Cord Blood Bilirubin as a Predictor of Neonatal Hyperbilirubinemia

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Abstract

Hospital readmission for neonatal hyperbilirubinemia is a cause of concern among clinicians in neonatal departments. While early Hospital discharge of neonates is currently recommended by the neonatologists, it carries the risk of delayed recognition of hyperbilirubinemia and the possibility of brain damage due to kernicterus. In our study we aimed to study whether umbilical cord serum (UCS) bilirubin values could predict the risk of significant hyperbilirubinemia requiring treatment in newborns.

Patients and Methods: In a prospective study carried out at the Neonatal Department of Al-Galaa Teaching Hospital, umbilical cord serum (UCS) bilirubin was collected from 234 newborns who were categorized into three groups according to UCS bilirubin levels, <2mg/dl, 2-4mg/dl & >4mg/dl respectively. All demographic data was collected from all included newborns and compared among the three groups. Maternal and neonatal blood groups were checked as well cord hemoglobin and hematocrit concentration. The neonates were then followed by TcB at 24hrs, 48hrs & 72hrs of postnatal age and those who showed significant high TcB values according to the hour-specific nomogram, were then sampled by venous blood for total & indirect bilirubin levels. Significant hyperbilirubinemia was interpreted as the need for medical intervention in the form of phototherapy and/or exchange transfusion.

Results: A cut-off value of neonatal hyperbilirubinemia in cord blood was 2mg/dl and the end point of the study was the need for treatment. The mean value for total bilirubin in cord blood was significantly higher among newborns whose bilirubin values required phototherapy. The specificity reached 94.2% with a negative predictive value (NPV) of 96.32%. At cut-off cord serum bilirubin level >4mg/dl, the specificity was 98.92% and the NPV was 99.1%.

Conclusion: Cord blood serum bilirubin can be used as a useful screening test for predicting neonatal hyperbilirubinemia and allowing safe postnatal Hospital discharge.

Key Words: Newborn – Cord blood bilirubin – Hyperbilirubinemia.

Introduction

JAUNDICE in newborn is quite common, affecting nearly 60% of term and 80% of preterm neonates during the first week of life [1]. It is the most common cause for Hospital readmission during the early neonatal period [2]. It is a cause of concern for the parents and the neonatologists. Despite improved understanding of the physiologic features of bilirubin and the mechanisms of bilirubin neurotoxicity, our ability to predict which infants are at greatest risk remains imprecise [3]. Early postnatal discharge of healthy term newborns after delivery has become a common practice mostly for medical and social reasons as well as economic constraints. However, this leads to the risk of readmission to the hospital, mostly for neonatal hyperbilirubinemia [2]. Such readmission, besides involving extra expenses for both the family and the institution and also exposing a probably healthy newborn to the Hospital environment, brings emotional problems and risks of interruption of breastfeeding, and is one of the causes of early weaning [4,5]. Although 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 together with other problems [6], there are difficulties in complying with these recommendations in our community due to limited facilities for follow-up and parental noncompliance. Knowledge of infants at risk of developing jaundice allows simple bilirubin reducing methods to be implemented before jaundice becomes significant and could influence a decision regarding early discharge from Hospital [7]. Hence, predicting the high risk neonates for subsequent hyperbilirubinemia is required to detect infants at low risk for postnatal hyperbilirubinemia and minimize an unnecessary prolongation of Hospitalization or Hospital re-admission for hyperbilirubinemia.

Aim of the study:

The present study was conducted to evaluate the predictive value of umbilical cord serum (UCS) bilirubin level for identifying term and near term
newborns with subsequent hyperbilirubinemia. We presume that the use of UCS bilirubin values as a screening tool may help recognizing neonates at risk of developing hyperbilirubinemia requiring treatment.

