Prospective study on cord bilirubin level as a predictor of Hyperbilirubinemia in term healthy neonates

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Abstract

Introduction: Neonatal jaundice or hyperbilirubinemia is a cause of concern for parents and pediatricians, with more than 60% being affected by this condition in the first few weeks. Prediction of high risk neonates for hyperbilirubinemia will help in developing appropriate follow-up programs for managing the condition. It will also help in reducing duration of hospital stay for low-risk neonates. **Objective:** To estimate the predictive value of umbilical cord blood bilirubin level for the development of significant hyperbilirubinemia in healthy, full term neonates. **Methodology:**A prospective study on 450 healthy full tem newborns was undertaken in the postnatal care ward of a tertiary level teaching hospital. The study focused on predictive ability of cord blood bilirubin levels and subsequent development of hyperbilirubinemia. **Results:**Clinically significant hyperbilirubinemia was detected in 254 out of 450 newborns (56%) neonates. Majority of participants had cord blood bilirubin levels ranging from 1.5-2.4mg/dl. Only 1.3% (3 neonates) had levels ≥3 mg/dl. Majority of newborns in our study (60%) had an intermediate risk of developing hyperbilirubinemia, and only 1.3% (31) belonged to the high risk category on stratifying risks. Cord bilirubin cut off value of 1.9 mg/dl predicted subsequent hyperbilirubinemia with sensitivity of 91.8% and specificity of 52.4%. **Conclusion:** Study highlights that risk stratification is an excellent method of tracking newborns with hyperbilirubinemia as newborns with hour-specific bilirubin value in low risk zone have reduced risk of developing subsequent significant hyperbilirubinemia. The probability of developing this condition in neonates was not significantly different in males and females.

Keywords: Neonatal jaundice, Neonatal hyperbilirubinemia, Cord bilirubin

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Introduction

Hyperbilirubinemia is a very common clinical condition affecting about 60% of neonates in the first few weeks [1]. These children, who are otherwise healthy, should be monitored as hyper bilirubinemia may affect the central nervous system [2]. Quantifying the level of jaundice has been the foundation for satisfactory management of hyperbilirubinemia.

Visual inspection is not a reliable indicator of serumbilirubin levels. Moreover the current risk factors to recognize infants who are likely torequire treatment for hyperbilirubinemia are not adequate.

Early discharge from hospital is being practiced for preventing infections, economic constraints of parents, reduced infrastructural facilities in the hospital and some social factors.

But this has increased the risk of significant hyperbilirubinemia that requires readmission and intervention. Some neonates with significant hyperbilirubinemia develop neurological symptoms even without any apparent hemolysis [3].

Prediction of high risk neonates for hyper bilirubinemia will help in developing appropriate follow-up programs for managing the condition. This will also help in reducing duration of hospital stay for low-risk neonates. Risk stratification based

on cord bilirubin values may help in scheduling timely follow-up after discharge for detection of this condition.

Cut-off value of bilirubin is influenced by factors like ethnicity, child rearing practices and other geosocial factors in a region [4].

Considering the heterogeneity of Indian population, studies from different parts are essential to authenticate the predictive nature and also to evaluate the cut-off value for the population.

The current study aims to estimate the predictive value of umbilical cord blood bilirubin level for the development of significant hyperbilirubinemia in healthy, full term neonates in Kerala.

Methodology

A total of 450 healthy full term newborns with birth weight ≥ 2.5 kg was prospectively followed to study the predictive ability of cord blood bilirubin levels and subsequent development of hyperbilirubinemia.

Place and type of study- This prospective study, conducted from January 2014 to June 2015, was undertaken in the postnatal care ward of a tertiary level teaching hospital.

Inclusion criteria- Inborn full term healthy neonates (≥37 weeks according to lastmenstrual period) with birth weight ≥2.5 kg

Exclusion criteria- Newborns with Rh in-compatibility, presence of significant illness requiring neonatal intensive care unit admission for more than 12 hoursand congenital malformations were excluded from the study.

Detailed evaluation of history, gestational assessment by Expanded Ballard score, and systemic general examination (with particular attention to the factors known to be associated with hyperbilirubinemia) were carried out for all participants. The study was approved by the institutional ethics committee.

Sampling Method- Cord blood was collected from umbilical cord by squeeze method, placed in clot activator vials for analysis of bilirubin level.

Serum bilirubin estimation was done using VITROS TBIL Slide test.

The neonates were followed up clinically every 12 hrs for 72hrs (till discharge).

Newborns found to have clinically significant jaundice around 72 hours were enrolled in the study and serum bilirubin level was measured at 72 ± 4 hours.

Primary outcome was defined as presence of hyperbilirubinemia (total serum bilirubin (TSB) ≥ 15mg/dl).

Based on cord bilirubin levels, newborns were classified into two groups -- Group 1: Serum bilirubin level ≥ 1.9 mg/dl and Group 2: Serum bilirubin level < 1.9 mg/dl.

