Can Haptoglobin be an Indicator for the Early Diagnosis of Neonatal Jaundice?

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Neonatal jaundice is the result of an imbalance between bilirubin production and elimination. Bilirubin conjugation in newborns is significantly impaired in the first few days; even a small increase in the rate of production can contribute to the development of hyperbilirubinemia. Hemolysis has a significant role in bilirubin increase in newborns. Intrauterine is tolerated by the maternal metabolism in life. When hemolysis takes place, a decrease is accepted in the haptoglobin and hemoexin blood levels binding hemoglobin in the environment. Therefore, it may be considered that haptoglobin and hemoexin from the early period umbilical cord (UC) blood in newborns may be an indicator in determining jaundice likely to develop in later stages. Babies were called to the control polyclinic in the third and fifth

days. Eighty-four babies with normal term birth were included in the study. Gestational age of the mothers was 39.5 ± 1.5 weeks in average. A significant negative correlation was found between the haptoglobin level from the UC taken during delivery and the bilirubin value in the fifth day ($r = -0.345$; $P = 0.001$). The haptoglobin value from the blood of the UC can be used as a guiding indicator to demonstrate the future occurrence of jaundice in newborns. This way, the babies with high jaundice risk may be detected earlier and closer follow-up of these babies can be obtained. As a result, the haptoglobin level of the blood from the UC during delivery allows us to make an early prediction on whether neonatal jaundice will occur. *J. Clin. Lab. Anal.* 22:409–414, 2008.

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INTRODUCTION

Neonatal jaundice is a common disorder, with more than half of all newborns being affected in the first 3–5 postnatal days. Because of the increasing number of early discharged newborns, there is a corresponding danger of failing to diagnose severe hyperbilirubinemia in time (and start the treatment), as reports about kernicterus in full-term healthy newborns demonstrate (1,2). Therefore, an early identification of newborn infants at risk of developing severe hyperbilirubinemia, along with a possible bilirubin-induced neurological dysfunction, and the prediction of a possible need of phototherapy continue to be a problem in neonatology (3). Although it is of no clinical significance, 6–10% of hyperbilirubinemia levels exceed the values considered to be physiological; 12.9 mg/dL for formula feedings and 15 mg/dL for breast feedings (4). Since 1991, cases of kernicterus or bilirubin encephalopathy have been

described in term newborns discharged early, generally breastfed, and without any other pathology that might justify the symptoms (5). In view of this, in 1995, the American Academy of Paediatrics (6) warned of the need to monitor these infants and considered in term newborns, the value for bilirubin 17 mg/dL after 72 hr of life should be taken as a significant hyperbilirubinemia, potentially dangerous (7) and eventually requiring treatment (8). At present, for essentially economic reasons, maternal discharges have to be scheduled early within 48 hr of childbirth, so most cases of neonatal jaundice cannot be detected (9).