**Patients and Methods**

This study was conducted at the Neonatal Department of Al-Galaa Teaching Maternity Hospital. A total of 234 healthy full-term (≥37 weeks) and near term (35<37 weeks) newborns born consecutively at the hospital during a six months period - June to December 2011 - were eligible for enrollment in the study. Clinical data of all studied neonates was collected including: Birth-weight, gestational age, mode of delivery, sex, Apgar score at 1 & 5 minutes, birth trauma, history of Rh isoimmunization, history of previous sib with neonatal hyperbilirubinemia requiring phototherapy (PT) or exchange transfusion (ET). Cord blood serum (UCS) bilirubin, and newborn’s blood group were obtained from all neonates at birth. The cord blood sample was collected by clamping the umbilical cord after delivery of the newborn between two cord clamps, 8-10cm apart, then the isolated section is cut and a blood sample is collected into a specimen tube. The blood sample was centrifuged and serum was used for estimation of conjugated, unconjugated and total serum bilirubin levels using Colorimetric method. The maternal blood group was obtained from the maternal medical record or if the data is unavailable, a venous sample was collected from the mother after birth. All neonates in the studied groups were assessed following birth, the neonates who were transferred with their mothers to the maternal ward, were carefully observed by pediatric resident for 48 hours at least, for the development of hyperbilirubinemia. After their discharge, the parents were asked to bring their baby for follow-up 24 hours later for confirmation of serum bilirubin values. Neonates who failed to come for follow-up and the third result of transcutaneous bilirubin (TcB) was not collected were excluded from the study. Neonates who needed admission to the neonatal intensive care unit (NICU) for different medical reasons were assessed regularly by the residents in charge. All neonates were monitored for developing hyperbilirubinemia by measurement of (TcB) using a non-invasive bilichek, at 24, 48 & 72 hours of age or daily till discharge. The neonates were categorized into three groups according to the umbilical cord serum (UCS) bilirubin level. Group (A) UCS bilirubin <2mg/ml, group (B) UCS bilirubin ≥2-4mg/ml, and group (C) UCS bilirubin >4mg/ml. Group (A) will act as the control group. If Tc bilirubin exceeds the appropriate values for gestational age, as matched to values on the percentile-based hour-specific transcutaneous nomogram and risk zones [8], were subjected to a serum venous bilirubin sample collection according to the clinical guidelines of our department for managing hyperbilirubinemia and the appropriate treatment was then applied accordingly. The need for phototherapy was determined according to AAP 2004 guidelines, [6] on the basis of gestational age, postnatal age, and the presence or absence of risk factors. All neonates who developed significant hyperbilirubinemia were evaluated with hematocrit measurement, peripheral blood smear, reticulocyte count, blood group analysis and direct Coombs test. Neonates with exaggerated hyperbilirubinemia who required phototherapy treatment were subjected to Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency testing. Gestational age was determined on the basis of first-trimester ultrasound findings (when available) or the date of the last menstrual period and was confirmed with the expanded New Ballard Score [9] within 24 hours after birth. Enrolled neonates were discharged from the Hospital according to department policy if Tc bilirubin did not cross the lower intermediate or low risk zone for gestational age on the bilirubin hour-specific nomogram. Venous serum bilirubin samples were analyzed using the colorimetric method. The frequency of hyperbilirubinemia at different postnatal ages and the need for phototherapy (PT) were compared among the three groups. An analysis of umbilical cord serum bilirubin (UCS bilirubin) as a predictor of later development of jaundice was performed.

**Inclusion criteria:**
- Gestation >35 weeks.
- Absence of major congenital malformations.

**Exclusion criteria:**
- Any complication arising during the Hospital stay that could aggravate the hyperbilirubinemia in these newborns.
- Neonates with direct hyperbilirubinemia (direct serum bilirubin 15% of total serum bilirubin levels).

**Ethical aspects:**

Parental counseling was done and an informed consent was obtained from all parents or guardians of the newborns enrolled in the study.

