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Original Article

Evaluation of the Predictive Value of Umbilical Cord Serum Bilirubin Level for the Development of Subsequent Hyperbilirubinemia in Term and Late-Preterm Neonates

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ABSTRACT

***Background*:** Considering the increasing rates of early hospital discharge and kernicterus in healthy full term newborns, timely identification of neonates at risk of severe hyperbilirubinemia is of great significance. The aim of this study was to investigate the predictive value of umbilical cord serum (UCS) bilirubin level for subsequent hyperbilirubinemia. Moreover, we compared the predictive value of UCS bilirubin with that of risk factor assessment and predischarge bilirubin level.

***Methods*:** In this prospective, cohort study, 450 healthy neonates born at the gestational age of ≥ 35 weeks were included. UCS bilirubin concentration, direct Coombs test results, and blood group were determined in the newborns. Total serum bilirubin level was re-assessed before hospital discharge. The subjects were followed-up for 1-4 days after discharge and the total serum bilirubin level was measured in neonates with clinical jaundice. Results of the assessment of risk factors for hyperbilirubinemia were recorded.

***Results*:** In total, 319 newborns were followed-up within the study period. The mean UCS bilirubin level in non-icteric and icteric neonates was 2.35 and 2.49 mg/dl, respectively. No significant relationship was found between UCS bilirubin level and development of hyperbilirubinemia (P=0.30), whereas a significant correlation was detected between predischarge bilirubin level and development of jaundice (P=0.009). Gestational age, birth weight, history of jaundice in siblings, and mode of delivery were the clinical risk factors which showed a significant correlation with postnatal hyperbilirubinemia.

Conclusion: Based on the findings, UCS bilirubin level could not predict subsequent hyperbilirubinemia. Therefore, the best predictive marker for neonatal jaundice is the assessment of clinical risk factors and predischarge bilirubin level.

Keywords: Hyperbilirubinemia, Neonate, Prediction, Prevention, Umbilical cord blood

Introduction

Neonatal hyperbilirubinemia remains one of the most common and important complications in newborns. Today, considering the increasing rate of early postnatal discharge from hospitals and prevalence of kernicterus in healthy full term newborns (1, 2), timely identification of neonates at risk of severe hyperbilirubinemia and bilirubin-induced neurologic dysfunction is a major priority. Moreover, detection of low-risk newborns for jaundice and avoiding unnecessary blood sampling are of great significance.

Several studies have been conducted to introduce an early marker to predict postnatal hyperbilirubinemia. The introduced markers include end-tidal carbon monoxide measurement (ETCOc) (3), predischarge serum bilirubin level (4), predischarge transcutaneous bilirubin level (5, 6), predischarge risk assessment (7, 8), and umbilical cord blood bilirubin level (9-16).

According to the literature, ETCOc measurement can predict hemolysis but not hyperbilirubinemia (3). Evaluation of predischarge serum bilirubin level is helpful for the detection of high-risk newborns (4), while blood sampling is a painful procedure for the neonates and requires educated staff. On the other hand, measurement of umbilical cord serum (UCS) bilirubin is a pain-free procedure for the newborns, and most importantly, the results are available immediately after birth.

According to a study by Jacobson et al. (9), the diagnostic value of routine UCS bilirubin

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measurement is limited. On the other hand, based on studies by Knudsen A (10), Satrya R (11), Kanchanabat S (12), Bernaldo AJ (13), Knupfer M (14), Sun G (15), and Nahar Z et al. (16), UCS bilirubin level is useful for the prediction of postnatal hyperbilirubinemia; however, these studies have not taken predischarge bilirubin level or clinical risk factors into account.

Considering the increasing prevalence of breastfeeding and early hospital discharge, hyperbilirubinemia is a common complication in south of Iran. Therefore, due to inadequate follow-up after discharge, early markers to detect subsequent hyperbilirubinemia are highly required. The aim of this study was to investigate the predictive value of UCS bilirubin level for subsequent hyperbilirubinemia. Moreover, we compared the predictive value of UCS bilirubin level with risk factor assessment and predischarge bilirubin level.

Methods

In this prospective, cohort study, all healthy neonates with a birth weight (BW) of ≥ 2 kg and gestational age (GA) of ≥ 35 weeks, delivered at the Department of Obstetrics of Hafez Hospital, affiliated to Shiraz University of Medical Sciences, were recruited during September 2006 and March 2007. Written informed consents were obtained from the parents before including the neonates. In total, 450 parents were willing to cooperate with the study.