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Discharging healthy term newborns from the hospital after delivery at increasingly earlier postnatal ages has recently become a common practice for medical, social, and economic reasons. However, it has been shown that newborns whose post delivery hospital stay is 72 hr are at a significantly greater risk for re-admission than those whose stay is 72 hr. Hyperbilirubinemia is the most commonly reported cause for re-admission during the early neonatal period, and 0.36% of healthy term newborns discharged after 72 hr of life with no more than mild hyperbilirubinemia may even develop a subsequent moderate to severe hyperbilirubinemia. In the United States, there were 22 reported cases of kernicterus developing after discharge within 48 hr of birth between 1991 and 1995. Furthermore, the safety of relying on follow-up visits after early discharge is questionable because 10% of the population fails to return for a follow-up visit (10). Increased heme catabolism is an important mechanism responsible for hyperbilirubinemia in the first days after birth (11). Hemoglobin released from erythrocytes into the circulation by intravascular hemolysis binds immediately with haptoglobin, a serum glycoprotein, and forms a stable hemoglobin-haptoglobin (Hb-Hp) complex. Hb binding by haptoglobin is thought to be important in the rapid hepatic clearance of hemoglobin from the plasma and in the inhibition of glomerular filtration of hemoglobin. The presence of specific receptors on liver parenchymal cells that recognize and endocytose the Hp-Hb complex has led to a widely held belief that the major function of Hb binding by Hp is to target plasma Hb for rapid clearance and degradation in the liver (12,13). Hemopoexin is a heme-binding plasma glycoprotein which, after haptoglobin, forms the second line of defense against hemoglobin-mediated oxidative damage during intravascular hemolysis. A decrease in plasma hemopoexin concentration reflects a recent release of heme compounds in the extracellular compartment. Heme-hemopoexin complexes are delivered to hepatocytes by receptor-mediated endocytosis after which, hemopoexin is recycled to the circulation. Hemopoexin is a heme-binding protein commonly used to assess the severity of intravascular hemolysis, because its plasma concentration starts to decrease when the hemoglobin-binding capacity of Hp is exceeded. Hemopoexin in combination with Hp has been proposed to be more useful than the other protein markers to assess severity of hemolysis (14). Therefore, it is important to determine which baby will face bilirubin increase for the newborns in early stages, especially before being discharged. In this period, discharge of the babies may be delayed or more frequent or close control may be provided. This, in turn, will allow early intervention to the development of

complications based on high bilirubin levels in newborns.

It is aimed to determine whether haptoglobin and hemopoexin is an early indicator of neonatal jaundice by checking haptoglobin and hemopoexin obtained from the umbilical cord (UC) during delivery.

MATERIALS AND METHODS

A total of 100 newborns were initially enrolled in the study, but 16 of these were excluded during the study because of various diagnoses, such as hypothyroidism, neonatal hepatitis, duodenal atresia, direct hyperbilirubinemia, and infection or sepsis, or because some of the parents did not want to continue participating in the study. Study was continued with the 84 babies with term birth in the delivery clinic.

During the study period, all newborns with a gestational age between 38 and 42 completed weeks were consecutively enrolled in the study. Gestational ages of newborns were determined according to the first day of the mother's last menstrual period (by the mother's statement) and were additionally confirmed by the Ballard scoring system¹⁵ and antenatal ultrasonographic estimation (or obstetric records if present). Infants whose mothers could not recall the exact date (first day) of last menstrual period and/or those who had a critical discrepancy (2 weeks) between two methods on gestational-age determination were not included in the study. Newborns with a gestational age of 37 weeks and 42 weeks were defined as preterm and postterm, respectively, and were not included in the study. Other exclusion criteria were small for gestational age and large for gestational age, any congenital malformation, respiratory distress, glucose-6-phosphate dehydrogenase deficiency, clinical or culture-proven sepsis, and inability to initiate or maintain oral feedings within 3 hr after birth due to various reasons. UC blood was obtained from the placenta immediately after delivery, and samples were stored in amber, not longer than 2 hr. Serum (S) was separated, and UCS bilirubin was determined by applying a standard dichlorophenyldiazonium tetrafluoroborate (DPD) method (Roche Diagnostics, Mannheim, Germany) using an automatic analyzer. Serum, which was separated by centrifuge of UC and fifth day blood to see the haptoglobulin and hemopoexin levels, was stored in -80°C until study was made. Hematocrit count, blood group including Rhesus, a direct antiglobulin (Coombs) test, glucose-6-phosphate dehydrogenase activity, and serum direct and indirect bilirubin levels were performed routinely in all cases at entry into the study. Infants who had any evidence of hemolysis (Rhesus hemolytic disease, anemia, a positive direct antiglobulin test, reticulocytosis, or a peripheral

blood smear compatible with hemolysis). Serum total bilirubin levels were measured with a colorimetric method (diazotized sulfanilic acid reaction, Roche Diagnostics). Photometric study was made with the haptoglobin kit (Roche) in the Haptoglobin Cobas Integra 400 (Roche) device. Nephelometric method was used in the study with the hemopoexin kit (Dade Behring, Marburg, Germany) in the hemopoexin Bn Prospecc (Dade Behring) device.