**Analysis of results:**

Maternal and neonatal clinical data was collected. Data was analyzed using descriptive analysis,
Neonatal jaundice in a previous sib was reported in Group (C) with CSB levels >2.0 mg% ([group (B) & group (C)] were compared with the nonjaundiced group (A) with CSB levels <2.0 mg% are listed in Table (1). As shown there is no statistically significant difference among the three groups as regards gestational age, birth weight & gender. The mean gestational ages in the three studied groups were 38.7±2.95 in group (A), 38.4±2.45 in group (B) & 37.9±2.83 in group (C). The mean birth-weight, in grams, in groups (A), (B) & (C) was 2783±392, 2722±485 & 2695±430 respectively. A history of neonatal jaundice in a previous sib was reported in 52 cases (37.7%) in group A; 16 (21%) in group B and 11 (55%) in group C. Group (B) showed a lower statistically significant value than groups (A) & (C) (p<0.05).

There was no significant difference among the three groups regarding the mode of delivery, whether vaginal delivery or cesarean section, as shown in Table (1).

There was no statistically significant difference among the three groups regarding the occurrence of birth trauma and the presence of gestational diabetes. Group (A) had 4 cases (2.2%) of birth trauma: 2 cases of cephalohematoma due to ventous extraction, 1 case of assisted breech delivery with superficial bruises on the chest wall and upper anterior abdominal wall, and 1 case of subcapsular hematoma of the liver diagnosed accidentally on performing abdominal ultrasound for this neonate for unexplained low hemoglobin level and abdominal guarding. Two cases (2.6%) of birth trauma were reported in Group (B) neonates: both were cases of cephalohematoma despite spontaneous vaginal delivery. One case (5%) of birth trauma reported in Group (C) was due to Erb’s palsy with a subapaneurotic bleed. The presence of Rh & ABO incompatibility was statistically significantly higher in Group (C) compared to Groups (A) & (B) (65% versus 2.9% & 10.5% respectively). Glucose-6-phosphate dehydrogenase deficiency was detected in 2 cases (2.6%) in Group (2) & 1 case (5%) in Group (C) but none in Group (A) neonates. Again cord blood hemoglobin was lower in Group (C) compared to Groups (A) & (B) but the difference did not reach statistical significance. (14.7±2.43 gm/dl versus 16.7±3.96 gm/dl & 16.3±3.25 gm/dl respectively). Table (2) shows that the mean (±SD) TcBilirubin level among the three groups, showed statistically significant increase in Group (C) compared to Groups (A) & group (B) at 24 hours of age, 3.3±0.75 & 5.5±2.2 in Groups (A) & (B) respectively against 10±3.1 in Group (C) (p<0.01). The same pattern was shown also at 48 & 72 hours of age; 4.9±1.44 & 8.1±2.8 versus 14±3.6 in Groups (A), (B) & (C) respectively at 48 hours of age (p<0.01 & p<0.05). At 72 hours of postnatal age, there was statistically increased level in Tc bilirubin in Group (C) versus Group (A) (7.2±2.79 versus 16±3.6 respectively; p<0.01). Fig. (1).

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<th>Table (1): Clinical characteristics of the study population.</th>
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<td>N (%)</td>
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<td>Male: female ratio</td>
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<td>Mode of delivery (VD/CS) N %</td>
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<td>Gestational Diabetes N %</td>
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<td>Neonatal jaundice in previous sibs N % (37.7%)</td>
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<td>Birth trauma N (%)</td>
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<td>Rh &amp; ABO incompatibility N (%)</td>
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<td>G-6-PD deficiency N (%)</td>
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<td>Cord blood hemoglobin (gm/dl) mean ± SD</td>
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There was progressive rise in mean total serum bilirubin (TSB) level as measured in the three groups to reach a peak of 10 ± 4.7 mg/dl at a mean postnatal age of 93 ± 19.8 hours in group (A) neonates & 14 ± 4.6 at a mean peak age of 88 ± 16.7 in group (B) compared to a more significant & rapid rise in group (C) (17 ± 4.3 mg/dl, p < 0.05) at an earlier postnatal age (68 ± 17.5 hour of age). Neonates in Group (C) had a statistically significant higher peak of serum bilirubin level (p < 0.01). Differences in cord blood bilirubin levels between the three groups were statistically significant (p < 0.001). Neonates with UCS bilirubin level < 2.0 mg/dl accounted for 58.97% of the study population. Only 5.8% of these neonates developed significant hyperbilirubinemia requiring phototherapy treatment.

