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The Predictive Value of First-day Bilirubin Levels in the Early Discharge of Newborns

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ABSTRACT

Background: TORCH Early discharge of newborns due to social, economic and medical reasons increases the rate of readmissions, especially for hyperbilirubinemia. Therefore, identification of high-risk neonates for subsequent hyperbilirubinemia is paramount. This study aimed to investigate the level of total serum bilirubin (TSB), which could be used to predict neonatal hyperbilirubinemia at the first day of birth.

Methods: Venous blood samples were obtained from 300 newborns during the postpartum period (i.e. 24±6 hours) to determine the blood group, direct Coombs test, TSB and direct bilirubin levels (DBL). Neonates were followed-up for 5 days, and TSB and DBL were recorded in 90 newborns presented with jaundice according to the Kramer's scale within 120±6 hours of birth.

Results: In total, 23.3% of the studied newborns (N=90) required phototherapy. The cut-off value of TSB to determine high-risk newborns for subsequent hyperbilirubinemia at the first day of birth was 6.50 mg/dl with positive and negative predictive values of 19.75% and 97.72%, respectively. At this point, the sensitivity and specificity were 76.19% and 76.70%, respectively.

Conclusion: According to the results of this study, TSB cut-off point of 6.5 mg/dl at the first day of birth could predict the risk of subsequent hyperbilirubinemia in healthy, term infants with early discharge. Since TSB cut-off point is economic and available, use of this method is recommended in all healthcare centers.

Keywords: Early discharge, Hyperbilirubinemia, Newborn

Introduction

In recent years, discharge of full-term healthy newborns within the shortest time interval has become common at hospitals. Consequently, the mother-infant interaction starts early at home, leading to a significant increase in the frequency of breastfeeding within the first days after birth. Additionally, risk of nosocomial infections decreases in these infants.

Short length of hospital stay is economical for the infant's family and promotes the use of hospital facilities (1). On the other hand, those against early neonatal discharge claim that follow-up can be difficult outside the hospital, causing delays in the diagnosis of conditions such as hyperbilirubinemia, nutritional problems, congenital anomalies and some cardiac diseases. In developing countries, early discharge of newborns and delayed diagnosis of severe hyperbilirubinemia can hinder the prompt treatment of this condition due to geographical, climatic and financial factors (2).

Advantages and disadvantages of early postnatal discharge have been extensively discussed. Readmission to hospital due to neonatal hyperbilirubinemia has been noted in various cases. Therefore, the need for reforms in region-based strategies for neonatal jaundice has been highlighted and early neonatal discharge has been under debate (3).

In addition to recent trends, high hospital occupancy rates have also given rise to early postnatal discharge in Turkey. However, considering the high frequency of kernicterus in Turkey, further research concentrating on the follow-up of neonatal jaundice is crucial (4, 5). Although some risk factors such as blood incompatibility, history of jaundice in siblings and cephalohematoma can predict hyperbilirubinemia, inexpensive, accessible predictive tests, used within the first days after birth, are needed.

Therefore, in this study, we aimed to determine which level of total serum bilirubin

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(TSB) in the first 24 hours of life could be a predictive parameter for identifying high-risk newborns for subsequent hyperbilirubinemia.

Method

This prospective, cohort study was conducted at Zeynep Kamil Maternity and Children's Training and Research Hospital in Istanbul, Turkey between May and August 2009. The study sample consisted of 300 healthy newborns, who met the inclusion criteria: 1) gestational age > 37 weeks, based on the last menstruation date; 2) birth weight ≥ 2500 g, based on the modified Dubowitz score; 3) one- and five-minute Apgar scores ≥ 7; and 4) normal physical examination.