The exclusion criteria were as follows: 1) GA < 35 weeks, 2) BW < 2 kg, 3) major illness followed by NICU or hospital admission, and 4) discharge before 18 h after birth. GA was extracted from the medical records of mothers and the first-trimester ultrasound examinations. If the recorded data in the medical records were unreliable, GA was estimated by the Ballard Scale.

Immediately after delivery, about 5 cc blood samples were obtained from the maternal side of the umbilical cord and transferred to the laboratory. The serum was separated within two hours of sample collection and refrigerated at 2-8°C until the serum bilirubin measurement was completed. Total serum bilirubin (TSB) level was determined using Diazo method with dichloroaniline (DCA).

Blood group, Rh blood group, and direct Coombs test results were determined in the newborns. Rooming–in care was applied for all the neonates. The newborns were followed-up according to the routine protocol for healthy neonates. All the subjects were examined on a daily basis and evidence of jaundice and clinical risk factors was assessed until discharge.

Universal predischarge screening for TSB was performed on capillary blood samples; these samples were obtained by puncturing the newborn's heel. TSB measurements were performed, using UNISTAT Bilirubinometer (USA) and direct spectrophotometric assay with an accuracy (bias) of ±5%. All measurements were performed by the skilled personnel of the clinical chemistry laboratory of the hospital.

The neonates were categorized into four groups as follows: low-risk zone (A≤ 40^{th} percentile), low-intermediate-risk zone (B= 40^{th}-75^{th} percentile), high-intermediate-risk zone (C= 75^{th}-95^{th} percentile), and high-risk zone (D≥ 95^{th} percentile). This classification was performed according to predischarge hour-specific bilirubin level with respect to the neonate's age by the use of Bhutani Nomogram (Figure 1) (4).

Before discharge from the hospital, data were obtained from the parents, nurses, and physicians at the obstetric unit. Information on the risk factors for hyperbilirubinemia, such as sex, GA, BW, history of jaundice, glucose-6-phosphate dehydrogenase (G6PD) deficiency in siblings, mode of delivery, maternal age, and maternal diseases was gathered. The subjects were encouraged to attend the follow-up sessions 1-4 days after discharge.

The time and frequency of follow-ups were determined based on the neonate's age at the time of discharge and presence or absence of risk factors for hyperbilirubinemia, according to the American Academy of Pediatrics (AAP) guidelines (8). In the post-discharge follow-up, the neonates' weight and percentage of change in BW were determined. Moreover, data on the frequency of feeding, voiding, and stooling in 24 hours were recorded.

The subjects were evaluated in terms of the presence or absence of jaundice, and TSB was measured in all neonates with clinical or possible jaundice. TSB measurement was performed by a spectrophotometer on capillary blood samples. If TSB level was > 17 mg/dl, re-assessment was carried out on 2 ml venous blood samples, using the DCA method.

The neonates were categorized in terms of jaundice, post-discharge bilirubin level, and guidelines for phototherapy (17): no jaundice (< 5

