O R I G I N A L   P A P E R

Analysis of the Relationship between Serum Bilirubin Levels and Frequency of Urination and Stooling in Infants in the First Week of Life

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Abstract

Background: There is risk of developing bilirubin encephalopathy (kernicterus) in cases in which early diagnosis and treatment of high bilirubin levels are not available. The follow-up and treatment of neonatal indirect hyperbilirubinemia are, therefore, important.
Aim: This study was conducted to evaluate the relationship between serum bilirubin levels and the frequency of urination and stooling in infants admitted to an outpatient neonatology department to determine the exact/cut off frequency of urination and stooling that will enable the prediction of high/critical serum bilirubin levels.
Methods: The study was carried out with the parents of 70 infants who were admitted to the outpatient Neonatology Department. Determination of the urination and stooling frequency of the infants included in this study was based on the number of changed urine wet diapers and the number of stooling in the last 24 hours before admission. The capillary bilirubin level measured at first routine control was recorded as the serum total bilirubin level.
Results: A statistically significant negative linear correlation was found between capillary serum bilirubin levels and the number of stoolings and number of changed urine wet diapers in the last 24 hours. A stooling number of ≤7 predicted being in the ≥50% risk group in terms of neonatal jaundice with 91.5% sensitivity, while ≤7 changed urine wet diapers in the last 24 hours also had 91.5% sensitivity.
Conclusions: This study will enable parents and health care providers to be aware of the exact frequency of urination and stooling that predicts high bilirubin levels. This simple observation will also make it possible to guide parents and health care providers about the critical serum bilirubin level for a risk of significant jaundice and related complications before high bilirubin levels develop dangerously.

Keywords: Hyperbilirubinemia, infant, serum capillary bilirubin, stooling, urination

Introduction

Clinically significant jaundice is seen in 50-70% of healthy term infants while this rate increases to 80% in preterm infants. There is the risk of developing bilirubin encephalopathy (kernicterus) in cases in which early diagnosis and treatment of high bilirubin levels are not available. The follow-up and treatment of neonatal indirect hyperbilirubinemia are, therefore, important. The United States of America has 27% while Singapore has 19% and Turkey has 16% reporting kernicterus indicating a need to perform more studies on neonatal jaundice in these countries (Chou et al. 2003; Ip et al. 2004; Petrova et al. 2006; Schwoebel & Gennaro 2006; Bhutani & Johnson 2009).

Although many newborns have physiological jaundice, there are important factors affecting its severity and duration. These factors can be classified as maternal and obstetric, and infant-related factors. Diabetes, maternal age, smoking, drugs and delivery method are maternal and obstetric factors while birth weight, gestational age, gender, inadequate caloric intake and weight loss, meconium passage and breast milk intake are infant-related factors. (Bertini et al. 2001; Chou et al. 2003; Huang et al. 2004; American Academy of Pediatrics 2004; Sarici et al. 2004; Smitherman, Stark & Bhutani 2006).

The exact level of bilirubin that causes neurological damage in infants is still not known. Early differentiation of physiological and pathological jaundice can enable the prediction of different conditions associated with dangerous serum bilirubin levels preventing the neurological damage that may develop due to high bilirubin levels (Schwoebel & Gennaro 2006).

The advisory Subcommittee on Hyperbilirubinemia of American Academy of Pediatrics has stated that 4 to 6 thoroughly wet diapers in 24 hours and the passage of 3 to 4 stools per day by the fourth day are evidence of adequate intake of breast milk helping prevent the development of high serum bilirubin levels associated with enterohepatic circulation of bilirubin in breastfed infants (American Academy of Pediatrics 2004).

The prediction or estimation of serum bilirubin levels according to the dermal distribution of jaundice is somewhat controversial (Hansen 2009; Bratlid, Nakstad & Hansen 2011). Furthermore detection of the critical extension of jaundice by the parents is more difficult. Thus many cases of kernicteric exclusively breast-fed newborns are still present in the medical literature today (Ip et al. 2004; Bhutani & Johnson 2009; Hansen 2011). Providing practical indicators or simple measures to parents personally involved in the care of newborn infants enables them to predict serum bilirubin levels of infants that can be critical and will be the easiest preventive approach to prevent the harmful effects of hyperbilirubinemia. Prediction of near-future (after 24 hours of life) significant hyperbilirubinemia has generally been based on the measurement of early (in the first 24 hours) serum bilirubin levels (Sarici et al. 2004). However prediction of significant hyperbilirubinemia or determination of significant jaundice on the basis of dermal distribution level of jaundice by the parents is in daily practice misleading and even impossible. Thus there is an obvious need for simple but reliable methods that can easily be used by the parents to predict or detect the later-developing significant jaundice in daily practice. For example a parent should have the ability of predicting near-future significant hyperbilirubinemia with the calculation or observation of simple defecation or urination patterns. This study was, thus, conducted to evaluate the relationship between serum bilirubin levels and the frequency of urination and stooling in infants admitted to an outpatient neonatology department and planned as a descriptive study in order to determine the exact frequency (cut-off level) of urination and stooling that will enable the prediction of high (critical) serum bilirubin levels.

