

# Does umbilical cord bilirubin level have predictive value in pathologic neonatal hyperbilirubinemia?

Ahmadshah farhat<sup>\*1</sup>, Anahita Alizadeh Ghamsari<sup>2</sup>, Ashraf Mohamadzadeh<sup>1</sup>, Azam Khodadadi<sup>3</sup>, Mehrieh Rezaei<sup>4</sup>

1- Neonatal Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

2- Toxicology Fellowship, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

3- Department of Microbiology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

4- Head nurse of NICU, Razavi Hospital Mashhad, Iran.

## Abstract

### Introduction

The increase in the use of breast feeding and the decrease in mothers' hospitalization in the past few years have caused an increase in the infant bilirubin level, so it is necessary to introduce methods which can identify infants with higher risks of hyperbilirubinemia.

The aim of this study is to determine the predictive value of measuring the umbilical cord bilirubin for pathologic hyperbilirubinemia, that is the bilirubin more than 15mg /dl.

### Materials and Methods

This prospective study was performed from November 2009 to December 2010 on the umbilical cord serum of 274 newborns who were born in Iran-Mashhad Razavi Hospital. The neonates' Apgar scores were above 7, weights more than 2.5 kg and gestational ages above 37 weeks.

Once again their bilirubin level was measured via skin during the third to fifth day.

Using the Smirnov test, one-sample Kolmogorov test, t-test, and Man Whitney test, we analyzed the data.  $P < 0.05$  was considered significant.

### Results

Out of 274 newborns, 178 cases were followed up. Ninety-three infants of the monitored cases had hyperbilirubinemia (total bilirubin  $\geq 15$  mg/dl or group A, 85 of the infants did not have pathologic hyperbilirubinemia (total bilirubin  $< 15$  mg/dl or group B). The average umbilical cord bilirubin for group A was  $2.32 \pm 0.78$  mg/dl, and for group B was  $1.98 \pm 0.72$  mg/dl; so statistically, there is a significant difference.

At the cut-off point of 2 mg/dl for umbilical cord bilirubin, sensitivity was obtained to be 68.86% and the specificity was obtained to be 61.18%.

### Conclusion

If the amount of bilirubin in the umbilical cord is more than 2 mg/dl, it can be considered as a contributing factor among other risk factors in the prediction of the infant's pathologic hyperbilirubinemia.

### Key words

neonate, umbilical cord, hyper bilirubinemia

### Introduction

Hyperbilirubinemia is a common and often benign disease in neonatal period. About 60% of term infants and 80% of immature infants suffer from jaundice. (1, 2)

The cause of jaundice is the aggregation of indirect soluble bilirubin pigments in skin and in other

tissues.

Certain concentrations of this form of bilirubin is neurotoxic under certain conditions. Evidence shows that probably bilirubin interferes by damaging the oxygen consumption of brain cells; therefore, it will be one of the damaging mechanisms for brain damage or kernicterus. (3)

On the other hand, pathologic hyperbilirubinemia with other risk factors such as asphyxia, infection, hypoglycemia and acidosis, can increase the risks of brain damage. (4)

Between the years 1959 and 1966, 5% of infants had a bilirubin of more than 13 mg/dl; while in recent years, 5% of infants have a bilirubin of more than 15.5 to 18 mg/dl because the length of infants' hospitalization after birth has decreased and the number of infants who are being breast fed has increased (from 30% in 1960 to 65% in 2001). (5) In another study, about 2% of term infants have had serum bilirubin level more than 20 mg/dl.

Also because of the high prevalence of jaundice in newborns and its potential risks for infants, it seems almost necessary to offer methods which make the identification of infants at risk of having pathologic hyperbilirubinemia possible.

Various ways have been suggested in order to predict neonatal jaundice such as physical examination, evaluation using total risk factor table, measuring total bilirubin before infant's discharge, using cutaneous measurement of bilirubin, and measuring the CO level of terminal expiratory.