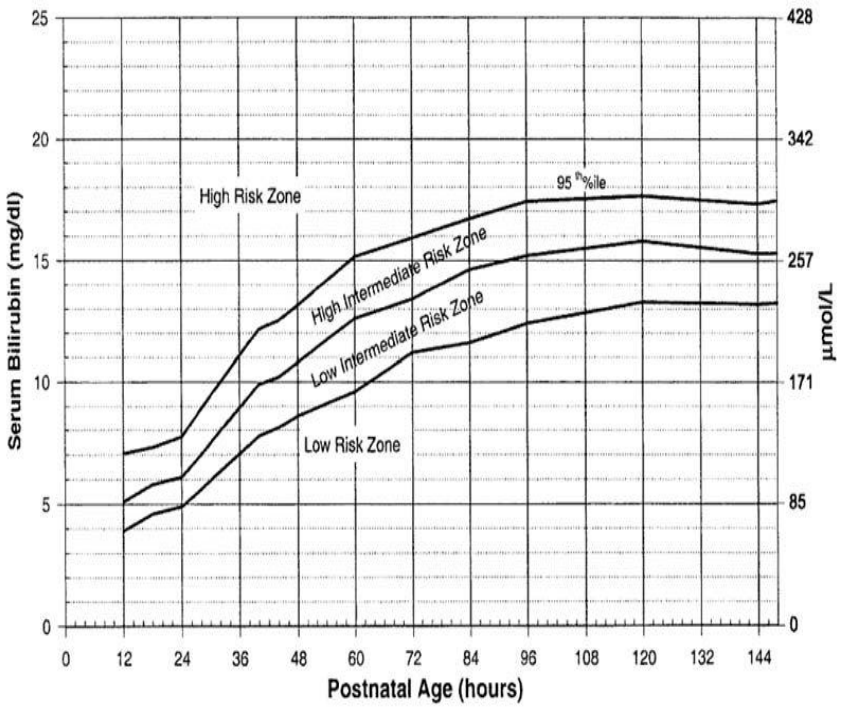

Figure 1. Nomogram for risk designation in term and near-term newborns based on the hour-specific serum bilirubin level (4)

mg/dl), mild hyperbilirubinemia (≥ 5 mg/dl, ≤ 95th percentile), and significant hyperbilirubinemia (≥ 95th percentile). The information obtained from the subjects' medical records, physical examinations, and laboratory assessments was recorded on a predesigned questionnaire.

Statistical analysis

Data analysis was performed, using descriptive statistics, independent sample t-test, Chi-square test, and logistic regression analysis. To compare the mean values of quantitative variables (e.g., cord blood bilirubin level) between the groups, t-test was used. Also, Chi-square test was applied to determine the association between qualitative variables (e.g., risk factors). All risk factors were assessed, using logistic regression analysis at the significance level of P<0.10.

The critical UCS bilirubin level with the highest sensitivity and specificity for predicting subsequent hyperbilirubinemia was determined, using the Receiver Operative Characteristic (ROC) curve. The analysis was carried out, using SPSS version 13.5 and a medical calculator. P-value less than 0.05 was considered statistically significant.

The study protocol was approved by the Neonatal Research Center and the University Ethics Committee. Written informed consents were obtained from the parents.

Results

In total, 450 healthy newborns were recruited in this study. However, 31 neonates were excluded due to hospital discharge before 18 hours after birth and NICU admission. Finally, 419 newborns were enrolled in the study, among whom 203 (48.4%) cases were male and 216 (51.6%) cases were female.

Overall, 100 neonates missed the follow-up sessions and only UCS bilirubin and predischarge bilirubin levels were determined and evaluated. In total, 319 neonates were followed-up and assessed in terms of post-discharge bilirubin level. According to the clinical evaluation in post-discharge follow-ups, jaundice was reported in the majority of neonates (n=213, 66.8%), while bilirubin level suggesting the need for intensive phototherapy was reported in seven (2.2%) newborns; none of the subjects required exchange transfusion. No case of Rh incompatibility was reported in the newborns, whereas 2.1% of neonates had ABO incompatibility (between the mother and neonate).

All newborns had negative Coombs test results. In total, the mean UCS bilirubin level was 2.44±1.15 mg/dl among neonates. The UCS

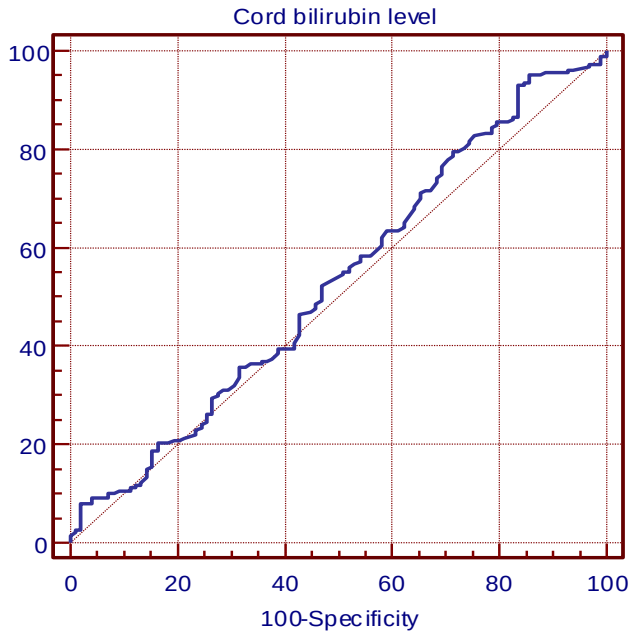

Figure 2. Receiver operating characteristic (ROC) curve of umbilical cord blood bilirubin level for predicting the development of subsequent hyperbilirubinemia (area under ROC curve=0.530, 95% CI=0.471-0.590)

bilirubin level was not significantly associated with jaundice. According to t-test results, the mean UCS bilirubin level was 2.49±1.08 mg/dl among icteric newborns and 2.35±0.97 mg/dl in non-icteric cases (P=0.30).

