ORIGINAL ARTICLE

USEFULNESS OF CORD BILIRUBIN AS A SCREENING TEST TO PREDICT NEWBORNS AT RISK OF HYPERBILIRUBINEMIA

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Abstract

Aim: To assess the utility of cord bilirubin as a screening test to predict subsequent neonatal hyperbilirubinemia.

Study Setting and Design: Retrospective study in departments of Pediatrics & Obstetrics and Gynecology (OBG) of a tertiary care teaching hospital in Chennai.

Methods: A total of 1114 term and near term babies born between January 2008 and December 2009 were included in the study. Umbilical cord bilirubin levels were analyzed in all the children. Serum bilirubin was obtained from neonates who were clinically jaundiced on day three. Total bilirubin of 14mg% and above was defined as hyperbilirubinemia. Correlation of cord bilirubin and subsequent hyperbilirubinemia was analyzed.

Results: Out of 1114 study subjects, 12.6% developed hyperbilirubinemia. The cord bilirubin level of 1.5 mg/dl had much stronger and statistically significant association with neonatal hyperbilirubinemia compared to all other cut off levels (Odds ratio - 2.75, 95% CI 1.51 to 5.02, p-value-0.001). However when cord bilirubin level of 1.5 mg/dl was used as screening test, the area under Receiver operating characteristic (ROC) curve was 0.6, which is closer to the null value of 0.5 (95% Cl 0.55 to 0.66, p-value 0.001). The positive predictive value (PPV) ranged from 11% to 17% with different levels of cord bilirubin. The negative predictive value was 96% with cord bilirubin level above 1.5 mg/dl and consistently maintained above 90% with increasing levels of cord bilirubin up to 3mg/dl making it difficult to set a cut off value.

Conclusion: Utility of umbilical cord serum bilirubin levels as a screening test to predict subsequent neonatal hyperbilirubinemia was very poor.

Key Words: Cord bilirubin, neonatal hyperbilirubinemia, screening test

Introduction

Hyperbilirubinemia is a common problem in neonates. Jaundice is observed in the first week of life in approximately 60% of term and 80% of preterm infants. (1) The greatest risk associated with hyperbilirubinemia is development of neurologic dysfunction. There have been studies of various strategies of predicting and dealing with neonatal hyperbilirubinemia in the literature. These strategies include, follow up of infants discharged at or before 48 hours, routine transcutaneous bilirubin measurements, predischarge bilirubin measurement and clinical assessment of risk factors for the development of jaundice. (2) The recommendations of routine post discharge follow up after 2-3 days, use of transcutaneous bilirubin measurements or predischarge bilirubin measurements have limited practical applicability in resource limited countries such as India. Availability of a simple, economical and non invasive method to predict subsequent hyperbilirubinemia, which can aid clinicians in early discharge of the children and selective follow up of the high risk infants, will be ideal in these settings. An association between cord bilirubin levels and subsequent risk of hyperbilirubinemia has been reported. (3-10) However, the utility of cord bilirubin as a screening test to predict subsequent hyperbilirubinemia has been widely debated. (11-14) In the wake of this ambiguity, the present retrospective study was undertaken to evaluate the predictive value of cord bilirubin in identifying term and near term infants at risk of hyperbilirubinemia.

Materials and Methods

This retrospective study was conducted in the pediatrics, obstetrics and gynecology departments of a tertiary care teaching hospital, between January 2008 and December 2009. Maternal and neonatal data were collected from the case records from the medical records department. The study population included healthy term and near term infants delivered during study period and infants readmitted with hyperbilirubinemia. All infants had gestational age of more than 35 weeks based on New Ballard score, had no significant illness requiring neonatal Intensive care unit (NICU) admission and were exclusively breast fed. Infants with major congenital anomalies, prolonged rupture of membranes (more than 24 hours), sepsis and perinatal hypoxia were excluded from the study. Maternal and neonatal data obtained from case records included birth weight, gender, mode of delivery, gestational age and blood group of mother. The data on blood grouping, Rh typing and umbilical cord bilirubin levels at birth were routinely performed in all cases. Bilirubin levels were obtained if the new born was clinically diagnosed as being jaundiced on day three. Significant hyperbilirubinemia was defined as total serum bilirubin of than 14 mg% or more on day three. The data were analyzed using descriptive statistics, chi square and binary logistic regression. Sensitivity, specificity and positive and negative predictive values of different cut off points of the cord bilirubin were obtained. Receiver operating characteristic (ROC) analysis was carried out to evaluate the usefulness of cord bilirubin as a screening test to identify neonates at risk for hyperbilirubinemia.