In all cases, gender, birth weight, gestational age, delivery route, feeding pattern, maternal age, Apgar scores, whether the mother smoked or had any chronic diseases (hypertension, diabetes mellitus, etc.) before or during gestation, and whether there was enclosed hemorrhage, abnormal weight loss, or any siblings with neonatal jaundice were recorded. Those with abnormal parameters were excluded from the study. Babies whose UC blood was not taken, those who did not come to the third and fifth day control, and those with insufficient samples were excluded from the study. The study was approved by the local ethics committee, and informed consent was obtained from all parents of the newborns in the study. Statistical data were analyzed with the descriptive analysis and the frequency and Pearson Correlation test SPSS 11.5 program. Correlation is significant at the 0.05 level (2-tailed).

RESULTS

Mothers aged between 19 and 40 with the average of 26.3 ± 6.3 . Their gestational age was 39.5 ± 1.5 . Number of deliveries was between 1 and 9 with an average of 2.1 ± 1.6 . Sixty mothers having normal delivery (71.4%) and 24 mothers having cesarean section delivery (28.6%).

Birth weight of the babies were measured as $3,311 \pm 463$ g in average. There was no case where vacuum extraction was applied during delivery. All cases were breastfed after delivery. The whole blood and biochemical values of the mothers and babies during control were within normal limits. The thyroid hormone levels of the babies were found normal and TORCH results were found negative. No newborns had a serum total bilirubin level of 17 mg/dL in the first five days of life. UC blood serum haptoglobin value was between 0 and 13.6 mg/dL (average 2.6 ± 3.3). Fifth day serum haptoglobin value was between 0 and 143.6 mg/dL (average 31.1 ± 34.4). UC blood serum hemopoexin value was between 0.13 and 1.05 (average 0.24 ± 0.13). Fifth day serum hemopoexin value was between 0.19 and 1.0 (average 0.32 ± 0.17). UC bilirubin value was between 0.7 and 2.7 mg/dL (average 1.6 ± 0.5), fifth day bilirubin value was between 0.7 and 15.7 mg/dL (average 8.4 ± 4.0). Pearson correlation test between UC blood serum haptoglobin value and fifth day serum bilirubin value demonstrated statistical significance

($r = -0.345$, $P = 0.001$). Pearson correlation test between UC blood serum hemopoexin value and fifth day serum bilirubin value did not demonstrate statistical significance. The definitive properties of the mothers and babies are illustrated in Tables 1 and 2. The correlation between UC haptoglobin values and the first and the fifth day blood bilirubin values are shown in Figs. 1 and 2 graphics.

TABLE 1. Definitive Properties of Mothers

Mothers	Mean	Std. deviation
Age (yr)	26.36	6.14
Number of delivery	2.10	1.62
Hemoglobin (g/dL)	12.20	1.11
Htc	35.63	3.17
MCV	82.69	7.39
Rdw	16.75	2.03
WBC (mm^3)	11.37	3.64
Thrombocyte	210.60	60.76
Reticulocyte (%)	1.38	0.33

TABLE 2. Definitive Properties of Babies

Baby	Mean	Std. deviation
Weight (g)	3,311.90	463.39
Height (cm)	51.08	2.04
Head circumference (cm)	33.38	1.58
APGAR	8.18	0.55
Hemoglobin (g/dL)	16.21	1.86
MCV	96.80	3.45
Rdw	17.14	1.05
Leukocyte (mm^3)	11.69	3.22
Thrombocyte	224.65	80.98
Reticulocyte (%)	2.37	1.43

Fig. 1. Correlation graphic between UC blood haptoglobin values and the fifth day blood bilirubin values.

Fig. 2. Correlation graphic between UC blood haptoglobin values and the first day blood bilirubin values.

