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Value of First-day Serum Bilirubin Measurement in Predicting the Development of Neonatal Hyperbilirubinemia

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ABSTRACT

To determine the value of first day serum bilirubin level in prediction of subsequent development of significant hyperbilirubinemia in the newborn population. It was conducted during the period from August 2011-2012. One hundred healthy newborns were enrolled in the study. Serum bilirubin was estimated for all enrolled cases within the first day of life. Babies were followed up clinically for the appearance and progression of jaundice daily up to the fifth day of life. Jaundice was clinically detected in 74 (74%) newborn. The best cut off value of Total Serum Bilirubin (TSB) at the first day in predicting jaundice was 2.7 mg dL^{-1}. The first day TSB of neonates who developed jaundice was significantly higher than those who didn't develop jaundice (4.1, 2.3 mg dL^{-1}, respectively). Significant hyperbilirubinemia was presented in 9 (9%) of cases. The mean first day TSB level was higher in cases with significant jaundice than that of neonates without significant jaundice (7.4, 3.3 mg dL^{-1}, respectively). The best cut off value of TSB at first day in predicting significant hyperbilirubinemia was 6 with a sensitivity of 100.0% and specificity of 100.0%. Based on results of the present study, first day measurements of total serum bilirubin is a good predictor of significant development of hyperbilirubinemia in the subsequent days. The cutoff point is 6 mg dL^{-1} in the first day.

Key words: Serum bilirubin, hyperbilirubinemia, jaundice

INTRODUCTION

In newborn infants, hyperbilirubinemia (significant increase of bilirubin above normal values) represented one of the most common condition requiring evaluation and intervention (Watson, 2009). Neonatal jaundice (yellowish discoloration of skin, sclera and other tissues) has been a topic of considerable interest for pediatricians since it is the commonest abnormal finding in the first week of life. It affects nearly 70% term and 80% preterm infants. It is usually physiological event but in several neonates pathological jaundice occurs (Randev and Grover, 2010). Unconjugated (indirect) hyperbilirubinemia occurs as a result of excessive bilirubin formation and because the neonatal liver can not clear bilirubin rapidly enough from the blood. In addition, in healthy jaundiced newborns, the monitoring is mandatory as bilirubin is potentially toxic to the central nervous system (Maisels and McDonagh, 2008). The most common cause of readmission within neonatal period is jaundice or hyperbilirubinemia. The recognition, follow up and early treatment of jaundice has become more difficult since earlier discharge of newborns from hospitals

(Kavehmanesh *et al.*, 2008). The earlier discharge of jandicied newborns without adequate follow up can lead to development of more severe jaundice cases passed unnoticed by family members (Facchini *et al.*, 2007).

According to the American Academy of Pediatrics (AAP), early discharge (less than 48 h) with no early follow up (within 48 h of discharge) is a potential cause of kernicterus (bilirubin-induced brain dysfunction) (Anthony and Barbara, 2007). Routine obstetric and neonatal hospital stays have decreased markedly in the world during the past 15-20 years and consequently newborns require follow up can not obtain it. Thus, the need of the role of prediction of neonatal jaundice evolved in such conditions. There have been reports of correlation between bilirubin values on day one of life and subsequent development of hyperbilirubinemia (Randev and Grover, 2010). The concept of prediction of jaundice offers an attractive option to pick up babies at risk of neonatal hyperbilirubinemia (Agarwal *et al.*, 2002).

Aim of the work: The aim of this work is to determine the first day Total Serum Bilirubin (TSB) value to predict neonates likely to develop subsequent significant hyperbilirubinemia.

MATERIALS AND METHODS

The present study was a cross sectional analytical study which was conducted during the period from August 2011-2012. One hundred healthy newborns that are early discharged and not routinely followed up after a short period of discharge were enrolled in the study.

Exclusion criteria: Babies who are candidate for admission or near follow up e.g., gestational age <35 weeks; weight <2 kg; conjugated hyperbilirubinemia, Rh incompatibility, congenital hypothyroidism, cephal-hematoma, plethora, bruising and evidence of sepsis clinically or by investigation (+ve CRP) as causes of pathological jaundice.

All cases were subjected to the following: careful history taking, full clinical examination, New Ballard Score to detect the gestational age. The New Ballard Score is a set of procedures developed by Ballard *et al.* (1991) to determine gestational age through neuromuscular and physical assessment of a newborn fetus and anthropometric measurements including birth weight, length, head circumference and abdominal circumference.