The mean UCS bilirubin level was 1.96±1.44 mg/dl in neonates who received intensive phototherapy and 2.49±1.07 mg/dl among those who did not (P=0.33). As shown in ROC curve (Figure 2), the area under the curve was 0.530 (95% CI: 0.471-0.590); therefore, UCS bilirubin level was not an appropriate index for identifying icteric neonates. The sensitivity, specificity, and positive predictive value of UCS bilirubin level for the prediction of subsequent jaundice are presented in Table 1.

There was a significant correlation between predischarge bilirubin level and development of jaundice (P=0.009). Moreover, GA, BW, history of jaundice in siblings, and mode of delivery were the clinical risk factors which had a significant correlation with postnatal hyperbilirubinemia (P=.012, P=.006, P=.023, and P=.004, respectively).

On the other hand, post-discharge hyperbilirubinemia was not significantly correlated with risk factors such as maternal age ≥ 25 years (P=0.65), maternal diabetes (P=0.92), sex (P=0.66), method of feeding (P=0.98), early discharge (P=0.06), weight loss ≥ 10% (P=0.57), or family history of G6PD deficiency (P=0.90). All risk factors were assessed, using logistic regression analysis at P=0.10. The results are presented in Table 2.

Table 1. Sensitivity, specificity, and positive predictive values of umbilical cord blood bilirubin level for the prediction of subsequent hyperbilirubinemia

Cut-off points for umbilical cord blood bilirubin level	Sensitivity	Specificity	Positive predictive value
1	95	6.1	76.8
1.5	84.7	18.4	77.3
2	63.9	37.8	77.1
2.5	36.1	63.3	76.3
3	20.6	81.6	78.6
3.5	13.1	85.7	75.0
4	8.4	92.9	80.0
4.5	5.6	98.0	90.0

Table 2. Results of logistic regression analysis

Variables	B coefficient	P-value	Odds ratio	95% CI for odds ratio
Birth weight	0.736	0.046	2.087	1.015-4.295
Mode of delivery	0.619	0.028	1.857	1.071-3.221
Family history	0.282	0.670	0.326	0.362-4.852
History of jaundice				
Age at hospital discharge	0.410	0.331	0.664	0.291-1.516
Gestational age	0.579	0.018	1.785	1.104-2.886
Constant value	0.450	0.397	1.569	

Discussion

The recently increased rate of early hospital discharge of newborns and breastfeeding has resulted in a higher incidence of bilirubin encephalopathy (1). Moreover, hyperbilirubinemia is one of the most common causes of readmission in newborns. Early hospital discharge of newborns in developing countries such as Iran, the limited follow-up facilities, and inadequate awareness of parents and some healthcare providers about the complications of severe hyperbilirubinemia highlight the necessity of a safe marker for early prediction of severe hyperbilirubinemia.

Detection of high-risk neonates allows early phototherapy before bilirubin reaches critical levels. In this study, we assessed the efficacy of UCS and predischarge bilirubin levels in screening subsequent neonatal jaundice. In general, a screening tool should have high sensitivity and acceptable specificity. The present study demonstrated that UCS bilirubin level cannot predict the development of hyperbilirubinemia or its severity.

Conflicting results have been reported on the predictive value of UCS bilirubin level for subsequent hyperbilirubinemia. In a previous study, Bernaldo and Segre (13) showed that phototherapy is significantly associated with blood group incompatibility between the mother and newborn and unconjugated bilirubin level in the cord blood. In the mentioned study, 10% of neonates had ABO incompatibility, and 53% of the newborns with UCS bilirubin level > 2 mg/dl required phototherapy by the third day of life.

According to a study by Knupfer et al. (14), UCS bilirubin level can be a helpful marker for predicting postnatal bilirubin level. In their study, blood group, Rh blood group, and Coombs test results in the umbilical cord blood were not determined; therefore, the cause of hyperbilirubinemia remained unknown in the mentioned study.

In addition, Jacobson and Bernstein (9) compared UCS bilirubin levels among 87 neonates who received standard phototherapy for neonatal jaundice and 95 non-icteric neonates. There was no significant difference in UCS bilirubin level between the two groups; therefore, this index could not predict significant hyperbilirubinemia.