DISCUSSION

The growing practice of early hospital discharge of newborns has resulted in a re-emergence of bilirubin-related neurological sequelae. Severe hyperbilirubinemia can occur without apparent reason in healthy infants, and some may develop kernicterus. Therefore, it is important to establish safe markers for the development of excessive jaundice in these infants (16,18). The prevention of fatal outcomes is based on the early detection of children at risk of developing significant hyperbilirubinemia, and especially of detecting those in further need of therapeutic interventions. Our data clearly demonstrate that the quantification of UCS haptoglobin as a noninvasive risk assessment is a useful tool to predict hyperbilirubinemia in healthy term newborns. Therefore, it could help in targeting clinical interventions and may also help to avoid unnecessary blood specimen collections (3). Although there has been a decrease in the length of post delivery hospital stays for newborns and their mothers in recent years, there is still much controversy about when, early (48 hr after delivery) or late (72 hr after delivery), a mother-child dyad should be discharged. Opponents of the early discharge suggest that various risks, such as hyperbilirubinemia; breast-feeding difficulties and feeding problems leading to dehydration and malnutrition; missed identification of congenital anomalies and newborn screening; re-admission, and maternal postpartum cognitive deficits, are all associated with early discharge. In contrast, proponents of the early discharge regard it as safe and advantageous because of various medical, social, and economic reasons. Although an influencing effect of early discharge on morbidity and mortality of the newborns has not been established yet, and first studies have not demonstrated any adverse outcomes or

any increased re-admission risks of early discharge, more recent studies suggest that newborns discharged early are at increased risk for rehospitalization during the neonatal period. The current guidelines of the American Academy of Pediatrics recommend a follow-up for newborns discharge before 48 hr of life at 2–3 days postnatally. However, a complete follow-up is not always possible because of the geography and climate of the area, personal safety, or patient incomppliance and, thus, there is a need to identify newborns who are at risk for developing significant hyperbilirubinemia as early as possible (18).

We aimed, in this study, to prospectively determine the critical UC blood haptoglobin level to predict significant hyperbilirubinemia in healthy term newborns based on serum bilirubin measurements made within 5 days of life. The incidence of significant hyperbilirubinemia depends on regional variations, ethnic make up of the population, laboratory variability in the measurement of bilirubin, and the incidence of breastfeeding (17,18). In our study group, there were no significant differences between the cases. The prevention of fatal outcomes is based on the early detection of children at risk of developing significant hyperbilirubinemia, and especially of detecting those in further need of therapeutic interventions (3). After publishing practical guidelines for the management of hyperbilirubinemia in healthy term newborns (15), a decrease in PT use has been observed. Some authors have discussed this development. They were aware of the re-appearance of kernicterus in the 1990s as a result of a reduced concern for hyperbilirubinemia, a decreased awareness of signs of bilirubin toxicity, medical care cost constraints, and the problem of early discharge without adequate follow-up (3). It is difficult to obtain laboratory documentation of mild degrees of hemolysis among newborns. Such infants are unlikely to have decreasing hemoglobin concentrations, elevated reticulocyte counts, or abnormalities on peripheral smears. In any case, these laboratory tests are generally nonspecific and insensitive for newborns (11). Test results of our cases did not show any significant property. Because the ability of newborns to conjugate and to clear bilirubin is significantly impaired in the first few days, even a small increase in the rate of bilirubin production can contribute to the development of significant hyperbilirubinemia (11). Several studies have tried to identify these newborns by measuring carbon monoxide in end-tidal breath corrected for ambient carbon monoxide, but this method did not really improve the predictive ability of serum bilirubin values (18). Others have investigated the predictive value of serum bilirubin concentrations during the first postnatal days. In a very complex manner, Bhutani (18,21) defined hour specific serum

bilirubin values for newborns and characterized percentile curves that are very useful for detecting babies at risk (3).