Material and Methods

The study was carried out with the parents of 70 infants who were admitted to the outpatient Neonatology Department of Medical Academy between February and May 2010. The study was approved by the ethics committee of the Gulhane Military Medical Academy. Parents of infants born at 34 or more weeks of gestation, with no psychological disorder, perceptual problems, cognitive impairment, hemolytic disease, Rh incompatibility, ABO incompatibility, asphyxia, infection, major congenital anomalies, or respiratory failure and whose capillary bilirubin levels were measured were included in the study if they agreed to participate. A consent form was obtained from the parents participating in the study before the data collection form was completed. A patient information form consisting of 26 questions was prepared by the researchers to determine the sociodemographic characteristics of the infants and their parents and the factors affecting hyperbilirubinemia in infants with hyperbilirubinemia. The frequency of urination and stooling and the serum bilirubin levels of infants were recorded on this form.

The frequency of urination and stooling of infants was monitored for the 24 hours before they came to the clinic and during the period they were present for follow-up or received phototherapy**.** The parents were asked to record the number of times they changed diapers, how many of these contained stool and how many of these urine wet in the last 24 hours before the time of interview. Determination of the urination and stooling frequency of the infants included in this study was based on the number of changed urine wet diapers and the number of stooling in the last 24 hours before admission. The capillary bilirubin level measured at the first routine control was recorded as the serum total bilirubin level.

The sensitivity and specificity of detecting whether infants included in the study were in the ≥50% risk group in terms of hyperbilirubinemia according to the number of changed urine wet diapers and the number of stooling were calculated. The risk zones of bilirubin levels of the infants were determined in reference to the nomograms obtained from healthy and jaundiced newborns in the Turkish population (If the infants were in the risk zones of ≥50 percentile, they were deemed to have risk of jaundice) (Alpay et al. 2000; Sarici et al. 2004). The bilirubin levels of 70 infants out of 79 included in our study were evaluated to be in the ≥50% risk zone according to the cut-off levels published in these studies. The sensitivity and specificity values were calculated according to the number of stoolings and number of changed urine wet diapers in the ≥50% risk zone. The cut-off serum total bilirubin levels implying the bilirubin levels at or above ≥50% risk zone are presented in Table 1 (Alpay et al. 2000; Sarici et al. 2004).

Table 1. The cut-off serum total bilirubin levels implying the bilirubin levels at or above ≥ 50% risk zone

Postnatal age (hours)	Serum capillary bilirubin level (mg/dl)
24	5.5
30	6.2
36	7
42	7.6
48	8
54	8.5
60	8.8
66	9
72	9.2
78	10
84	10.6
90	11.2
96	12
102	12.1
108	12.2
114	12.3
120	12.5

Statistical Analysis

Statistical analysis was performed using the SPSS for Windows V 15.0 package software. The frequency distribution and percentage mean and standard deviation, and the Student t-test, Mann-Whitney U-test and Chi-Square tests were used for statistical analysis. The Spearman correlation coefficient was calculated to assess the linear relationship between the variables. ROC analysis was conducted to determine whether an infant with hyperbilirubinemia presenting at the clinic was in the ≥50% risk group according to the number of stoolings and number of changed wet diapers. $p<0.05$ was accepted for statistical significance in all analyses.

Results

55.7% of the infants included in the study were boys. Half of the infants (50.0%) were the second baby of the family. The mode of delivery was vaginal in 54.3%. More than half (68.6%) were breast-fed. The percentage of siblings receiving phototherapy treatment was 80.9% in infants who were not the first baby of the family (n=42) (Table 2).

Table 2. Distribution of the infants included in the study according to descriptive characteristics

Descriptive characteristics	N	%
Gender of infants (n=70)		
Female	31	44.3
Male	39	55.7
Rank among siblings (n=70)		
First baby	28	40.0
Second baby	35	50.0
Third baby	6	8.6
Fourth baby or higher	1	1.4
Delivery method (n=70)		
Vaginal delivery	38	54.3
Cesarean section	32	45.7
Feeding method (n=70)		
Breast milk	48	68.6
Formula	1	1.4
Breast milk together with formula	21	30.0
Whether previous siblings received phototherapy (n=42)		
Yes	8	19.1
No	34	80.9