Based on a study by Knudsen (10), 2.9% of infants with UCS bilirubin level < 20 μmol/L developed jaundice, unlike 85% of newborns with UCS level > 40 μmol/L. Also, 57% of icteric neonates with UCS bilirubin level > 40 μmol/l required phototherapy. According to a study by Satrya et al. (11), UCS bilirubin level ≥ 2.54 mg/dl could predict the development of hyperbilirubinemia with sensitivity and specificity of 90.5% and 85%, respectively. On the other hand, Carbonell et al. (18) showed that umbilical cord bilirubin with a cut-off point of 38 μmol/L was not a useful predictor of neonatal jaundice.

According to a study in Tehran, Iran on 643 healthy term neonates, UCS bilirubin level could not identify newborns with significant hyperbilirubinemia (19). Based on the findings, 11.8% of newborns developed significant hyperbilirubinemia (TSB ≥ 14 mg/dl) on the third day; the incidence of Rh and ABO incompatibility was 6.2% and 12%, respectively. In the mentioned study, the mean UCS bilirubin level in neonates with and without significant hyperbilirubinemia was 37.4 μmol/L and 34 μmol/L, respectively.

A discrepancy was found between the results of conducted studies. Two simple explanations can justify these differences. First, the cause of hyperbilirubinemia varies in different study populations. Elevated UCS bilirubin level may be identified in infants with increased bilirubin production (e.g., hemolysis), while it may not be identified in neonates with delayed or impaired bilirubin conjugation. In this study, we assessed the blood group, Rh blood group, and Coombs test results in the umbilical cord blood as contributing factors for hemolysis. However, the percentage of

ABO incompatibility was low (2.1%) and Coombs test results were negative in all cases; therefore, statistical analysis was implausible.

Knudsen A (10) assessed hemoglobin level in the cord blood and indicated no significant difference between icteric and non-icteric neonates, while a significant difference was detected between the groups in terms of UCS bilirubin level. However, the sample size in Knudsen's study was limited; therefore, further research is required to address this subject by assessing hemoglobin level, reticulocyte count, or ETCOc as predictors of hemolysis.

The second cause of discrepancy between the reported findings is the difference in the method and time of follow-up between the studies. We followed-up the neonates according to the AAP guidelines and assessed predischarge bilirubin level. In our study, there was a significant correlation between predischarge bilirubin level and development of jaundice (P=0.009); this finding was similar to a study by Bhutani et al. (4) and AAP guidelines (6). GA, BW, history of jaundice in neonate's siblings, and mode of delivery were clinical risk factors, which had a significant correlation with postnatal hyperbilirubinemia, as reported in a study by Maisels and colleagues (6).

The present study was not in line with previous research, since we checked the predischarge bilirubin level and clinical risk factors and compared UCS bilirubin and predischarge bilirubin levels. Today, according to the most recent protocol for the management and follow-up of neonatal hyperbilirubinemia (20), a combination of predischarge bilirubin, GA, and risk factors is used for the prediction of subsequent hyperbilirubinemia.

The present study had several limitations. First, the mechanism and etiology of hyperbilirubinemia were not determined. Second, the number and percentage of neonates who developed significant hyperbilirubinemia and required hospital admission was low (n=7, 2.2%). In fact, risk factor assessment, systematic follow-up, and promotion of frequent breastfeeding in our study might have decreased the incidence of significant hyperbilirubinemia.

Kaplan M et al. (21) screened 18,079 term and near-term neonates before discharge with regard to risk factors for hyperbilirubinemia. Predischarge serum bilirubin level was measured when visible jaundice was apparent and formal post-discharge follow-up was integrated. In total, 342 (1.9%) newborns were treated with phototherapy, while four cases required exchange transfusion; also, 74 (0.41%) infants were readmitted for hyperbilirubinemia. Maisels (22) and Punaro (23) also showed that risk assessment, predischarge bilirubin level, and systematic follow-up are the key factors for the prevention of severe hyperbilirubinemia.

Conclusion

UCS bilirubin level had a limited diagnostic value for subsequent neonatal hyperbilirubinemia. The best marker for the prevention of neonatal jaundice is the evaluation of clinical risk factors, determination of predischarge bilirubin level, and identification of high-risk newborns for severe hyperbilirubinemia; early management and treatment should be applied if required.

Conflicts of interest

No conflicts of interest were declared by the authors.

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