Additionally, newborns were divided in three risk zones as given inthe studydone by Bhutaniet al [5].

• High risk zone- Bilirubin level above 95th centile.

• Intermediate risk zone- Bilirubin level between 40th to 95th centile

• Low risk zone- Bilirubin level less than 40th centile.

Statistical analysis- Maternal and neonatal data were collected in predesigned and pretested proforma.

Sensitivity, specificity, negative and positive predictive values of test were also calculated. Analysis was done using Epi Info.

Results

Clinically significant hyperbilirubinemia was detected in 254 out of 450 newborns (56%) neonates, out of which 27 did not meet the inclusion criteria.

Thus a total of 227 newborns were prospectively followed up during the study period. The maternal characteristics of these children are given in **Table 1**.

Table-1: Maternal characteristics of the neonates included in the study.

(PIH - pregnancy-induced hypertension; BOH- bad obstetric history; ROM - Rupture of membranes; CPD - Cephalopelvic disproportion).

Maternal characteristics	N (%)
Type of delivery	
Cesarean section	188 (82.8%)
Normal vaginal	34(15%)
Instrumental	5(2.2)
Parity	
1	69(30.3)
2	77(33.9)
3	54(23.7)
4 or more	27(11.9)
Oxytocin use	94(42)
High-risk antenatal factors	
PIH	30(13.2)
Diabetes mellitus	14(6.2)
BOH	13(5.7)
ROM ($\geq$ 18 hours)	8(3.5)
Heart disease	2(0.9)
CPD	2(0.9)
Others	22(9.6)
Blood group	
O	95(41.8)
A	60(26.4)
B	51(22.4)
AB	11(4.8)

Pregnancy induced hypertension was the most common among the different high risk factors in mothers, with 13.2% showing symptoms of this condition. Eight women had rupture of membrane for more than 18 hours.

Most of the neonates (85%) belonged to the gestational age of 37-39 weeks. Neonatal characteristics of the study population are given in **Table 2**.

All newborns were exclusively breast fed within two hours of birth. None of the newborns developed kernicterus, or required exchange transfusion.

Table-2: Neonatal characteristics of the study population.

Neonatal characteristics	n(%)
Sex	
Male	138(61)
Female	89(39)
Birth weight (g)	
2500-3000	150(66)
3000-3500	61(26.8)
3500-4000	12(5.2)
>4000	4(1.7)
Blood group	
O	84(37)
A	70(31)
B	62(27)
AB	11(5)
Gestational age (weeks)	
37	60(26.4)
38	73(32.1)
39	60(26.4)
40	29(12.7)
41	5(2.2)

Cord bilirubin levels in the participants are given in **Table 3**

Table- 3: Cord bilirubin levels in the participants

Cord bilirubin (mg/dl)	Number of newborns	Percent
1-1.4	24	10.5
1.5-1.9	92	40.5
2-2.4	90	39.6
2.5-2.9	18	7.9
3 or more	3	1.3
Total	**227**	**100**

Majority of participants had cord blood bilirubin levels ranging from 1.5-2.4mg/dl. Only 1.3% (3 neonates) had levels ≥3 mg/dl. Cord blood bilirubin levels at 72 ± 4 hours are given in **Table 4**

Table- 4: Bilirubin level at 72 ± 4 hours.

Cord bilirubin (mg/dl)	Number of newborns	Percent
<5	3	1.3
5-9.9	23	10.1
10-14.9	140	61.6
15-19.9	59	25.9
20 or more	2	0.9
Total	**227**	**100**

Majority of newborns in our study (60%) had an intermediate risk of developing hyperbilirubinemia, and only 1.3% (31) belonged to the high risk categoryon stratifying risks (**Table 5**).

Table- 5: Risk categorization of neonates based on cord bilirubin levels.

Risk zone	Number of newborns	Percent
Low risk(<40th centile)	59	25.9
Low Intermediate risk	71	31.2
High intermediate risk	66	29
High risk (>95th centile)	31	13.7
Total	227	100

A total of 59 newborns had low risk of developing this condition. Considering the arbitrary cut-off value of 15 mg%, 73% of the participants had more than this value. Among the male newborns 51% had significant hyper bilirubinemia, which was close to 49% among female newborns who developed clinically significant form of hyperbilirubinemia. There was no significant difference between genders in the development of this condition.

Clinically significant hyperbilirubinemia was found in 56% of newborns included in the study. Chi-Square test for cord bilirubin levels at 72 hours is given in **Table 6**.

Table- 6: Chi-square test for cord bilirubin levels at 72 hours.