The frequency of patients with hyperbilirubinemia or phototherapy increased with increasing UCS bilirubin levels. While patients with UCS bilirubin levels between 2-4 mg/dl had a 44.7% chance of developing significant hyperbilirubinemia requiring phototherapy and of these, 1.3% needed further treatment with exchange transfusion. The group of neonates with UCS bilirubin > 4 mg/dl, all had progressive increase in mean serum bilirubin levels at subsequent postnatal age, reaching a level requiring phototherapy treatment in all (100%) of cases in group (C). Three neonates (15%) in group (C) still needed exchange transfusion despite earlier phototherapy as total serum bilirubin levels crossed the accepted values for postnatal age.

The optimal cut-off level for prediction of neonatal jaundice using umbilical cord blood bilirubin was 2.0 mg/dl; hyperbilirubinemia requiring intervention can be predicted by 96.25% clinical sensitivity. The probability of neonates with a CSB value < 2.0 mg/dl developed hyperbilirubinemia was 34.94% (positive predictive value, PPV). Likewise, the probability that neonates who did not develop significant hyperbilirubinemia (not requiring medical intervention) had CSB values < 2.0 mg/dl was 94.2% (specificity), while the probability of neonates without significant hyperbilirubinemia had CSB values < 2.0 mg/dl was 97.32% (negative predictive value, NPV). At UCS bilirubin cut-off levels of > 4 mg/dl, the specificity approached 98.92% & the NPV was 99.1%. The probability of newborns having UCS bilirubin levels < 2 mg/dl developing hyperbilirubinemia requiring clinical intervention by phototherapy was 6.5%, while the probability of newborns with UCS bilirubin levels > 2 mg/dl requiring phototherapy was 91%. The probability of newborns in Group (B) requiring phototherapy treatment was 55.3%, while those in Group (C) was 100%.

The receiver operating characteristic (ROC) curve demonstrates that UCS bilirubin > 4 mg/dl had a high sensitivity approaching 97% and specificity 98.92% that predict the newborn that would develop significant hyperbilirubinemia requiring medical intervention and a NPV of 99.1%. The area under curve = 0.8722 (Fig. 2).
Discussion