Laboratory investigations: A two mL of venous blood were collected from each enrolled neonate. Blood was centrifuged and serum was separated for measurement of serum bilirubin and C-reactive protein. Measurement of serum bilirubin (with direct fraction) using spectrophotometer based on diazo method. Assay of C-Reactive Protein (CRP) by latex based on agglutination method. Neonatal Rh in cases of negative maternal Rh. Serum bilirubin was estimated for all enrolled cases within the first day of life. Babies were followed up clinically for the appearance and progression of jaundice everyday up to the fifth day of life. TSB estimation was repeated if clinical assessment of jaundice was more than 10 mg dL^{-1} using Kramer's rule which stated that, rather than estimating the level of jaundice by simply observing the baby's skin color, one can utilize the cephalocaudal development of jaundice. Attention to the observation that jaundice starts on the head and extends towards the feet as the level rises had been drawn. This is useful in deciding whether or not a baby needs to have the serum bilirubin measured. Kramer divided the infant into 5 zones, the serum bilirubin range associated with progression to the zones is as follows: Significant hyperbilirubinemia was defined as TSB ≥12 mg dL^{-1} at 25-48 h of life, ≥15 mg dL^{-1} between 49 and 72 h of life and ≥17 mg dL^{-1} beyond 72 h of life (Randev and Grover, 2010).

Statistical analysis of data: The collected data were organized, tabulated and statistically analyzed using Statistical Package for Social Sciences (SPSS) version 16 (SPSS Inc, USA), running on IBM compatible computer. Fore quantitative data, mean and Standard Deviation (SD) were calculated and for comparison between two means, the independent samples student (t) test was used. Qualitative data were represented as frequency and percent distribution Chi square test (X^2) was used for comparison between groups. For prediction, simple linear regression was calculated and for estimation of sensitivity, specificity and best cut off values, the Receiver Operator Curve (ROC) was used. The strength of test prediction was calculated from Area Under the Curve (AUC). For interpretation of results, significance was adopted at $p \leq 0.05$.

RESULTS

The present study included 100 neonates, 50% of them were males and 50% were females; gestational age of studied neonates ranged from 35-42 weeks with a mean of 38.22±1.63 weeks; 45% of them were delivered by normal vaginal route and 55% delivered by cesarean. As regard maternal characteristics, it was found that parity ranged from 1-4 with a mean of 1.92±0.8; maternal Rh was negative in 2% of cases whom babies are of negative Rh; diabetes was reported in 2% while hypertension was reported in 3% and PROM reported in 5% of cases that have no evidence of sepsis clinically or by investigation (CRP). Finally, family history of jaundice in a previous sibling was reported in 3% of cases (Table 1).

As regard vital signs of studied neonates, heart rate ranged from 126-160 beat/minute with a mean of 143.1±8.5 beat/minute, while respiratory rate ranged from 30-60 cycle/minute with a mean of 46.0±4.9 cycle/minute and finally, temperature ranged from 36.7-37.3°C with a mean of 37.0±0.1°C. Birth weight ranged from 2.2-4.4 kg with a mean of 3.3±0.4 kg, while length ranged from 45-52 cm with a mean of 49.3±1.5 cm. In addition, head circumference ranged from 32-37 cm with a mean of 34.7±0.9 cm. Finally, abdominal circumference ranged from 29-37 cm with a mean of 32.7±1.2 cm. Total serum bilirubin in the first day, it was ranged from 1.2-9 with a mean of 3.7±1.6 mg dL^{-1} (Table 2).

As regard to relative frequency of jaundice in the studied neonates according to the day of appearance of jaundice. We found that 74% of all studied neonates were jaundiced by the fifth day. The majority of them was appeared in the third and fourth day of life(33-29%, respectively) (Table 3). In the present work, first day TSB among the studied neonates in relation to the day of appearance of jaundice. We found that, the mean first day TSB in neonates with jaundice was

Table 1: Demographic characteristics of the studied cases and their mothers

Paramaters	Values
Characteristics of studied cases	
Male gender (n, %)	50 (50%)
Gestational age (Mean±SD, range)	38.2±1.6, 35- 42
Normal vaginal delivery of delivery (n, %)	45 (45.0%)
Maternal characteristics	
Parity (Mean±SD, range)	1.92±0.80, 1-4
Positive maternal Rh (n, %)	98 (98%)
Diabetes (n, %)	2 (2.0%)
Hypertension (n, %)	3 (3.0%)
PROM (n, %)	5 (5.0%)
Family history of jaundice in a previous sibling (n, %)	3 (3.0%)