Results

Out of 1159 subjects included in the study, 28 subjects were excluded because of low birth weight (< 2 kg), which is an established risk factor for hyperbilirubinemia. Another 17 subjects were excluded from the analysis for the lack of complete data. A total of 1114 subjects were included in the final analysis. Out of the total 1114 subjects, 552 (49.6%) were delivered by vaginal delivery, 532 (47.8%) were by lower segment cesarean section (LSCS) and another

Table 1. Descriptive analysis of study participants (N= 1114)

	Frequency (%)	Hyperbilirubinemia Frequency (%)
Mode of delivery		
NVD	552 (49.6)	33(6)
LSCS	532 (47.8)	50(10.9)
AVD	30(2.7)	5(16.7)
Gestational age		
Term	1040 (93.4)	84(8.1)
Preterm	74 (6.6)	12(16.2)
Birth weight of the baby		
AGA	1013 (90.9)	83(8.2)
SGA	94 (8.4)	12(12.8)
LGA	7 (0.6)	1(14.3)
ABO Incompatibility	291 (26.1)	65(7.9)
Rh Incompatibility	39 (3.5)	92(8.6)

Note - NVD = normal vaginal delivery, LSCS= lower segment caesarean section, AVD= assisted vaginal delivery, AGA=appropriate for gestational age, SGA= small for gestational age, LGA=large for gestational age

30 (2.7%) were delivered by assisted vaginal delivery (AVD). A total of 1040 (93.4%) were term babies and 74 (6.6%) were pre term babies. Regarding the birth weight, 1013 (90.9%) were appropriate for gestational age (AGA), 94 (8.4%) were small for gestational age (SGA) and 7 (0.6%) were large for gestational age (LGA) babies. There were 291(26.1%) babies born with ABO incompatibility and 39 (3.5%) were having RH Incompatibility. (Table 1)

There is statistically significant association between cord bilirubin levels above 1.5 mg/dl, above 2 mg/dl and hyperbilirubinemia. The odds of hyperbilirubinemia are 2.75 times higher in children with cord bilirubin levels above 1.5 mg/dl as compared to the children with cord bilirubin levels below 1.5 mg/dl (Odds ratio - 2.75, 95% CI 1.51 to 5.02, p-value-0.001). The odds of hyperbilirubinemia are 1.72 times higher in children with cord bilirubin levels above 2 mg/dl as compared to the children with cord bilirubin levels below 2 mg/dl (Odds ratio - 1.72, 95% CI 1.09 to 2.73, p-value-0.027). Even though the Odds of hyperbilirubinemia are high for other higher cut off levels of cord bilirubin, they are statistically not significant as mentioned in the table. (Table 2)

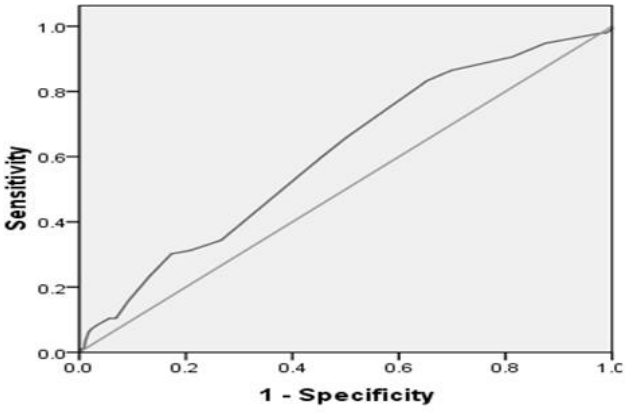
Controlling for all other risk factors, the odds of hyperbilirubinemia are 2.6 times more in children with high cord bilirubin (>1.5 mg/dl) as compared to children with low cord bilirubin (Odds ratio -2.6, 95% CI - 1.45 to 4.8, p value-0.002), which is statistically significant. Mode of delivery by LSCS (Odds ratio 1.8, 95% Cl 1.15 to 2.8, p value-0.01) and by AVD (Odds ratio 3.19, 95%CI 1.1 to 9.0, p-value-0.02) was positively associated with the development of hyperbilirubinemia compared to the normal vaginal deliveries. Pre term babies were 1.79 times at risk of developing hyperbilirubinemia, compared to term babies. Small for gestational babies were 1.6 times (Odds ratio 1.64, 95%CI 0.8 to 3.1, p-value-0.14) and large for gestational babies were 1.8 times