	Bilirubin at 72 hours ≥15mg/dl	Bilirubin at 72 hours < 15 mg/dl	
Cord bilirubin ≥ 1.9 mg/dl	56	79	135
Cord bilirubin < 1.9 mg/dl	5	87	92
Total	61	166	227

Cord bilirubin levels of the newborns ranged from 1.1-3.8 mg/dL. More than 80% of the children had cord bilirubin levels in between 1.5 – 2.4 mg/dL. Cord bilirubin values at 72h for two different values showed a positive predictive value of 41.4% and negative predictive value of 94.5% (χ = -36.0183, $p<0.05$). Sensitivity of the test was 91.8%, and specificity was 52.4%. Thus newborns with cord bilirubin values less than 1.9 mg% have a reduced risk (5.5%) of developing clinically significant hyperbilirubinemia. All newborns who had clinically significant hyperbilirubinemia were exclusively breastfed within 2 hours of birth. None of them developed Kernicterus.

Discussion

In neonates the serum bilirubin levels increases<5 mg/dl/day and peaks around two to three days [6]. A correlation was found between cord blood bilirubin level and development of hyperbilirubinemia in a population of 423 neonates by Sun et al [7]. Cord blood bilirubin was reported to be a strong predictor of hyperbilirubinemia in neonates in a study conducted by Zeitoun et al [8]. This is a non-invasive technique for which results are available within few hours. Thus, neonates who are at risk of hyperbilirubinemia can be identified before the mother and baby leave the hospital, few days after delivery. On the other hand, identifying high risk neonates will help to reduce the duration of hospital stay for other children who have a low risk of developing hyperbilirubinemia [9].

The cutoff value for prediction of hyperbilirubinemia is different in different studies. Prospective study conducted by Ahire reported that neonates with cord blood bilirubin ≥ 3mg/dl should be monitored more frequently [10]. The cut-off point for cord blood bilirubin in full-term neonates was given as 2.15 mg/dl in another prospective clinical study [8]. Similar value was suggested by Sehgal et al, with a negative predictive value of 0.965 for hyperbilirubinemia [11]. A 99.45% negative predictive value was assessed for cord bilirubin levels of <1.89mg/dl by Pabbati et al [12]. The negative predictive value was found to reach 99.1% with a specificity of 98.92% for cord serum bilirubin level >4mg/dl in a study conducted by Hamdi et al [13]. In the present study, 1.9 mg/dl was

used as the optimum cut-off value for predicting hyperbilirubinemia. Cord bilirubin cut off value of 1.9 mg/dl predicted subsequent hyperbilirubinemia with sensitivity of 91.8% and specificity of 52.4%. Thus, this cut-off value can predict more than 90% of the newborns who develop jaundice/hyper bilirubinemia later.

In the current study, 56% of the newborns had clinically significant hyperbilirubinemia, and cord blood bilirubin ranged from 1.1 mg/dl to 3.8mg/dl. Newborns with hyper bilirubinemia had significantly higher levels of cord bilirubin than those without hyperbilirubinemia. These values are in tune with other studies conducted in India, including Dhanjal et al [14]. In our study negative predictive value is more significant, proving that newborn with bilirubin less than cut off value or bilirubin level in low risk zone can be discharged safely and early.

Study also highlights that the risk stratification is an excellent method of tracking newborns with hyperbilirubinemia as newborns with hour-specific bilirubin value in low risk zone have reduced risk of developing subsequent significant hyper bilirubinemia. Sixty one neonates developed significant hyper bilirubinemia requiring phototherapy with no newborn requiring exchange transfusion and none developed kernicterus. Total of 56 had there cord bilirubin levels ≥ 1.9 mg/dl.

Male gender, though known as a risk factorfor developing hyperbilirubinemia,did not show any significant difference from female neonates [15]. Induction of labor using oxytocin also did show a significant relation with cord blood bilirubin levels. The incidence of significant hyperbilirubinemia did not show a significant difference between presence and absence of high risk antenatal factors in mothers.

Conclusions

Present study show that increased levels of cord blood bilirubin can define a group of neonates who are at risk of developing hyperbilirubinemia. Cord blood bilirubin value 1.9 mg/dl can be used as an optimum cut-off value to detect more than 90% of the neonates who are high risk of developing hyperbilirubinemia. The probability of developing this condition in neonates was not significantly different in males and females. Oxytocin-induced

labor and high-risk antenatal factors also did not influence the development of this condition in newborns.

Value addition to existing knowledge- This study ascertains the predictive significance of cord blood bilirubin in significant hyperbilirubinemia in neonates. It also helps to validatethe cut-off value of 1.9 mg/dl as optimum for a population in this region. Further, it also highlights the importance of risk stratification for timely follow-up that will enable detection of hyperbilirubinemia.

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How to cite this article?

Bindu A, Shinoj, Kutty P.M. Prospective study on cord bilirubin level as a predictor of Hyperbilirubinemia in term healthy neonates. J PediatrRes. 2017;4(09):552-558.doi:10. 17511/ijpr.2017.i09.03.
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