Table 3. Certain characteristics of the infants included in the study

Characteristics	Values*
Maternal age (Years)	29.5±4.6
Gestational age (Weeks)	38.6±1.8
Hospitalization period after delivery (Hours)	32.8±13.4
Age of infant (Hours)	114.4±35.8
Birth weight (Grams)	3262.0±519.9
Presentation weight (Grams)	3125.4±506.5
Number of changed urine wet diapers	6.2±2.4
Number of stoolings	5.6±3.2
Capillary serum total bilirubin level (mg/dl)	14.0±3.0

* Values are given as mean ± standard deviation

Table 4. Comparison of the infants who were fed breast milk and breast milk plus formula in terms of certain variables

Variable	Breast milk (n=48)	Breast milk plus formula (n=21)	p value
Delivery method (n, (%))			
Vaginal delivery	31 (64.6)	7 (33.3)	0.016*
Cesarean section	17 (35.4)	14 (66.7)	
Number of changed urine wet diapers**	6.3±2.4 (6)	6.5 ± 2.7 (6)	0.672***
Number of stoolings**	5.4±2.6 (5)	6.4 ± 4.1 (5)	0.594***
Capillary serum total bilirubin level (mg/dl)**	13.9±3.1 (13.4)	13.7 ± 3.2 (14.3)	0.948***

* with Chi-Square test

** Results are given as mean ± standard deviation (median)

*** with Mann-Whitney U-test

Table 5. Correlation coefficients of capillary serum bilirubin levels with number of stoolings and number of changed urine wet diapers in the infants included in the study

	Number of defecations	Number of changed urine wet diapers
Capillary serum total bilirubin levels*	r=-0.582, p<0.001	r=-0.679, p<0.001

* r = Correlation coefficient (Spearman correlation coefficient was calculated in this table)

Table 6. Sensitivity and specificity values for being in the ≥50% risk group according to the number of stoolings in infants included in the study (n=70)

Number of stoolings	Number of infants in the ≥ 50% risk group	Number of infants who are not in the ≥ 50% risk group	Total
≤7	54	7	61
≥8	5	13	18
Total	59	20	*79

* Some infants had more than one bilirubin level belonging to different days (ROC analysis was performed in this table)

Area under the curve (AUC)=0.844

Sensitivity=54/59×100=91.5%

Specificity=13/20×100=65%

Positive predictive value (PPV)=54/61×100=88.5%

Negative predictive value (NPV)=13/18×100=72.2%

$p<0.001$

Table 7. Sensitivity and specificity values of being in the ≥50% risk group according to the number of changed urine wet diapers of infants included in the study (n=70)

Number of changed urine wet diapers	Number of infants in the ≥50% risk group	Number of infants who are not in the ≥50% risk group	Total
≤ 7	54	6	60
≥ 8	5	14	19
Total	59	20	*79

* Some infants had more than one bilirubin level belonging to different days (ROC Analysis was performed in this table)

Area under the curve (AUC)=0.883

Sensitivity=54/59×100=91.5%

Specificity=14/20×100=70%

Positive predictive value (PPV)=54/60×100=90%

Negative predictive value (NPV)=14/19×100=73.7%

$p<0.001$

Mean maternal age was 29.5±4.6 years, mean gestational age 38.6±1.8 weeks, mean hospitalization period of the mother after delivery 32.8±13.4 hours, mean age of the infants 114.4±35.8 hours, mean birth weight 3262.0±519.9 gr and mean weight at the first visit (presentation) 3125.4±506.5 g. The mean number of changed urine wet diapers was 6.2±2.4, mean number of stoolings 5.6±3.2, and the mean capillary serum total bilirubin level 14.0±3.0 for the infants included in the study (Table 3).

A statistically significant difference was found between the infants fed breast milk and fed breast milk plus formula regarding the delivery method ($p=0.016$). The breast feeding frequency was higher in those with a vaginal delivery (64.6%). No statistically significant difference was found between the infants fed breast and fed breast milk plus formula regarding the number of changed urine wet diapers the number of stoolings and mean capillary serum total bilirubin levels ($p>0.05$) (Table 4).

Table 5 presents the correlation coefficients between the capillary serum total bilirubin levels of infants and the number of changed urine wet diapers and number of stoolings. A statistically significant negative linear correlation was detected between capillary serum bilirubin levels and the number of defecations and number of changed urine wet diapers in the last 24 hours ($r=-0.582$, $p<0.001$; $r=-0.679$. $p<0.001$). Serum total bilirubin levels decreased as the number of stoolings and changed urine wet diapers increased.

The sensitivity and specificity values for being in the ≥50% risk group according to the number of stoolings are presented in Table 6.

The sensitivity and specificity values for being in the ≥50% risk group according to the number of changed urine wet diapers are presented in Table 7.

Discussion

Factors affecting the development of hyperbilirubinemia in the early neonatal period are reported as gender of the infant, maternal age, delivery method, birth weight, gestational age, feeding method, being the first baby, presence of a sibling with a history of receiving phototherapy, and the hospitalization period of the mother at the hospital (Chou et al. 2003; American Academy of Pediatrics 2004; Alkalay & Simmons 2005; Watchko 2009). Parents included in our study were therefore evaluated in terms of the characteristics given in Table 1 and Table 2.