Table 2: Association between cord bilirubin and hyperbilirubinemia

Cord Bilirubin (mg/dl)	Hyperbilirubinemia N (%)	Odds Ratio	95% CI		p-value
Above 1.0 (N=1111)	95 (8.6%)	0.18	0.01	2.08	0.237
Above 1.5 (N=794)	83 (10.5%)	2.75	1.51	5.02	0.001
Above 2 .0 (N=242)	30 (12.4%)	1.72	1.09	2.73	0.027
Above 2.5 (N=67)	10 (14.9%)	1.96	0.96	3.97	0.70
Above 3.0 (N=12)	2 (16.7 %)	2.14	0.46	9.93	0.277

(Odds ratio 1.8, 95%CI 0.2 to 16.1, p-value-0.59) at risk of developing hyperbilirubinemia, compared to appropriate for gestational age babies. But both these associations are not statistically significant. Children with ABO Incompatibility had 1.43 times increased odds of hyperbilirubinemia (Odds ratio 1.43, 95%CI 0.9 to 2.2, p-value-0.12), and Rh incompatible children had 1.54 times increased odds of hyperbilirubinemia (Odds ratio 1.54, 95%CI 0.5 to 4.6, p-value-0.43). The area under ROC curve is 0.6 (95% CI 0.55 to 0.66, p-value 0.001) when cord bilirubin level of 1.5 mg/dl was used as a screening test. (Figure 1)

Figure 1: Receiver operating Characteristic (ROC) curve to assess the ability of cord bilirubin to predict hyperbilirubinemia



The positive predictive value (PPV) of cord bilirubin as a screening test to predict the clinical hyperbilirubinemia was ranging from 11% to 17%. The negative predictive values of with different levels of cord bilirubin was 96% with cord bilirubin level above 1.5 mg/dl and consistently maintained above 90% with increasing levels of cord bilirubin up to 3mg/dl. (Table 3)

Discussion

Reports of bilirubin induced brain damage occurring in healthy term infants even without hemolysis (3) have increased the concerns regarding neonatal hyperbilirubinemia. About 8-11% of well baby population may require intervention for hyperbilirubinemia and nearly 30% required continued monitoring. (4) The incidence of hyperbilirubinemia of 12.6% in our study is slightly higher than the incidence of hyperbilirubinemia between 6% and 10.3% reported by various studies. (5,6) A non invasive, and reliable identification of babies at risk of hyperbilirubinemia can aid in early discharge of the low risk babies and at the same time helps in proper follow up of the high risk babies.

Various parameters like gestational age, Rh incompatibility, cord bilirubin levels were reported to have statistical association with hyperbilirubinemia (3-10) Some of these factors alone or in combination were also assessed for their predictive value as a screening test of subsequent neonatal hyperbilirubinemia. Out of all, cord bilirubin was the most widely studied parameter in this regard. (3-14)

Gestational age was observed to have significant effect on hyperbilirubinemia in studies by Singhal et al (16.7%) (7) and Narang et al (47.9%). (8) However some researchers did not observe any significant effect of gestational age on hyperbilirubinemia. (9,10) In our study 93.4% of the babies were term and 6.6% babies were preterm. 8.1% of term and 16.2% of preterm babies developed hyperbilirubinemia.

In our study the incidence of hyperbilirubinemia was higher in both small for gestational age and large for gestational age babies but the association was not statistically significant. The number of ABO incompatibility cases in our study group was 291(26%) and 10.7% developed hyperbilirubinemia which is similar to results from other studies. (6,11,12)

In 1986 Rosenfeld (13) found that babies with umbilical cord bilirubin level of lower than 2mg% had 4% chances of developing significant jaundice, in comparison with a 25% chance presented by babies with levels higher than 2mg%. In 1977 Risemberg et al (11) concluded that newborns with ABO incompatibility and with cord bilirubin levels higher than 4mg% were at risk of developing severe hyperbilirubinemia. Bernaldo and Segre (12) found 2mg% as the cutoff point for unconjugated bilirubin in cord blood. Several other studies have shown significant associations of cord bilirubin with significant hyperbilirubinemia, though at varying levels. (5,14-20) However, in a retrospective study Jacobsen et al (21) observed no significant differences in cord bilirubin levels of 87 neonates who received standard phototherapy for neonatal jaundice and 95 neonates without neonatal jaundice.