Table 2: Vital signs, anthropometric measurements and first day TSB of studied neonates

Variables	Mean±SD	Range
Heart rate	143.1±8.5	126-160
Respiratory rate	46.0±4.9	30-60
Temperature	37.0±0.1	36.7-37.3
Birth weight	3.3±0.4	2.2-4.4
Length	49.3±1.5	45.0-52.0
Head circumference	34.7±0.9	32.0-37.0
Abdominal circumference	32.7±1.2	29.0-37.0
First day total serum bilirubin	3.7±1.6	1.2-9.0

Table 3: Relative frequency of jaundice in the studied neonates according to the day of appearance of jaundice (n = 100)

			Total	
Days of appearance	No.	(%)	No.	(%)
2nd	11	11.0	74	74.0
3rd	33	33.0		
4th	29	29.0		
5th	1	1.0		
No jaundice	26	26.0	26	26.0
Total	100	100.0	100	100.0

Table 4: Sensitivity, specificity and best cut off value of TSB at the Ist day in predicting jaundice

Jaundice		
Positive if 1st day TSB greater than or equal to	Sensitivity	Specificity
2.4500	0.905	0.346
2.5500	0.905	0.269
2.6500	0.878	0.231
2.7500	0.865	0.231
2.8500	0.811	0.192
3.0500	0.784	0.192
3.2500	0.716	0.192

Area under the curve = 0.88, 95% confidence interval was 0.81-0.95

higher than those without jaundice throughout the days of the study. There was a statistically high significant difference in the 2nd, 3rd and 4th days. While in the 5th day, there was a statistically non significant difference. In addition, first day TSB among all studied neonates in relation to the presence of Jaundice. We found that the first day TSB of neonates who developed jaundice was higher than those who didn't develop jaundice (4.1, 2.3 mg dL^{-1}, respectively) with high statistically significant difference (data not tabulated).

Using receiver operator curve, total serum bilirubin at the first day giving high predictive power for development of jaundice; area under the curve was 0.88. The best cut off value for jaundice was 2.7 with sensitivity of 88% and specificity of 77% (Table 4). As regard to relative frequency of significant hyperbilirubinemia among all studied neonates in relation to first day TSB. We found that significant hyperbilirubinemia occurred in 9% of all studied neonates with mean first day TSB level higher than those who didn't develop significant hyperbilirubinemia with a statistically high significant difference. As regard to relative frequency of significant hyperbilirubinemia in the

Table 5: Regression analysis to detect predictability of total serum bilirubin in Ist day to develop significant hyperbilirubinemia

Statistics	Significant hyperbilirubinemia
R	0.75
β	-4.13
95% confidence interval	-4.83-3.41
p value	<0.001*

Table 6: Sensitivity, specificity and best cut off value of TSB at the Ist day in predicting significant hyperbilirubinemia

Significant jaundice		
Positive if 1st day TSB greater than or equal to	Sensitivity	Specificity
5.05	1.000	0.066
5.15	1.000	0.055
5.25	1.000	0.033
5.35	1.000	0.022
5.55	1.000	0.011
6.05	1.000	0.000
6.55	0.889	0.000
6.75	0.778	0.000
6.85	0.667	0.000

Area under the curve = 1.0, 95% confidence interval was 1.0-1.0

studied neonates according to the day of appearance. We found that significant hyperbilirubinemia developed in 2 (2%) cases in the 2nd day, 3 (3%) cases in the 3rd day, 3 (3%) cases in the 4th day and only one (1%) case in the 5th day (data not tabulated).

Running simple linear regression analysis, total serum bilirubin at the first day can predict in a powerful manner the development of significant hyperbilirubinemia (Table 5). The best cut off value of TSB at first day in predicting significant hyperbilirubinemia was 6 with a sensitivity of 100.0% and specificity of 100.0% (Table 6).