In Iran, considering the current cultural and economical status, infants post discharge follow up faces many difficulties, thus we decided to study umbilical bilirubin level in predicting infant pathologic hyperbilirubinemia.

### Methods

This study was conducted prospectively at Razavi Hospital, Mashhad, Iran. According to the conducted pilot study (B=19%, X=5%) about 84 infants were needed to be monitored and studied. 274 umbilical cord blood samples were taken, from which 178 cases continued with the study; the rest, however, did not attend.

The umbilical cord blood serum of the infants with good health, with no asphyxia, with over 2.5 kg of weight and with 37-40 gestational age were taken to be studied. Infants with obvious malformations, asphyxia, ecchymosis, cephalohematoma, infants of diabetic mothers and infants with mothers who consumed oxytocin were excluded from the study. The umbilical cord bilirubin was measured with a precision of 0.05 using the (BT 3000) device manufactured by the Italian, Biotechnical company. On the third day of the birth, infants were examined for neonatal jaundice. Newborns were divided into two groups: the first group of infants was those who had pathologic hyperbilirubinemia

( $bil \geq 15$  mg/dl). They were evaluated within 3 to 5 days after birth. The second group was those who did not have pathologic hyperbilirubinemia ( $bil < 15$  mg/dl). The results were assessed and analyzed by the software (SPSS 11.5) and statistical tests such as t test, chi-square, and one sample Kolmogorov, Smirnov, Man-Whitney.  $P < 0.05$  was considered significant

### Results

In this study, out of the 274 infants who were enrolled, 29 were excluded because they had risk factors or had bad general condition. From the remaining 245 infants, 178 infants were re-examined 3- 5 days after birth. From these infants 93 (52.2%) had hyperbilirubinemia ( $bil \geq 15$  mg/dl) which were investigated or treated (Group 1) and 85 infants (47.8) didn't have high bilirubin ( $bil < 15$  mg/dl) (Group 2).

In this study, infants' feeding style, mother's age, birth weight, type of delivery and infant's gender did not have any significant difference in both groups (table 1).

**Table1: relative frequency of correct answers regarding to neonatal generalized surveillance.**

Group	1	2	P-value
Number	93	85	
Birth weight	3255 ± 468	3105.07 ± 654	P= 0.08
Gender			
Male	50	44	P= 0.37
Female	43	41	
Umbilical cord bilirubin	total= 2.32 ± 0.78 Direct= 0.3 ± 0.06	total= 1.98 ± 0.72 Direct= 0.3 ± 0.07	P= 0.000
Mother age	29.54 ± 5.36	28.46 ± 5.01	P= 0.173
Delivery type	c/s 92.4%	c/s 84.5%	P= 0.1
Education level Higher than high school	% 46.9	% 44.9	P= 0.22
Feeding type	<b>All of them were breastfed</b>		

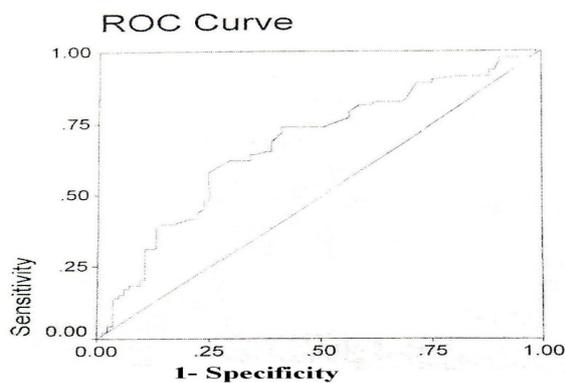
The results of different amounts of umbilical cord bilirubin and its sensitivity, specificity, positive predictive value and negative predictive value can be observed in table 2.

As we can see, when the umbilical cord bilirubin equals 2 mg/dl, it has a good sensitivity and specificity. Therefore, the obtained ROC chart is acceptable.

With umbilical cord bilirubin of 2 mg/dl, we will have a positive predictive value of 66%, a negative predictive value of 64.2%, sensitivity of 68.86% and specificity of 61.8%.