In our present study, the cord bilirubin level of 1.5 mg/dl had much stronger and statistically significant association with neonatal hyperbilirubinemia compared to all other cut off levels. The high statistical association continued to exist even after controlling for all the

Table 3: Validity & predictive values of Cord bilirubin in assessing hyperbilirubinemia

Cord Bilirubin	Sensitivity	Specificity	PPV*	NPV †
1.5 mg/dl	86%	30%	11%	96%
2.0mg/dl	31%	79%	12%	92%
2.5 mg/dl	10%	94%	15%	92%
3.0 mg/dl	2%	99%	17%	92%

* PPV-Positive Predictive value, † NPV - Negative Predictive Value

other factors like gestational age, mode of delivery, ABO incompatibility by logistic regression.

Just as there are conflicting reports of the statistical association of cord bilirubin with neonatal hyperbilirubinemia and the levels of cord bilirubin at which this association exists, there are conflicting reports of its utility of cord bilirubin as a screening test for predicting subsequent hyperbilirubinemia. Taksande et al (5) reported a high negative predictive value (98.7%) but a low positive predictive value (38.6%) with a cord bilirubin of 2mg%. Gatea et al (19) also reported a high negative predictive value (98%) and a low positive predictive value with a cod bilirubin of 2mg%. However, Nahar et al (14) found positive and negative predictive values of 96% and 91% respectively with a cord bilirubin of 2.5mg%. Rostami et al (22) concluded that cord serum bilirubin levels cannot identify newborns with subsequent risk of hyperbilirubinemia. However Carbonell et al (23) showed umbilical cord bilirubin with a cutoff point of 2.2mg% was not a useful predictor of neonatal jaundice.

In the present study, the cord bilirubin level of 1.5mg% was studied for its utility as a screening test. The ability of cord bilirubin of 1.5mg/dl to discriminate between children with or without clinical hyperbilirubinemia was very poor as depicted by the area under ROC curve. The area under ROC was 0.6, which was very close to the null value of 0.5. Positive predictive values of all cut-off values of cord bilirubin were very poor. The negative predictive values were consistently high with all levels of cord bilirubin making it difficult to set a particular cut off level below which we can discharge the child. Therefore, the utility of cord bilirubin as a screening test to predict hyperbilirubinemia is poor.

Conclusion

It can be concluded that cord bilirubin levels cannot predict the risk of neonatal hyperbilirubinemia. We still require a reliable and non invasive screening tool to identify neonates who will develop subsequent hyperbilirubinemia. Systematic assessment of clinical risk factors as recommended by American Academy of Pediatrics (24) and routine follow up of newborns discharged early might help in prevent neurological dysfunction.

What is already known?

There is an association between cord bilirubin and neonatal hyperbilirubinemia.

What this study adds:

Cord bilirubin is not a valid & reliable screening tool to predict neonates who will develop subsequent hyperbilirubinemia.