DISCUSSION

Several studies suggest that neonatal hyperbilirubinemia represented the most common cause for readmission of healthy full term babies who were discharged early (Maisels and Kring, 1998; Hall *et al*., 2000). Such babies require follow-up within 48 h where, there is difficulty in accessing and maintaining hospital admission. Here comes the role of prediction of neonatal hyperbilirubinemia. Thus, the present study was designed-as a cross sectional study-to determine the value of first day serum bilirubin level that will predict subsequent significant hyperbilirubinemia in the newborn population. It was conducted during the period from August 2011-2012. One hundred healthy newborns that are early discharged and not routinely followed up after a short period of discharge were enrolled in the study.

In agreement with results of the present study, Alpay *et al*. (2000) reported that, there were no significant differences between the cases who did and who did not develop significant hyperbilirubinemia with respect to various factors that may be associated with the risk of hyperbilirubinemia. Those risk factors may include hemoglobin level, gender, gestational age, neonatal birth weight, mode of delivery, type of feeding and maternal smoking.

As regard total serum bilirubin in the first day, it was ranged from 1.2-9 with a mean of 3.7 mg dL^{-1}. In a study done by Agarwal *et al*. (2002) the TSB in the first day was ranged from

2-15 with a mean of 5.9 mg dL^{-1}. These results are higher than that of our study. This difference may be attributed to the age at which bilirubin was estimated. It was done at the first 24 h in our study while in the other study it was done between 20-30 h.

Clinically detectable jaundice during the first five days of life was present in 74 (74%) infants. This result goes in agreement with that reported by Agarwal *et al.* (2002) who reported that clinically detectable jaundice was present in 164 (77%) infants. This result goes also in agreement with that reported by Ip *et al.* (2004) who reported that, hyperbilirubinemia is a common problem in neonates with an incidence of 70-80%. The majority of newborns with jaundice in our study were appeared in the third and fourth day of life (33-29%, respectively). This result goes in agreement with that reported by Porter and Dennis (2002) who reported that jaundice typically appeared on the third and fourth day of life then declines over the first week after birth.

In the present work, 9 of one hundred newborns (9%) followed for 5 days developed significant hyperbilirubinemia and their mean bilirubin was 15.8 mg dL^{-1}. Significant hyperbilirubinemia was defined as TSB ≥12 mg dL^{-1} at the 2nd day of life, ≥15 mg dL^{-1} at the 3rd day of life and ≥17 mg dL^{-1} beyond the 3rd day of life (Randev and Grover, 2010). Significant hyperbilirubinemia developed in 2 (2%) cases in the 2nd day, 3 (3%) cases in the 3rd day, 3 (3%) cases in the 4th day and only one (1%) case in the 5th day. These results go in agreement with that of Agarwal *et al.* (2002) who reported that TSB of ≥17 mg dL^{-1} was present in 22 (10.3%) newborns. In a similar study by Alpay *et al.* (2000), no newborns had a serum total bilirubin level of >17 mg dL^{-1} in the first 72 h of life. Sixty of 498 newborns (12.05%) followed for 5 days had total serum bilirubin levels of >17 mg dL^{-1} after 72 h of life. When the first 5 days' mean bilirubin levels of the cases who did and who did not develop significant hyperbilirubinemia were compared, the cases who later developed significant hyperbilirubinemia had significantly higher bilirubin levels on each day. In addition, Keren *et al.* (2008) reported that, 48 (6%) infants developed significant hyperbilirubinemia. This value is less than that reported in the present work and may be attributed to the large sample size, different sociodemographic characteristics and also to the 61(7%) infants who were lost to follow-up.

On the other hand, in a study reported by Sarici *et al.* (2004), twenty-three newborns (10.5%) in the term group and 37 newborns (25.3%) in the near-term group had significant hyperbilirubinemia and required phototherapy, with any of the first week's serum bilirubin levels exceeding the threshold levels defined for significant hyperbilirubinemia. These results are more than those of our study. The possible explanation for this difference may be attributed to the large number of cases included in their study when compared to the present study or to the duration of follow up which was 7 days in this study while we followed newborns for only 5 days. Furthermore, Varvarigou *et al.* (2009) in a study included 2035 live birth infants; significant hyperbilirubinemia was documented for 122 neonates (6%). This wide difference may be attributed to different inclusion criteria, as they included all live births, while we included a specific group of live birth. In addition, their sample size is huge in comparison to that of the present work. In our study by running simple linear regression analysis, total serum bilirubin at the first day can predict in a powerful manner the development of significant hyperbilirubinemia. The best cut off value of TSB at first day in predicting significant hyperbilirubinemia was 6 with a sensitivity of 100.0% and specificity of 100.0%. In a study done by Randev and Grover (2010) they reported that, hypothesis was that a high serum bilirubin level soon after birth i.e., within 24±6 h of life, would also predict a high peak subsequently. By demonstrating a significant difference in the first day serum bilirubin values of infants who subsequently did and those who did not develop significant