The exclusion criteria were as follows: 1) known prenatal diseases or haemolytic condition; 2) complications such as severe bruising, hemotoma, sepsis, Down syndrome, hypothyroidism and glucose-6 phosphate dehydrogenase deficiency; and 3) hospitalization in the neonatal intensive care unit due to life-threatening conditions, e.g., perinatal asphyxia, acidosis, respiratory distress, persistent hypothermia, hypoglycemia, hyponatremia, hemolysis, sepsis, meningitis and clinical jaundice in the first 24 hours after birth.

A questionnaire was completed for each newborn. Maternal (e.g., mode of delivery, oxytocin use, preeclampsia, premature rupture of membranes, multiple gestation, history of diabetes and blood group) and neonatal (e.g., gender, birth weight, gestational age, Apgar score, blood group, direct Coomb's test results, feeding method, pathological weight loss and history of icteric siblings) factors were recorded in the forms.

By obtaining venous blood samples from the newborns at 24±6 hours after birth, the blood group, direct coomb's test, TSB and direct bilirubin level were determined. The newborns were followed-up for five days and TSB and direct bilirubin levels were re-determined at 120±6 hours of age, according to the evaluation of Kramer's dermal zones (6). Physical examination and evaluation of Kramer's dermal zones were performed by physicians, who were unaware of the initial TSB levels.

TSB level ≥ 17 mg/dl at 120±6 hours of age was defined as "significant hyperbilirubinemia", according to the American Academy of Pediatrics (AAP) (7). Total and direct bilirubin values were measured by the Dade Behring auto-analyzer via the aqueous method and venous blood samples. Direct Coombs' test was performed in Diamed-ID Centrifuge 12S II device by employing the micro-column gel card diffusion method.

For data analysis, SPSS version 13.0 for Windows was applied. P-value less than 5% was considered statistically significant. Mean and standard error values were calculated. Mann-Whitney U test or Student's t-test was applied for the comparison of quantitative variables, without a normal distribution. Descriptive statistical methods (e.g., calculation of mean and standard deviation) were also applied. For qualitative data, screening tests (e.g., sensitivity and specificity) and Chi-square test were employed. Moreover, Receiver Operating Characteristic (ROC) analysis was performed to determine the TSB cut-off point.

Informed consents were obtained from the parents of newborns, and an approval was obtained from the ethics committee of Zeynep Kamil Maternity and Children's Training and Research Hospital.

Results

The present study was conducted on 300 healthy term newborns with the mean gestational age of 39.04±0.07 weeks and mean birth weight of 3218±248 g. Of all newborns, 131 (43.7%) and 169 (56.3%) cases were female and male, respectively. The distribution of risk factors was as follows: oxytocin use (n=67, 22.3%), maternal preeclampsia (n=10, 3.3%), premature rupture of membranes (n=37, 12.4%) and maternal diabetes (n=10, 3.3%). Moreover, 7% (n=21) of cases were multiple gestations and 5% (n=15) had a prior history of icteric siblings.

On the fifth day after birth, 83.3% (n=250) of newborns were breastfed, 2.6% (n=8) were formula-fed and 14% (n= 42) were both breastfed and formula-fed. Also, 8% of newborns (n=24) experienced pathological weight loss. TSB level was not significantly different between newborns with and without the risk factors (P>0.05). Among newborns, 20% (n=60) had ABO incompatibility
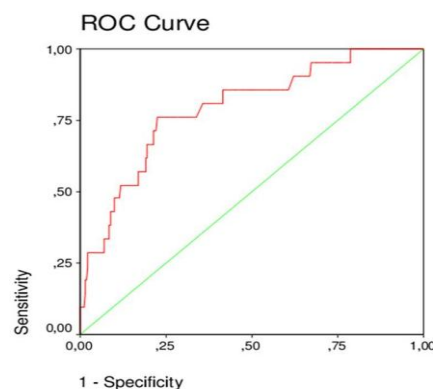
Figure 1. ROC analysis TSB levels in predicting subsequent hyerbilirubinemia

and 9.3% (n=28) had Rh incompatibility. As expected, there was a significant difference in TSB level between newborns with and without blood incompatibility. The mean TSB levels were 6.07±1.6 and 5.39±1.5 mg/dl in these newborns at 24±6 hours after birth, respectively (P=0.001).