**Table2: Umbilical cord bilirubin and its sensitivity, specificity, positive predictive value and negative predictive value.**

Umbilical cord bilirubin mg/dl	sensitivity	specificity	PPV	NPV
1	% 97.8	% 3.5	% 52.6	% 60
1.5	% 91.4	% 16.5	% 54.5	% 63.6
2	% 68.86	% 61.18	% 66	% 64.2
2.5	% 28	% 89.4	% 74.3	% 53.1
3	% 11.8	% 96.5	% 78.6	% 50
3.5	% 5.4	% 96.5	% 62.5	% 48.2
4	% 4.3	% 975.6	% 66.7	% 48.3



**Discussion**

Infant jaundice is very common and when severe, it can lead to infant's morbidity and mortality. According to available resources, umbilical cord bilirubin can have a predictive value in neonatal jaundice. In our study on the amount of umbilical cord bilirubin, the cut-off point of 2 mg/dl had prediction value for the pathologic hyperbilirubinemia with a good sensitivity and specificity; in such a way that if neonatal umbilical cord bilirubin is less than 2 mg/dl, the probability of the infant not having jaundice is 64.20%. (p=000). The sensitivity and specificity in this study were respectively obtained to be 68.86% and 61.18% and the NPV 64.20% and PPV= 66% were obtained. In a similar study carried out by Rostami et al. in ShaheedBeheshti University of Medical Sciences on 643 term infants, the study results showed that 92.4% of infants whose umbilical cord bilirubin was less than 3 mg/dl did not have pathologic hyper bilirubinemia. They had  $p < 0.04$ , sensitivity

18.4%, specificity of 92.4%, PPV 24.6% and NPV 89.4% (10).

In the mentioned study, the sensitivity and the amount of PPV and the cut-off point of 3 is lower than the present study. However, it is noteworthy that in Rostami et al.'s study, the cut-off point of 2mg/dl had the sensitivity of 59.2% and the specificity of 48.1% which is somewhat close to the present study(10).

In another study, Rosenfeld showed that only 4% of infants whose umbilical cord bilirubin was less than 2 mg/dl suffered from pathologic hyperbilirubinemia, but from infants whose umbilical cord bilirubin was > 2 mg/dl, 25% had pathologic hyperbilirubinemia. This study results was similar to our study's (11).

Another study which also had similar results is the study performed by Knudsen et al. which showed that if the umbilical cord bilirubin is less than 1.4%, only 29% of infants have a chance of suffering from pathologic hyperbilirubinemia, but if umbilical cord bilirubin is more than 2.5 mg/dl, 85% of infants will suffer from pathologic hyperbilirubinemia (12). Other reports show that umbilical cord bilirubin more than 2.5mg/dl can predict the pathologic hyperbilirubinemia with the sensitivity of 71% and 94% specificity (10). Furthermore, Bernalda AJ reported that 52% of infants whose umbilical cord bilirubin was more than 2 mg/dl need phototherapy until the third day of their birth (13).

Among other studies, we can point out Agarwal et al's study which showed that if the amount of total bilirubin in infant's serum is < 6 mg/dl within the first 24±6 hours after birth, this infant will not have pathological jaundice, with a sensitivity 95%, specificity of 70.6%, PPV of 27.2 %, NPV of 99.3%. Only one of 136 infants with umbilical cord bilirubin less than 6 mg/dl had pathologic jaundice (14).

On the other hand, Carbonall et al. showed that umbilical cord bilirubin cut-off point of 2.25 mg/dl is not a suitable predictor for the pathological hyperbilirubinemia, which goes against our study results (16).

Also, Jacobson et al. retrospectively compared 87 infants' umbilical cord bilirubin who received phototherapy treatment to 95 infants' umbilical cord bilirubin that didn't need phototherapy. They concluded that the umbilical cord bilirubin cannot be an appropriate predictor for pathological hyperbilirubinemia (17).

In another study by Seiman et al., it was shown

that we can identify high risk infants for jaundice by investigating the creator risk factors and by measuring total serum bilirubin when infants are prepared for discharge (18).