Jaundice is a clinical condition that constitutes a major issue in neonatal practice. Higher cord bilirubin levels among neonates who later became jaundiced compared to cord bilirubin levels in non-jaundiced neonates indicate that mechanisms of importance for the subsequent jaundice are already active in late fetal life. Nearly all fetal bilirubin is unconjugated, due to a limited ability of the fetal liver to conjugate bilirubin. In plasma, unconjugated bilirubin is tightly bound to albumin, which is the dominant bilirubin binding protein in plasma. Under normal circumstances no bilirubin deposition in fetal tissue takes place. Unconjugated bilirubin is rapidly transferred to the maternal circulation by the placenta, whereas only small quantities of conjugated bilirubin cross the placenta. Thus bilirubin produced by the fetus is excreted by the mother, who presumably has a large reserve capacity for bilirubin excretion, and only minor differences in maternal bilirubin concentrations can be expected [10]. A clear correlation between umbilical cord serum bilirubin (UCB) & subsequent development of hyperbilirubinemia was shown among all three studied groups. Newborns presenting levels higher than 4mg/100ml were a group at risk of developing severe hyperbilirubinemia and should be followed up and reassessed, since this group presented mean serum bilirubin levels that were higher than 16mg/dl at 72 hours of postnatal age with a peak level of 17±4.3mg/dl at 68±17.5 hours of postnatal age. There was also a significant association between the serum bilirubin in cord blood and the newborn's bilirubin level at several postnatal ages. In 1986, Rosenfeld [11] analyzed a group of 108 full-term newborns according to their risk of developing severe hyperbilirubinemia and concluded that babies with an umbilical cord blood bilirubin level of lower than 2mg/dl had a 4% chance of developing significant jaundice, in comparison with a 25% chance presented by the ones with levels higher than 2mg/100ml. In addition, the latter group also presented a higher chance of needing to undergo phototherapy. Knudsen, [12] in 1989, carried out a study to demonstrate that jaundiced newborns presented higher umbilical cord blood bilirubin levels than newborns without clinical jaundice. In addition, the number of jaundiced newborns undergoing phototherapy was significantly higher when these levels were higher than 2.0mg/dl, in comparison with the number of jaundiced newborns with no need for treatment and whose bilirubin levels were lower than or equal to 2.0mg/dl. This proved the possibility of defining a newborn risk group for developing neonatal hyperbilirubinemia at birth. In the present study, the most useful cutoff point for the serum bilirubin levels in cord blood was 2.0mg/dl. With this cutoff point, whenever values that were equal to or greater than this were found, the newborn had a probability of more than 50% that phototherapy would be needed. Adélia & Conceição in 2004, [13] speculated that it may be considered that the umbilical cord blood to be a kind of “file” for the newborn, as it could be collected, stored and used for further analysis of bilirubin levels, should a slightly or moderately jaundiced neonate be considered for early discharge from hospital. Such a proposal may therefore constitute an additional predictive method that is available for evaluating the occurrence of severe hyperbilirubinemia by the third day of life. Accordingly, this proposal may help in assuring safer early discharge for these newborns. Alpay et al., [14] observed that a serum bilirubin >6mg/dl on the first day of life had 90% sensitivity of predicting a subsequent TSB >17mg/dl between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97.9%. No cases with TSB of <6mg/dl in the first 24 hours required phototherapy treatment. The study done by Seidman et al., found that the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5mg/dL at 24 hours of life, whereas that risk was 6.6% in cases whose bilirubin level was 5mg/dL at 24 hours of life [15]. The incidence of significant hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin, and the incidence of breastfeeding. Rataj et al., [16] reported that if cord bilirubin was less than 1mg%, the jaundice occurred in 2.4% newborns, where as 89% of the infants with cord bilirubin above 2.5mg% became jaundiced. Knudsen, [17] found that if cord bilirubin was below 20umol/l, 2.9% became jaundiced as opposed to 85% if cord bilirubin was above 40umol/l. Furthermore, 57% of jaundiced neonates with cord bilirubin above 40umol/l required phototherapy, but only 9% if cord bilirubin was 40umol/l or lower (p<0.003). In our study, the cord bilirubin level of >2mg/dl had the highest sensitivity (89.5%), and this critical bilirubin level had a very high (98.7%) negative predictive value and fairly low (38.6%) positive predictive value. According to our findings, the critical cut-off level of cord bilirubin 2mg/dl, predicted 90% of the newborns who developed jaundice. However, the cord bilirubin level of <2mg/dL did not completely exclude the development of significant hyperbilirubinemia; only 2.05% of the newborns with cord bilirubin levels of <2mg/dL developed jaundice. A 98.7% negative predictive value in the present study suggests that
measurement of cord serum bilirubin can help in identify those newborns that are unlikely to require further evaluation and intervention.

**Conclusion:**

The results of our study confirm that measurement of umbilical cord serum bilirubin (UCS) level can be used as a screening tool for predicting the development of significant hyperbilirubinemia requiring interventional therapy. Levels (UCS) bilirubin equal to or greater than 2mg/dl in term and near term newborns indicated a 91% probability for the need of phototherapy. The use of UCS bilirubin values will help predict neonates at low or high risk for hyperbilirubinemia and minimize an unnecessary prolongation of hospitalization as it will encourage neonatologists in decisions of early postnatal discharge. Newborns with UCS bilirubin values below 2.0mg/dl are at very low risk of developing hyperbilirubinemia and the further need of phototherapy.

**References**