After the five-day follow-up, jaundice was developed in 90 (30%) out of 300 newborns, and 21 cases (23.3%) required phototherapy. Gender, gestational age and birth weight were not significantly different in icteric newborns (P>0.05). The mean TSB level at 24±6 hours after birth was significantly higher in newborns receiving phototherapy. In seven newborns, direct coomb's test results were positive and three cases received phototherapy. Exchange transfusion was not required in any of the subjects.

Sensitivity, specificity, positive and negative predictive values, accuracy and relative risk values for each TSB level at 24±6 hours after birth are reported in Table 1. ROC analysis was performed for evaluating the first-day TSB levels to obtain a "cut-off" point for predicting subsequent hyperbilirubinemia (Figure 1). Based on ROC analysis, 6.50 mg/dl, showing the highest relative risk (8.65), was defined as the "cut-off" point.

At this point (6.50 mg/dl), the negative predictive value (97.72%) and specificity (76.70%) were rather high (Table 1). The sensitivity reduced, while the specificity increased with elevating TSB level at 24±6 hours after birth. Moreover, among newborns with TSB level ≥ 6.50 mg/dl at 24±6 hours after birth, phototherapy was more common (P<0.01, χ2:7,089).

Discussion

Neonatal hyperbilirubinemia remains the most common and perhaps the most preventable problem in full-term and near-term infants during the early postnatal period. Since the shortened length of hospital stay for newborns was established in the last decade, neonatal readmission due to hyperbilirubinemia has increased in Turkey, as well as developed/developing countries (8-13).

Although kernicterus is thought to be a rare condition, given the advent of exchange transfusion, maternal rhesus immunoglobulin prophylaxis and phototherapy, cases of kernicterus are still being reported in healthy, near-term and full-term infants, with no evidence of hemolytic disease or other risk factors (1, 14).

Table 1. Sensitivity, specificity, positive and negative predictive values, accuracy and relative risk values, accuracy and relative risk values for each TSB level

TSB levels (mg/L)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy	Relative risk
5,45	85,71	48,75	11,18	97,84	51,33	5,18
5,50	85,71	49,82	11,39	97,89	52,33	5,39
5,60	85,71	51,61	11,76	97,96	54,00	5,76
5,70	85,71	53,05	12,08	98,01	55,33	6,08
5,80	85,71	56,27	12,86	98,13	58,33	6,86
5,90	80,95	61,29	13,60	97,71	62,67	5,95
6,00	80,95	63,80	14,41	97,80	65,00	6,56
6,10	76,19	66,31	14,55	97,37	67,00	5,53
6,15	76,19	68,82	15,53	97,46	69,33	6,12
6,20	76,19	70,61	16,33	97,52	71,00	6,60
6,30	76,19	73,12	17,58	97,61	73,33	7,35
6,40	76,19	75,99	19,28	97,70	76,00	8,37
6,50	76,19	76,70	19,75	97,72	76,67	8,65
6,60	71,43	77,78	19,48	97,31	77,33	7,24
6,70	66,67	79,21	19,44	96,93	78,33	6,33
6,80	61,90	81,00	19,70	96,58	79,67	5,76
6,90	57,14	83,15	20,34	96,27	81,33	5,45
7,00	52,38	83,87	19,64	95,90	81,67	4,79
7,10	52,38	85,30	21,15	95,97	83,00	5,25
7,20	52,38	86,74	22,92	96,03	84,33	5,7
7,40	52,38	88,17	25,00	96,09	85,67	6,4

Incidence of kernicterus has been the highest in the United States (27%), Singapore (19%) and Turkey (16%) (15). considering the high prevalence of kernicterus in Turkey, further research on the risk factors and follow-up programs is essential.