We used UC blood, which is free for use in nearly all cases, and the logistic system for the bilirubin determination is easy to organize. Furthermore, it keeps the baby free from pain and, most importantly, the data are available immediately after birth. So, high-risk children might be detected with high certainty, even if parents would like to leave the hospital within the first postnatal hours (3). In the USA, Bhutani found 4.6% of term newborns equaling or exceeding bilirubin values of 17 mg/dL (20,22) and 1.2% exceeding 20 mg/dL (23). In Argentina, Martóñez reported 12% (22) and in Israel Sheidman reported 1.7% (25) with the proportion of breast milk feeding being 63, 100, and 93%, respectively. In our study, bilirubin value did not exceed 17 mg/dL in any of the term newborns and breast-feeding nutrition was 100%. The fact that the bilirubin values of all babies in the study group did not exceed 17 mg/dL may be linked to that the study covered a group without term risk factor (9). The practice of early discharge seems to generate a higher number of re-admissions specifically for hyperbilirubinemia and suspected infection. In a study of more than 30,000 newborn infants, 391 (1.26%) were readmitted, 65.1% for hyperbilirubinemia, in the first week (26). The increase in the number of re-admissions is evident if comparison is made with discharges before 72 hr as compared with discharges after the third day (27,28). Six cases in our study group (7.14%) were accepted to the hospital after discharge to receive phototherapy treatment. None of the cases reported to the hospital for a reason other than phototherapy and no case needed blood exchange. This may be because of the fact that the study group consisted of mothers and babies who did not carry any risk factors. It would appear that identification of newborn infants at risk for hyperbilirubinemia before discharge would reduce the re-admission rate (26). Though jaundice is not the only problem associated with early discharge (29), the increase in hyperbilirubinemia, and probably in bilirubin encephalopathy, points toward a need to assess bilirubin values after 24–48 hr (28). Ideally, devising a method for detecting infants at risk with the least possible number of blood sampling. Early maternal discharge “within 72 hr” is acceptable for term newborns who are normal, but these infants must be visited by a healthcare professional within the 2–3 days after discharge (28). All newborns were controlled in the pediatric polyclinic 2–3 days after discharge and in the fifth day. Haptoglobin level measured in the serum obtained from the UC provides information on turnover (30). The major problem in clinics today is the fact that the mothers are discharged early after the delivery

because of economic problems and insufficient number of beds, and thereby because of insufficient monitoring of the babies under risk. Therefore, it is essential to have an early determination of the increase in the bilirubin values through the indicators to be controlled from the blood of the UCs of the newborns. A significant correlation was found between the haptoglobin in the UC blood and fifth day bilirubin values of the newborns ($P = 0.001$). No statistical correlation was found between the haptoglobin in the UC blood and the bilirubin values in the same serum. The haptoglobin level decreases in the UC blood without any increase in the bilirubin level in the same serum. Similarly, no meaningful relation was found between the fifth day bilirubin level and the hemopoexin UC blood, which is an indicator of hemolysis. It was believed that the reason of the fact there was no relation between the hemopoexin and high bilirubin levels was first that the haptoglobin was used during hemolysis and if insufficient hemopoexin was used. It may be possible to predict neonatal jaundice with the haptoglobin to be checked in the UC blood. However, it will be possible to reveal these in prospective and wider studies to be carried out with bigger series. The number of newborns in the study is not big enough to reveal the sensitivity, specificity, and positive and negative productivity of this test. To target limited healthcare resources more effectively toward high-risk newborns after the era of early discharge of newborns from hospitals, there is an obvious need to develop practical guidelines to predict which newborns will develop significant hyperbilirubinemia or will require further and close follow-up or intervention (18). It is important that negative correlation was found between the UC blood haptoglobin and fifth day serum bilirubin values and therefore reference value ranges may be determined when our study is made with bigger series. It will also be possible to determine which cases need to be definitely monitored and controlled.

In conclusion, our data clearly demonstrate that the quantification of umbilical blood haptoglobin is a useful test to predict hyperbilirubinemia in healthy term newborns. As a result of the study, we can determine in advance that the healthy term neonatal jaundice will increase by checking the haptoglobin in the UC blood and prevent problems based on early discharge by closer monitoring of the babies, who we determine as risky in terms of hyperbilirubinemia. Besides, with this method, it is possible to determine the newborns with low hyperbilirubinemia risk and to prevent unnecessary monitoring and care of numerous cases. However, results of the present study should be confirmed in additional studies that include larger numbers of newborns with significant hyperbilirubinemia and hemolytic disease of the newborn.

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