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References

1. Ambalavanan N, Carlo WA. The foetus and neonatal infant, digestive system disorders: Jaundice and hyperbilirubinemia in the newborn, In: Kliegman M, Stanton BF, St.Geme JW, Schor NF, Behrman RE(eds). Nelson Textbook of Paediatrics. 19th ed. Philadelphia. Saunders-Elsevier. 2011: 603-612
2. Martin CR, Cloherty JP. Neonatal hyperbilirubinemia. In: Cloherty JP, Eichenwald EC, Stark AR (eds). Manual of Neonatal care. 6th edn. Philadelphia. Lippincott Williams & Wilkins. 2008: 181 -212
3. Maisels MJ, Newman TB. Kernicterus in otherwise healthy, breastfed term neonates. Pediatrics 1995; 96; 730-733
4. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour- specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near term newborns. Pediatrics 1999; 103: 6-14
5. Taksande A, Vilhekar K, Jain M, Zade P, Atkari S, Verkey S. Prediction of the development of neonatal hyperbilirubinemia by increased umbilical cord blood bilirubin. Curr Pediatr Res. 2005; 9: 5-9
6. Agarwal R, Kaushal M, Aggarwal R, Paul VK, Deorari AK. Early neonatal hyperbilirubinemia using first day serum bilirubin level. Indian Pediatr. 2002; 39: 729-730
7. Singhal PK, Singh M, Paul VK, Deorari AK, Ghorpade MG. Spectrum of neonatal hyperbilirubinemia: An analysis of 454 cases. Indian Pediatr 1992; 29: 319-325.
8. Narang A, Gathwala G, Kumar P. Neonatal jaundice: An analysis of 551 cases. Indian Pediatr. 1997; 34: 429-432.
9. Awasthi S, Rehman H. Early prediction of neonatal hyperbilirubinemia. Indian J Pediatr. 1998; 65:131-39.
10. Alpay F, Sarici SU, Tosuncuk HD, Serdar MA, Inanc N, Gokcay E. The value of first-day bilirubin measurement in predicting the development of significant hyperbilirubinemia in healthy term newborns. Pediatrics 2000; 106: 16-21.
11. Risemberg HM, Mazzi E, MacDonald MG, Peralta M, Heldrich F. Correlation of cord bilirubin levels with hyperbilirubinaemia in ABO incompatibility. Arch Dis Child. 1977;52: 219-222.
12. Bernalda AJ, Segre C. A Bilirubin dosage in cord blood: could it predict neonatal hyperbilirubinaemia? Soa Paulo Med J 2004; 122: 99-103 [PubMed]
13. Rosenfeld J. Umbilical cord bilirubin levels as a predictor of subsequent hyperbilirubinaemia. J Fam Pract. 1986;23(6):555-55823.Carbonell EX, Botet MF, Figueras AJ, Riu GA. Hyperbilirubinaemia in full term newborns. Predictive factors. An Esp Pediatr 1999;50:389-392.
14. Nahar Z, Abdul Mannan S, Dey SK, Mitra U, Selimuzzaman SM. The value of umbilical cord blood bilirubin in predicting the development of significant hyperbilirubinemia in healthy newborn. Bangladesh J Child Health. 2009; 33: 50-54.
15. Knudson A. Prediction of the development of neonatal jaundice by increased umbilical cord blood bilirubin. Acta Paediatr Scand. 1989; 78: 217-221. [PubMed]
16. Sun G, Wang YL, Liang JF, Du LZ. Predictive value of

umbilical cord blood bilirubin level for subsequent neonatal jaundice. Zhonghua Er Ke Za Zhi. 2007; 45: 848-852
17. Knupfer M, Pulzer F, Gebauer C, Robel-Tillig E, Vogtmann C. Predictive value of umbilical cord blood bilirubin for postnatal hyperbilirubinaemia. Acta Paediatr. 2005; 94: 581-587.
18. Suchonska B, Wielgos M, Bobrowska K, Marianowski L. Concentration of bilirubin in the umbilical blood as an indicator of hyperbilirunemia in newborns. Ginekol Pol. 2004; 75: 749-753. [PubMed]
19. Gatea SK. Cord bilirubin level as predictor for newborns at risk for post natal hyperbilirubinemia. Kufa Med Journal. 2009; 12: 109-117.
20. Rataj J, Kornacka M, Korman E. Usefulness of measuring bilirubin levels in cord blood for predicting hyperbilirubinemia in newborns. Ginekol Polv. 1994: 276-280.
21. Jacobson MP, Bernstein HH. Limited diagnostic value of routine cord blood bilirubin determinations. Clin Pediatr (Philia) 1982; 21: 610-612.
22. Rostami N, Mehrabi Y. Identifying the newborn at risk for developing significant hyperbilirubinemia by measuring cord bilirubin levels. J. Arab Neonatal Forum. 2005; 2: 81-85.
23. Carbonell EX, Botet MF, Figueras AJ, Riu GA. Hyperbilirubinemia in full term newborns. Predictive factors. An Esp Pediatr. 1999; 50: 389-392
24. American Academy of Pediatrics Subcommittee on hyperbilirubinemia. Clinical Practice Guidelines: Management of hyperbilirubinemia in the newborn infants 35 or more weeks of gestation. Pediatrics 2004; 114: 297-316

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