On the other hand, due to high birth rates and hospital occupancy in Turkey, early hospital discharge has become a necessity. Under these circumstances, identifying newborns with a high risk of subsequent hyperbilirubinemia is essential for the prevention of bilirubin-induced brain damages (4). For this reason, various laboratory parameters, which might predict jaundice, have been investigated by considering various familial and ethnic factors.

A predictive test for jaundice should be easy to perform, economic and applicable in the first 24 hours after birth. Therefore, end-tidal carbon monoxide measurement (ETCOc) (16), transcutaneous bilirubin (TCB) (17, 18), umbilical cord blood bilirubin (4, 19, 20) and TSB level (1, 3, 21) within six and twenty-four hours after birth have been recommended as the markers of TSB production.

ETCOc measurement requires advanced instrumentation and is associated with high costs (22). Moreover, TCB level, which has a good correlation with plasma TSB level, should be avoided as a screening tool since it is affected by melanin pigmentation in the skin and may underestimate the serum bilirubin level (23, 24).

So far, according to several studies, pre-discharge TSB level, along with the assessment of clinical risk factors, has led to improvements in the prediction of subsequent hyperbilirubinemia (25, 26). In the literature, different TSB values have been defined as the cut-off points, with different sensitivities and specificities due to the heterogeneity of the study groups.

Bhutani et al. in a study on 2,840 infants by evaluating TSB level before hospital discharge (27) demonstrated a strong relationship between hour-specific pre-discharge TSB level and the likelihood of subsequent hyperbilirubinemia; therefore, the predictive values of pre-discharge TSB and TCB levels were confirmed.

In Turkey, Alpay et al. (2) introduced a bilirubin level of 6 mg/dl as the cut-off point, with a positive predictive value of 26.2% and a negative predictive value of 97.9%. Similarly, in a study on 213 newborns by Agarwal et al. (28), the cut-off point was 6 mg/dl with a positive predictive value of 27.2%, and negative predictive value of 99.3%. Moreover, in a recent study on 200 newborns, TSB level of 6.4 mg/dl (first-day TSB level) had the best predictive ability for subsequent hyperbilirubinemia, with a positive predictive value of 37.5% and a negative predictive value of 97.92% (13).

In the present study, with the aim to introduce a practical, economic predictive test, which can be performed with limited facilities, we tried to determine a cut-off TSB level to be used on the first day of birth for the prediction of significant neonatal hyperbilirubinemia in our region. In our study, hyperbilirubinemia was developed in only 5 out of 147 cases. TSB level was below 6.5 mg/dl on the first day in a total of 300 cases, whereas in 16 out of 153 cases, TSB level was higher than 6.5 mg/dl. Therefore, 6.50 mg/dl was defined as the cut-off point with a positive predictive value of 19.75% and negative predictive value of 97.72% (sensitivity of 76.19% and specificity of 76.70%).

Similar to previous research, a high negative predictive value was reported in our study. Therefore, we can consider patients with TSB level ≤ 6.5 mg/dl on the first day as "low-risk patients" for subsequent hyperbilirubinemia. Correspondingly, Randev et al. indicated that the mean TSB level was significantly different among newborns who received phototherapy and those who did not (13).

The limitations of the present study were the heterogeneity of the study group and the frequency of late-onset severe hyperbilirubinemia; therefore, further large-scaled studies are highly recommended.

Conclusion

In conclusion, the TSB cut-off point was determined to be 6.5 mg/dl on the first day after birth. This test, which is available in all healthcare units, can be used for predicting the risk of subsequent hyperbilirubinemia in healthy, full-term newborns. Also, it seems safe to follow-up early-discharged infants with an appropriate risk assessment tool. Although the application of this test for the management of icteric newborns is unlikely to succeed in eliminating all cases of kernicterus, it might significantly reduce its occurrence, especially in hospitals with limited facilities (14, 29).

Acknowledgment

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