hyperbilirubinemia, the study has proved the usefulness of the test. The area under the ROC Curve is 0.8 which also makes the test fall under the category of a good test. The authors have determined a cutoff value of 6.4 mg dL^{-1} for the prediction of neonatal hyperbilirubinemia. They added, the negative predictive value at this level of serum bilirubin is high, meaning thereby that the neonates having serum bilirubin below this level are at very low risk of subsequent hyperbilirubinemia. The value in this study is greater than ours and this may be due to different inclusion criteria as they included only full term newborns while we included full term and near term newborns. Alpay *et al.* (2000) reported that, with ROC analysis, a mean serum bilirubin level of 6 mg dL^{-1} in the first 24 h of life was determined to have the highest sensitivity (90%) to predict the newborns that would develop significant hyperbilirubinemia. Of the 206 newborns who had a serum total bilirubin level of >6 mg dL^{-1} in the first 24 h of life, 54 (26.21%) developed significant hyperbilirubinemia after 72 h of life, whereas only 6 of the 292 newborns (2.05%) who had a serum total bilirubin level of <6 mg dL^{-1} on the first day developed significant hyperbilirubinemia later on the fourth and fifth days of life. These results are in agreement with that of the present work. Bhutani *et al.* (1999) tested the same hypothesis in a large cohort in Philadelphia, U.S.A. They proved 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 levels at different postnatal ages in near-term and term infants who were direct coombs test negative. They found that 6.1% neonates had predischarge serum bilirubin in the ≥95th percentile range and 32.1% of these neonates subsequently developed significant hyperbilirubinemia.

In the present study, we did not evaluate data on nomograms and preferred to determine the cutoff value which would better reflect the geographic and social characteristics distinctive to the present population as compared to (Bhutani *et al.*,1999) We believe that this would be more accurate as the environmental and genetic influences might affect the distribution of the bilirubin values. In a similar study by Seidman *et al.* (1996) the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was ≤5 mg dL^{-1} at 24 h of life, whereas that risk was 6.6% in cases whose bilirubin level was ≤5 mg dL^{-1} at 24 h of life. In their series of 1075 newborns, this critical bilirubin level (5 mg dL^{-1}) was reported to have a high specificity (91.9%) and a low sensitivity (45.5%) for detecting significant hyperbilirubinemia; the positive predictive value was very low (8.9%) and the negative predictive value was very high (99.0%).

In contradiction to results of the present work, Awasthi and Rehman (1998) reported a value of 3.99 mg dL^{-1} to have a sensitivity of 64.2 and 67.4% for subsequent requirement of phototherapy. However, there were major flaws in the study. The cutoff value was not determined using ROC analysis but rather the mean serum bilirubin at 18-24 h was used as the cutoff for developing the 'Prediction test'. Moreover, complete follow-up was conducted in infants who stayed in the hospital either for neonatal illness or some maternal reason. More than 50% of the neonates, who were healthy, thus discharged early, were not studied. These factors can explain the contradiction between both studies. In addition, in a study by Agarwal *et al.* (2002) the predictive ability of TSB = 6 mg dL^{-1} at 24±6 h of life was evaluated and a sensitivity of 95%, specificity of 27.2% and negative predictive value of 99.3% were determined. These results are in accordance with that of the present work. Also, Stevenson *et al.* (2001) concluded that, their study supports previous observations that the practice of measuring TSB before discharge may provide some assistance in predicting infants who are at risk for the subsequent development of hyperbilirubinemia. Such screening could identify infants who might need early intervention with phototherapy or additional diagnostic workup and/or follow up for jaundice after discharge. It is

important to recognize that infants with increased bilirubin production, who may handle the bilirubin load well, also may have other clinical problems that require diagnosis and follow-up, such as late anemia in the presence of hemolysis.

CONCLUSION

Based on results of the present study, first day measurements of total serum bilirubin predict efficiently cases that will develop significant hyperbilirubinemia in the subsequent days. Cases with values equal to or more than 6 mg dL^{-1} in the first day are likely to develop significant hyperbilirubinemia.

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