The gender distribution of the infants with a various range of bilirubin levels included in the study was 44.3% female and 55.7% male (Table 2). Neonatal jaundice is reported to be seen more frequently in male infants (Maisels & Kring 1998; American Academy of Pediatrics 2004; Ip et al. 2004). Our gender rate (55.7% male) in this study is consistent with the other reports.

No statistically significant difference was found when infants fed breast milk and breast milk plus formula were compared with respect to serum capillary bilirubin levels although the average serum capillary bilirubin levels were higher in breast milk-fed infants. Breast milk-fed infants have been reported to have a higher risk of developing jaundice, and the severity and duration of the jaundice have been more marked when breast milk-fed infants were compared to formula-fed infants (Shapiro 2003; Huang et al. 2004). Bulbul et al. found no statistically significant difference between infants fed breast milk, formula and breast milk plus formula in terms of mean bilirubin levels although the highest median total serum bilirubin values were seen in the breast milk fed infants (Bulbul et al. 2005). Our study shows similarities with the study of Bulbul et al. (2005). We believe there was no statistically significant difference between the groups in terms of the mean serum capillary bilirubin levels as the breast milk was adequate in breast milk-fed infants and the babies could receive adequate nutrition while infants fed breast milk and formula also received adequate nutrition as inadequate breast milk was reinforced with formula**.** In the present study formula feeding was not compared since there was one infant fed with formula only.

The delivery method of the infants included in the study was vaginal in 54.3% and cesarean section in 45.7%. The breast feeding frequency was higher in those who had vaginal delivery (64.6%). Studies have reported higher breast feeding rates in the first hours following vaginal delivery than cesarean section (Ekman & Todia 2003; Duang, Binns & Lee 2004). Our results are consistent with those studies.

A kind of starvation condition occurs if an infant receives inadequate breast milk or the calorie intake of infant is restricted due to dehydration in the first few days of life. Starvation status, weight loss and dehydration in newborn infants are reported to be important risk factors for hyperbilirubinemia. Pathological weight loss indirectly indicates that the infant is undernourished and the enterohepatic bilirubin passage is increased. These infants defecate less in the first few days of life due to starvation and therefore the passage of meconium with a high bilirubin load is delayed. Bilirubin that becomes water-soluble is excreted with the urine and feces. The delay in meconium passage and the decrease in frequency of meconium passage contribute to the development of jaundice in undernourished infants (Chou et al. 2003; American Academy of Pediatrics 2004; Sarici et al. 2004; Behrman, Kliegman & Jenson 2008). Serum capillary bilirubin levels increased when the number of stoolings and number of changed urine wet diapers decreased in the infants included in our study. Our study results are in consistent with the literature on the explanation that serum bilirubin levels are affected by the enterohepatic circulation.

Hereditary and environmental factors affect the occurrence of hyperbilirubinemia. The prevalence rate is lower in the black race than Caucasians, while jaundice is more common in East Asian and East Mediterranean countries. The identification of the bilirubin percentile limits for every community and defining the appropriate approach and treatment accordingly are therefore recommended (Huang et al. 2006). We used the bilirubin levels from the neonatal jaundice risk curve identified for Turkish children by Alpay et al. in 2000 and Sarici et al. in 2004 for the ≥ 50% risk group as the cut-off point for ≥ 50% risk. Sensitivity, specificity, positive and negative predictive values according to the number of stoolings and number of changed urine wet diapers were calculated in the ≥50% risk group. A number of ≤7 stoolings in the last 24 hours indicated being in the ≥50% risk group in terms of neonatal jaundice with 91.5% sensitivity. A number of changed urine wet diapers of ≤7 in the last 24 hours also showed being in the ≥ 50% risk group in terms of neonatal jaundice with 91.5% sensitivity.

Conclusion

A statistically significant negative linear correlation was found between capillary serum bilirubin levels and the number of stoolings and number of changed urine wet diapers in the last 24 hours in infants included in the study. A decrease in the number of stoolings and changed urine wet diapers correlated with an increase in serum capillary bilirubin levels. A stooling number of ≤7 predicted being in the ≥50% risk group in terms of neonatal jaundice with 91.5% sensitivity, while ≤7 changed urine wet diapers in the last 24 hours also had 91.5% sensitivity.

We believe this study will enable parents and health care providers to be aware of the exact frequency of urination and stooling that predicts high bilirubin levels. This simple observation will also make it possible to guide parents and health care providers about the critical serum bilirubin level for a risk of significant jaundice and related complications so as to bring their infants to the hospital to get treatment before high bilirubin levels develop dangerously.

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