### Conclusion

According to this study if umbilical cord bilirubin is  $\geq 2$  mg/dl, it can be a factor assisting the diagnosis of high risk infants for pathologic hyperbilirubinemia.

### Acknowledgments

The authors would like to thank from Research Deputy of Mashhad University of Medical Sciences for supporting this study.

### References

1. Stoll BJ. The fetus and the neonatal infant. In: Kliegman RM, Behrman PE, Jenson HB, et al. Nelson textbook of pediatrics. 18th ed. Philadelphia, Saunders Elsevier; 2007:756.
2. Camillia R, Martin and Cloherty JP. Neonatal hyperbilirubinemia. Cloherty JP, Eichenwald EC, Stark AR. manual of neonatal care. 6th ed. Wolters kluwer: LWW; 2008:181.
3. Stoll BJ. The fetus and the neonatal infant. In: Kliegman RM, Behrman PE, Jenson HB, et al. Nelson textbook of pediatrics. 18th ed. Philadelphia, Saunders Elsevier; 2007:761.
4. Maisels MJ. Avery's neonatology pathology pathophysiology and management of the newborn. In: Macdonald MK, Seshia M, Mullett MD. Jaundice. 6th ed. Philadelphia: LWW; 2005:808.
5. Maisels MJ. Jaundice. In: Macdonald MK, Seshia M, Mullett MD. Avery's neonatology pathology pathophysiology and management of the newborn. 6th ed. Philadelphia: LWW; 2005:811.
6. Martin CR. Neonatal hyperbilirubinemia. In: Cloherty JP, Eichenwald EC, Stark AR. manual of neonatal care. 6th ed. Wolters kluwer: LWW; 2008:190.
7. Maisels MJ. Jaundice. In: Macdonald MK, Seshia M, Mullett MD. Avery's neonatology pathology pathophysiology and management of the newborn. 6th ed. Philadelphia: LWW; 2005:816.
8. Martin CR. Neonatal hyperbilirubinemia. In: Cloherty JP, Eichenwald EC, Stark AR. manual of neonatal care. 6th ed. Wolters kluwer: LWW; 2008:191.
9. Maisels MJ. Jaundice. In: Macdonald MK, Seshia M, Mullett MD. Avery's neonatology pathology pathophysiology and management of the newborn. 6th ed. Philadelphia: LWW; 2005:793.
10. Rostami N, Mehrabi Y. Identifying the newborns at risk for developing significant hyperbilirubinemia by measuring cord bilirubin levels- Arab neonatal forum 2005(2):81-85.
11. Rosenfeld J. Umbilical cord bilirubin levels as a predictor of subsequent hyperbilirubinemia. J from pract. 1986; 23:556-558.
12. Kundsén A. Prediction of development of neonatal jaundice by increased umbilical cord blood bilirubin. Acta paediatr Scand. 1989; 78:217-221.
13. Bernalda AJ, Segre CA. Bilirubin dosage in cord blood. Count it predict neonatal hyperbilirubinemia? Sao Paulo Med J. 2004; 122:99-103.
14. Agarwal R, Kaushal M, Agrwal R, et al. Early neonatal hyperbilirubinemia using first day serum bilirubin level. Indian pediatr. 2002; 724-730.
15. Aplay F, Sarici SU, Tosuncuk HD, et al. The value of first day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns. Pediatrics. 2000; 106(2): E16.
16. Carbonell EX, Botet M, Fiqueras AJ, Riu CA. Hyperbilirubinemia in full term newborns. Predictive factors. An Esp pediatr 1999; 50:389-392.
17. Jacobson MP, Bernstein HH. Limited diagnostic value of routine cord blood bilirubin determination. Clin pediatr (Phila). 1982; 21:610-612.
18. Seidman DS, Ergaz Z, Paz J, Laor A, Revel-Vilksh, et al. Predicting risk of jaundice in full-term healthy newborns. A prospective population based study. J perinatol. 1999; 19:564-567.