited neonatal care resources within our nation, it is imperative to establish practical guidelines that can accurately predict which healthy newborns are at risk of developing significant hyperbilirubinemia, thereby enabling the prevention of avoidable neurological impairments. Based on the findings of this study, it can be inferred that a bilirubin level exceeding 4.75mg/dl within a 24-hour period is indicative of a high likelihood of significant hyperbilirubinemia in healthy term newborns. Consequently, these infants are likely to necessitate phototherapy treatment within the initial days of their lives. Before discharging healthy neonates, it is imperative to consider factors such as oxytocin administration, induction of labor, male gender, and order of delivery. One of the primary constraints encountered in this study pertained to the limited size of the sample. Additional clinical follow-up of neonates has been conducted, although it is not considered optimal. Ideally, a more appropriate approach would have been to conduct follow-up measurements of bilirubin serum levels.

Conclusion

The current investigation has shown that a 24-hour aggregate serum bilirubin (TSB) level below 4.75 mg/dl may serve as an indicator for the likelihood of developing Hyperbilirubinemia in the future. The use of oxytocin, the male gender, and the sequence of delivery are all elements that provide potential risks when considering the premature discharge of healthy newborns. In order to alleviate the strain on constrained newborn healthcare resources, it is imperative to establish pragmatic protocols for the anticipation of noteworthy hyperbilirubinemia in neonates.

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